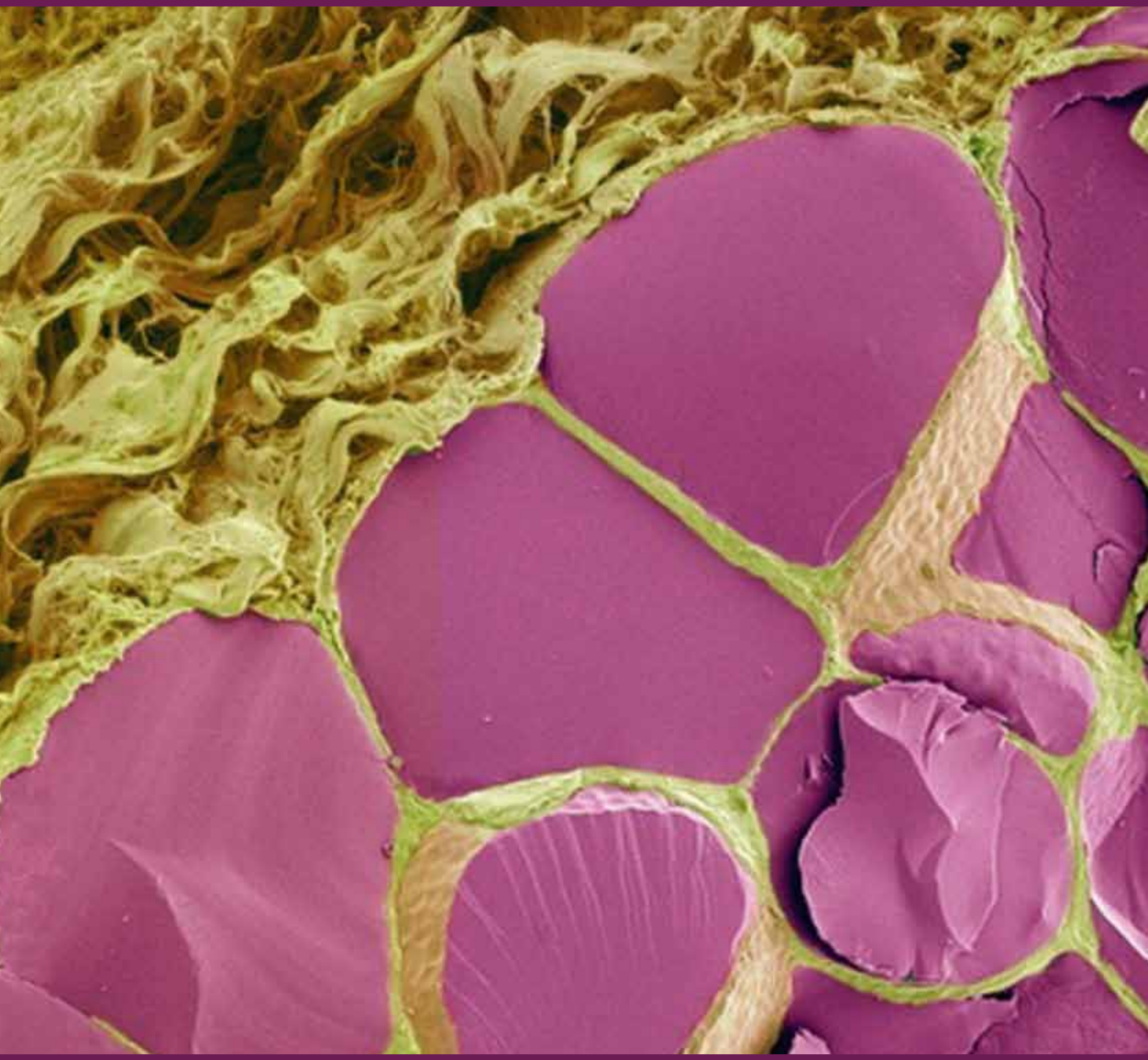
International Journal of Endocrinology

Sleep and the Endocrine Brain

Guest Editors: Jessica A. Mong, Deborah Suchecki, Kazue Semba, and Barbara L. Parry



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Editorial Board

Contents

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 967435, 2 pages
doi:10.1155/2010/967435

Editorial

Sleep and the Endocrine Brain

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Received 31 December 2010; Accepted 31 December 2010

Why most living organisms participate in sleep remains an enigmatic question. But in recent years, clinical and scientific studies have raised the awareness of the importance of proper sleep to overall health and quality of life. Quality sleep is imperative for the maintenance of good health. People suffering from sleep disturbances are not only fatigued but have impaired memory and learning, increased stress and anxiety, and decreased quality of daily life. While it is clear that sleep homeostasis is influenced by various neuroendocrine systems and pathological conditions, such as feeding, hormonal changes, shifts in light/dark cycles, stress, and infections to name a few, it is not clear how such conditions affect sleep homeostasis. Moreover, this is not a one-way street as neuroendocrine functions are affected by disruptions in sleep; people suffering from sleep disturbances are not only fatigued but also have impaired or dysfunctional neuroendocrine systems that affect the quality of daily life. Thus, the relationship between sleep and neuroendocrinology is an area of intense clinical and scientific interest. Understanding how neuroendocrine mediators affect sleep is central to advancing our understanding of sleep-related disorders.

The main focus of this special issue is on current findings and ideas that advance our understanding of the mechanisms underlying the neuroendocrine control of sleep and arousal. The manuscripts submitted to this special issue on sleep and the endocrine brain in the International Journal of Endocrinology center around (1) ovarian hormone control of sleep and women's health, (2) sleep and metabolism, and (3) sleep and stress.

While much is known about the mechanics of sleep, the investigation into sex differences and hormonal control of sleep and biological rhythms is in its infancy. Data from a number of species including humans suggest that sex hormones (estrogens, progestins, and androgens) influence the physiology and pathology of sleep and biological rhythms. Women have remained underrepresented in the studies of sleep disorders even though sleep complaints are twice as prevalent in women. In recent years, more sleep studies have included women resulting in exciting findings that are raising more interesting questions. For example, while sleep complaints are generally more frequent in women, objective measures (e.g., polysomnography) suggest that women have better sleep than men. The report by A. Shechter and D.B Boivin reviews the variation in sleep and circadian rhythms at different menstrual phases in healthy women and women with premenstrual dysphoric disorder. The review by M.M. Mahoney discusses the potential consequences of disrupted biological rhythms to female reproductive functions and endocrine profiles. From these reports, it becomes clear that a better understanding of how gonadal hormones influence sleep and rhythms is necessary if we are to gain better knowledge of how dysregulation of endocrine systems influences the mechanisms of sleep and rhythm disorders.

The link between sleep loss and metabolic dysfunctions, which potentially underlies the risk for obesity and diabetes mellitus, is growing increasingly stronger. The majority of our submissions call attention to this link between sleep and metabolism. First, S. Sharma and M. Kavuru provide an in-depth overview of the research showing that sleep

deprivation and sleep disorders, such as obstructive sleep apnea, have profound metabolic and cardiovascular implications. Two additional reviews focus on the associations of obstructive sleep apnea with (1) obesity, and neuroendocrine alterations in growth hormone, insulin-like growth factor-I, and the sleep-entrained prolactin rhythm (F. Lanfranco and colleagues) and (2) insulin resistance (S. Bopparaju and S. Surani). Several primary research articles investigating sleep and metabolism also are presented. Sleep duration has been inversely associated with body mass index, and M. -P. St-Onge and colleagues report gender differences in this association with their analysis of data taken from the CARDIA study. Two studies investigating sleep deprivation and glucose metabolism, one in humans and the other in rodents, present similar conclusions that sleep deprivation adversely affects glucose metabolism resulting in an increased risk for the onset of diabetes.

The hypothalamo-pituitary-adrenal (HPA) axis that controls the release of the stress hormones (cortisol in primates and corticosterone in rodents) is reciprocally connected to sleep. Sleep damps the HPA activity; however, activation of the HPA axis by a stressor is known to disrupt normal sleep patterns. In this issue, M. Balbo and colleagues discuss the potential consequences of HPA hyperactivity on sleep disturbances and the associated metabolic risks. Similarly, R.B. Machado and colleagues present findings from a rodent model of sleep deprivation that HPA-axis activation negatively impacts on sleep homeostasis. Tumors associated with the hypothalamus-pituitary axis affect endocrine functions. A clinical study by H.L. Müller in this issue reviews the association of increased daytime sleepiness and childhood craniopharyngioma.

Our understanding of the neuroendocrine factors influencing sleep and biological rhythms is advancing. Nevertheless, more work is needed to further our understanding about the cellular and molecular mechanisms through which these factors are working. With these advances, therapeutic targets may be elucidated that will help to alleviate the sleep pathologies associated with neuroendocrine dysfunctions.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 259345, 17 pages
doi:10.1155/2010/259345

Review Article

Sleep, Hormones, and Circadian Rhythms throughout the Menstrual Cycle in Healthy Women and Women with Premenstrual Dysphoric Disorder

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Received 13 August 2009; Accepted 16 October 2009

Academic Editor: Barbara L. Parry

A relationship exists between the sleep-wake cycle and hormone secretion, which, in women, is further modulated by the menstrual cycle. This interaction can influence sleep across the menstrual cycle in healthy women and in women with premenstrual dysphoric disorder (PMDD), who experience specific alterations of circadian rhythms during their symptomatic luteal phase along with sleep disturbances during this time. This review will address the variation of sleep at different menstrual phases in healthy and PMDD women, as well as changes in circadian rhythms, with an emphasis on their relationship with female sex hormones. It will conclude with a brief discussion on nonpharmacological treatments of PMDD which use chronotherapeutic methods to realign circadian rhythms as a means of improving sleep and mood in these women.

1. Introduction

A variety of hormones, including melatonin, cortisol, thyroid stimulating hormone (TSH), and prolactin (PRL), vary across the 24-hour day and are highly regulated by the circadian and sleep-wake cycles. Evidence suggests that these hormones, as well as other physiological rhythms like body temperature, play a role in sleep organization and can also be affected by sleep itself (or lack thereof). These relationships can be further modulated by the menstrual cycle, since fluctuations in gonadotropic and sex steroid hormones occurring throughout the menstrual cycle can influence sleep, body temperature, and other hormones.

Sleep disruptions are common in women, with reports of insomnia occurring 1.5–2 times more frequently than in men [1]. Indeed, sleep complaints commonly occur during the postovulatory luteal phase (LP) in healthy women [2]. These complaints reach a higher severity in women suffering from premenstrual dysphoric disorder (PMDD) [3], a DSM-IV classified menstrual cycle-related mood disorder. Since disturbed sleep and circadian rhythms have been correlated with increased incidence of obesity and diabetes [4], cardiovascular disease [5], and especially depression [6], and since depression already occurs with higher prevalence in women [7], it is necessary to understand how neuroendocrine changes across the menstrual cycle interact with circadian physiology and contribute to the greater susceptibility of sleep complaints in women.

The aim of this paper is to review studies which investigated how the menstrual cycle, and its associated variation in sex steroid hormones, affects sleep and circadian rhythms in both healthy women and women with PMDD. Additionally, we will address the inconsistencies that often characterize these experimental results, highlighting methods which can minimize various confounders, and offer suggested areas of further research. Articles were included if they were written in English, conducted on human research participants, and concerned changes in sleep and/or circadian rhythms on at least two menstrual cycle phases in healthy and/or PMDD women. Though there were no

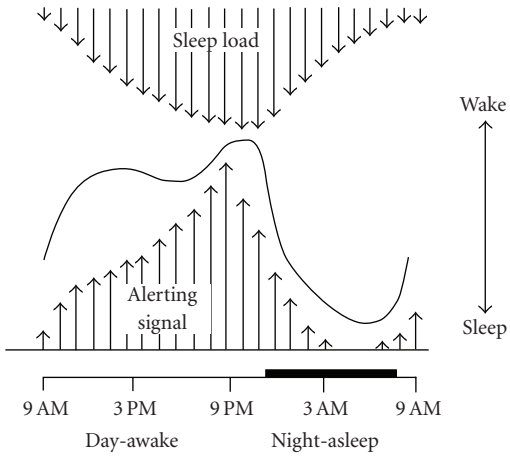

Figure 1: The interaction between circadian (C) and homeostatic (S) processes in an "opponent-process" results in an uninterrupted 8-hour nocturnal sleep episode and a wake period maintained throughout the 16-hour day. The homeostatic drive for sleep (illustrated as the "sleep load") increases throughout the waking period and reaches a peak just before habitual bedtime. The circadian drive for alertness (illustrated as the "alerting signal") reaches a peak at this time and is lowest near the end of the sleep episode. From [8].

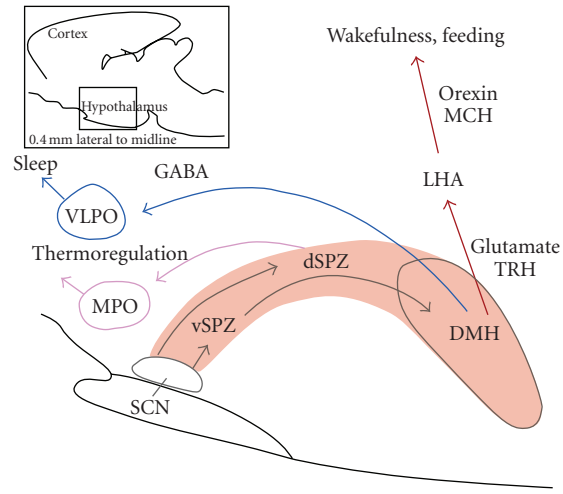

Figure 2: Pathways involved in the hypothalamic control of the circadian rhythms of sleep, wakefulness and body temperature. In the regulation of circadian sleep-wake patterns, outputs from the SCN relay at the vSPZ, and project to the DMH. The DMH then sends outputs to the VLPO (a sleep-activating center), and the LHA (where orexin neurons target downstream wake-promoting sites). The SCN regulates circadian body temperature rhythms through a relay at the dSPZ, which projects to the MPO. SCN, suprachiasmatic nucleus; vSPZ: ventral subparaventricular zone; dSPZ: dorsal subparaventricular zone; DMH: dorsomedial nucleus; VLPO: ventrolateral preoptic nucleus; LHA: lateral hypothalamic area; MPO: medial preoptic nucleus; MCH: melanin-concentrating hormone; TRH: thyrotropin-releasing hormone. Modified with permission from [9].

date restrictions, menstrual cycle-related research articles included were published between 1984 and the present.

2. Hormones and the Sleep-Wake and Circadian Cycles

2.1. Circadian and Homeostatic Regulation of the Sleep-Wake Cycle. The sleep-wake cycle is regulated by an interaction between homeostatic (process S) and circadian (process C) processes [10]. Throughout the course of the waking day, the homeostatic drive for sleep pressure increases and dissipates rapidly during the subsequent sleep episode. This process has been linked to the restorative aspects of sleep and is quantifiable with the amount of slow wave sleep (SWS; stage 3 + 4 sleep based on standard polysomnographic sleep analyses [11]) or more accurately slow wave activity (SWA; power density within the 0.5–4.5 Hz frequency range based on spectral analysis of the EEG signal), which was demonstrated to increase as a function of the duration of prior awakening [12]. It was hypothesized that increasing levels of adenosine in the basal forebrain during waking contributes to the buildup of the homeostatic drive for sleep [9].

At certain times of day, for example, just before habitual bedtime when the homeostatic drive for sleep is at its peak, and conversely at the end of the sleep episode when it is at its lowest, a strong circadian drive for wakefulness and sleepiness, respectively, counteracts process S. This interaction, referred to as the "opponent process," results in uninterrupted 8-hour nocturnal sleep and 16-hour waking episodes each day (Figure 1) [8, 13]. Circadian rhythms (i.e., endogenously generated biological rhythms of about 24 hours) are observable in many aspects of human physiology and behavior, including neuroendocrine secretion [14], sleep propensity and architecture [10], and subjective and EEG-based estimates of alertness [15]. The suprachiasmatic nucleus (SCN) of the anterior hypothalamus is the master circadian pacemaker [16] and coordinates endogenous physiology with the external light-dark environment [17]. Sleep parameters including sleep onset latency (SOL), sleep efficiency (SE), rapid eye movement (REM) sleep, REM sleep onset latency (ROL), and spindle frequency activity (SFA; spectral power density within the 12–15 Hz range) show a strong circadian modulation [10].

Signals originating in the SCN generate the circadian variation of sleep and wakefulness via major outputs to the ventral subparaventricular zone (vSPZ) and dorsomedial nucleus (DMH) (Figure 2) [9]. Some key arousal centers involved in this regulation are the histaminergic tuberomammillary nucleus (TMN), the noradrenergic locus coeruleus (LC), and the serotonergic dorsal and median raphe nucleus. The principle hypothalamic center for sleep initiation is the ventrolateral preoptic nucleus (VLPO). Activity in the VLPO is driven by the SCN via its projections to the vSPZ and DMH (Figure 2) [9]. Orexin neurons originating in the lateral hypothalamic area also receive projections from the SCN via the vSPZ and DMH, and promote wakefulness through their inputs to the TMN, LC, and raphe nucleus [9]. The sleep-wake system is presumed to be dependent on the mutually

inhibitory interaction between these key arousal and sleep centers [9]. According to this "flip-flop" model, sleep occurs when the VLPO dominates, whereas waking occurs when it is inhibited by histaminergic, noradrenergic and serotonergic inputs [9].

2.2. Circadian and Sleep-Wake Dependent Variation of Hormones. A variety of hormones cycle with a 24-hour rhythmicity, though some are more regulated by the endogenously generated circadian system, whereas others are more sensitive to the timing of sleep per se [14].

Melatonin and cortisol are two hormones which vary with a strong circadian component, and are therefore reliable markers of circadian phase, or the timing of the central circadian oscillator [18]. The two have different times of peak amounts, with high melatonin levels throughout the biological night, during which cortisol levels are minimal. When cortisol peaks in the early morning, melatonin secretion is already declining to reach almost undetectable levels during the day [18]. Both hormones are sensitive to environmental factors like retinal light exposure (which suppresses melatonin secretion) and stress (which stimulates cortisol release). Thus to most accurately assess their circadian expression, it is advised to study them under constant conditions, which will reduce the occurrence of confounding "masking effects" on their secretion [19].

Other hormones such as TSH and PRL cycle with a 24-hour rhythmicity but are also sensitive to sleep-wake state. Under normally entrained conditions, TSH levels begin rising before the nocturnal sleep episode, and progressively decline throughout the sleep period [18]. Sleep has an inhibitory effect on TSH secretion [20]; therefore when sleep is prevented, TSH levels remain high throughout the nighttime hours. In comparison, PRL is stimulated by sleep [20], with peak amounts detectable during the sleep episode, and a minor, but significant endogenously generated circadian variation when sleep is eliminated [18].

2.3. Relationship between Melatonin, Body Temperature, and the Sleep-Wake System. Melatonin levels vary concomitantly with body temperature and sleep propensity across the 24-hour day [21]. Specifically, under entrained conditions, the late evening rise in circulating melatonin levels triggers a thermoregulatory cascade, which, via an increase in the blood flow through distal skin regions and a subsequent decrease in core body temperature (CBT), favors sleep initiation (Figure 3) [21].

Core and distal body temperature levels show robust circadian rhythms, which are controlled by the SCN through projections to the dorsal subparaventricular zone (dSPZ) and ultimately the medial preoptic region (Figure 2) [9]. Constant routine experiments have illustrated this circadian variation for CBT, which reaches a peak in the late evening (21:00–22:00) and a trough during the latter part of the night (05:00–06:00) [24]. Distal skin temperature showed an inverse time course, that is advanced by 25–100 minutes with respect to the CBT curve [24]. Sleep is typically initiated on the declining limb of the CBT curve [25],

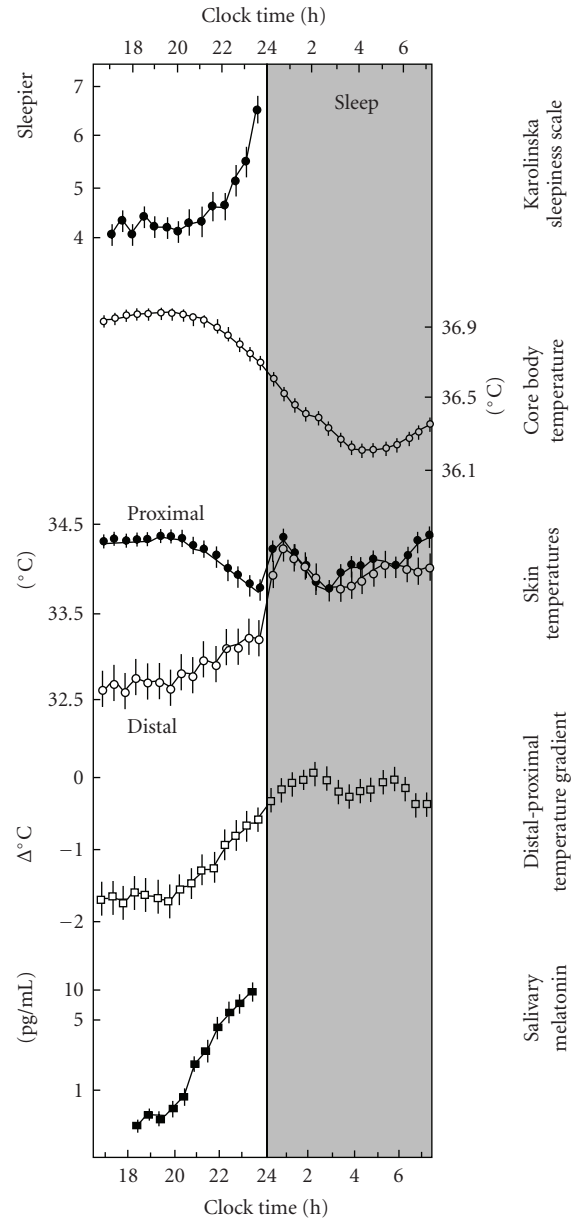

Figure 3: The relationship between melatonin secretion, body temperature and sleepiness. The onset of melatonin secretion during the early night causes an increase in heat loss at the extremities (i.e., rising distal skin temperature, and distal-proximal temperature gradient) and a drop in core body temperature, followed by an increase in sleepiness. From [21].

and statistical regression analyses revealed that the distal-proximal temperature gradient (a measure of heat loss at the extremities) is the best predictor of a rapid SOL [26]. Exogenous melatonin administered during the day (when endogenous levels are low) reduces CBT and increases skin temperature, with concomitant increases in sleepiness [27]. These results indicate that melatonin may achieve its soporific effects through a thermoregulatory pathway. In addition to increasing sleepiness and sleep propensity, exogenous melatonin can affect sleep architecture [28–30],

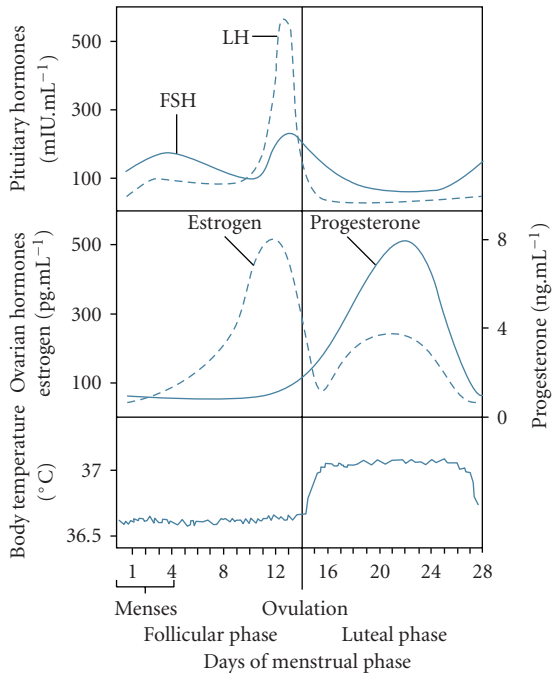

Figure 4: The variation of gonadotropic and sex steroid hormones, and the subsequent changes in daily body temperature across the full menstrual cycle. During the pre-ovulatory FP, estrogen levels are high. During the post-ovulatory LP, increasing levels of circulating progesterone are observed, along with increased daily body temperature. FSH, follicle stimulating hormone; LH, luteinizing hormone; FP, follicular phase; LP, luteal phase. From [22], as adapted from [23].

regardless of its effect on body temperature [31, 32]. These functional relationships and the localization of melatonin receptors throughout the brain and periphery [33] suggest that melatonin can affect the sleep-wake and circadian systems.

3. Normal Menstrual Cycle

3.1. Hormonal Regulation of the Menstrual Cycle. The menstrual cycle in healthy, ovulating females is regulated as well as defined by changes in the gonadotropic hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the sex steroid hormones, estrogen and progesterone (Figure 4). At the start of the cycle, during the pre-ovulatory follicular phase (FP), FSH stimulates ovarian follicles to grow and develop at which point circulating estrogen levels begin to rise and remain high throughout the FP. This culminates in ovulation at mid-cycle, when LH levels surge and stimulate the release of an oocyte. The subsequent secretion of sex hormones by the newly formed corpus luteum characterizes this post-ovulatory LP, when progesterone is the dominant hormone. If the egg is not fertilized, sex hormone levels drop at the end of the LP and trigger the shedding of the uteral lining (menstruation) [34].

3.2. Body Temperature Changes Associated with the Menstrual Cycle. Hormone changes across the menstrual cycle result in altered body temperature. Most notably, during the LP compared to the FP, there is an increase of ~0.3–0.4°C in CBT levels (Figure 4) [35, 36] as well as a significant reduction in the amplitude of the circadian variation of CBT [35–38], owing mainly to a blunted nocturnal decline of CBT. Skin temperature and vascular blood flow, which are important thermoregulatory responses, are affected by the menstrual cycle. Increased threshold for sweating [39, 40] and for vasodilation [39–41] as well as decreased thermal conductance and skin blood flow [42] is observed during the LP compared to the FP.

This upward shift in the thermoregulatory set-point is most likely due to progesterone, which possesses thermogenic properties [36, 43], and was shown to increase the firing rate of cold-sensitive (i.e., body warming) neurons in the preoptic anterior hypothalamus (POAH) [44].

4. Sleep across the Menstrual Cycle in Healthy Women

4.1. Standard Polysomnographic Sleep. A relatively limited number of studies have addressed sleep-wake patterns across the menstrual cycle in healthy women. These have indicated that while sleep homeostasis [49, 51, 55] and quality [43, 49, 52] remain stable at different menstrual phases, there are observable changes in sleep architecture [49, 51–53] (summarized in Table 1). Interestingly, women often report subjective complaints of disturbed sleep during the late-LP and premenstrual days, though polysomnography- (PSG-) based estimates indicating disrupted sleep during this time are less frequent [22]. Since most studies compared sleep at only two menstrual phases (e.g., mid-FP versus mid- or late-LP), inconsistencies still remain regarding the variation of SWS [45, 47, 52, 53] and REM sleep [43, 47, 54, 55] across the menstrual cycle.

In the first systematic study of sleep EEG across the menstrual cycle in healthy women, nocturnal sleep was recorded in the laboratory every other night throughout a full cycle [49]. This study showed no menstrual cycle-related change in SE (%), SOL (min), SWS (%) and wake after sleep onset (WASO; min) [49]. Non-REM (NREM) sleep and stage 2 sleep (%) significantly increased in the LP, while REM sleep (% of the NREM-REM sleep cycle) significantly decreased in the LP [49]. In a later study focusing on sleep-disordered breathing and the menstrual cycle, Driver et al. compared sleep at one visit during the FP and the LP [54]. They reported a significant increase in stage 2 sleep (%) during the LP, no change in SWS, and failed to replicate the significant decrease in REM sleep (%) generally reported during this phase [54].

A variety of studies compared sleep at either two or three phases of the menstrual cycle (mid-FP versus mid-LP [43, 53]; mid-FP versus late-LP [52, 55]; mid-FP versus mid-LP versus menses [51]). Across three phases, REM sleep (min) was significantly reduced during the mid-LP compared to the mid-FP, latency to stage 3 sleep was significantly reduced

Table 1: The variation of sleep across the menstrual cycle.

Authors [Reference]	Year	Sample size	Menstrual phases studied	Significant effect of menstrual phase	Significant effects in PMDD (versus NC)
Parry et al. [45]	1989	$n = 8$ healthy $n = 8$ PMS	early-FP late-FP early-LP late-LP	In healthy and PMS: variation of stage 3 (min) and intermittent awakening across cycle	↑ stage 2 (%) across cycle ↓ REM (min, %) across cycle
Lee et al. [46]	1990	$n = 6$ healthy $n = 7$ symptomatic	FP LP	none	↓ SWS (%) at both phases ↓ latency to stage 1 in LP
Ito et al. [47]	1993	$n = 7$ healthy	menses late-FP early-LP late-LP	↓ SWS (min) during early-LP and late-LP	N/A
Ishizuka et al. [48]	1994	$n = 5$ healthy	3 nights/week across full cycle	↑ SFA during late-LP	N/A
Driver et al. [49]	1996	$n = 9$ healthy	menses early-FP mid-FP late-FP ovulation early-LP mid-LP late-LP	↑ NREM (%) during LP ↑ stage 2 (%) during LP ↓ REM (% NREM-REM cycle duration) during LP ↑ SFA during LP	N/A
Chuong et al. [50]	1997	$n = 6$ healthy $n = 3$ PMS	mid-FP ovulation mid-LP	none	none
Baker et al. [51]	1999	$n = 10$ healthy	menses mid-FP mid-LP	↓ REM (%) during mid-LP versus mid-FP ↓ latency to stage 3 during mid-LP versus menses	N/A
Parry et al. [52]	1999	$n = 18$ healthy $n = 23$ PMDD	mid-FP late-LP	In healthy and PMDD: ↑ ROL, ↓ stage 3 (min and %), and ↓ REM (min) during late-LP In healthy: ↑ stage 1 (min, %) during late-LP	none
Shibui et al. [37]	2000	$n = 8$ healthy	FP LP	↑ number of SWS-containing naps during LP	N/A
Baker et al. [43]	2001	$n = 9$ healthy	mid-FP mid-LP	none	N/A
Baker et al. [53]	2002	$n = 13$ healthy	mid-FP mid-LP	↓ REM (%) during mid-LP ↑ SWS (%) during mid-LP	N/A

Table 1: Continued.

Authors [Reference]	Year	Sample size	Menstrual phases studied	Significant effect of menstrual phase	Significant effects in PMDD (versus NC)
Driver et al. [54]	2005	$n = 11$ healthy	FP LP	↑ stage 2 (%) during LP	N/A
Baker et al. [55]	2007	$n = 12$ healthy $n = 9$ PMS/PMDD	mid-FP late-LP	In healthy and PMS: ↑ WASO (min), ↑ microaraousals/hour, and ↑ SFA during late-LP	↑ ROL (min) at both phases
Lamarche et al. [56]	2007	$n = 8$ healthy $n = 10$ PMS	FP late-LP	In healthy and PMS: ↑ stage 2 (%), ↓ SWS (%), and ↓ REM (%) during late-LP	none

PMS: premenstrual syndrome; PMDD: premenstrual dysphoric disorder; FP: follicular phase; LP: luteal phase; REM: rapid eye movement sleep; ROL: REM onset latency; NREM: non-REM sleep; SWS: slow wave sleep; SFA: spindle frequency activity; WASO: wake after sleep onset.

during the mid-LP compared to menses, and there were no significant changes observed for stage 2 sleep (min) or SWS [51]. Comparing the sleep of healthy women at the mid-FP and mid-LP, one study found no significant differences between any sleep parameter (including SE, SOL, REM sleep and SWS) [43], whereas another report detailed significantly decreased REM sleep (%) and significantly increased SWS (%) at the mid-LP compared to the mid-FP [53]. Focusing on healthy women and women with premenstrual syndrome (PMS) at the mid-FP and late-LP, Baker et al. reported that healthy women had significantly increased WASO (min) and microarousals per hour during the late-LP compared to the mid-FP, with no other significant changes observed between menstrual phases [55]. The results from eighteen healthy controls studied by Parry et al. at the mid-FP and late-LP as part of a larger study of sleep in PMDD found increases in ROL (min) and stage 1 sleep (%), and decreased REM sleep (min) and stage 3 (min and %) during the late-LP compared to the mid-FP [52].

Two investigations studied PSG sleep across four phases of the menstrual cycle [45, 47]. The first, which included eight healthy participants at the early-FP, the late-FP, the early-LP and the late-LP, found significant menstrual phase variations for stage 3 sleep (min), with a trough at the late-LP, and intermittent awakenings, with a peak at the late-LP [45]. The second, which included recordings of seven healthy females at menses, the late-FP, the early-LP and the late-LP, only found a significant variation for SWS (min), which, like the aforementioned study [45], was lowest during the LP compared to the late-FP and menses [47].

Interested in studying the effects of the menstrual cycle on the circadian variation of sleep propensity, Shibui et al. applied an ultra-rapid sleep-wake cycle procedure to eight healthy females at the FP and LP [37]. Sleep propensity (defined in the study as the sum of the duration of stages 2, 3, 4 and REM sleep occurring at each 10-minute nap trial) varied significantly across the circadian day, but did not differ between menstrual phases. Their main finding was that from 09:00 to 16:30, the number of naps containing SWS was increased during the LP compared to the FP [37]. It should be noted, however, that their participants were sleep-deprived for 24 hours preceding the start of the ultra-rapid sleep-wake cycle, creating a situation that could have increased the homeostatic pressure for SWS propensity, thus potentially confounding these results.

4.2. Quantitative Sleep EEG. The effects of menstrual phase on quantitative sleep EEG have been investigated by a few groups, yet results indicate a very consistent pattern of findings, making the prominent increase in SFA during the LP the most characteristic menstrual cycle associated sleep change [48, 49, 55] (Table 1). The sleep of five healthy young women was recorded by Ishizuka et al. at least three nights per week across a complete menstrual cycle [48]. Defining a sleep spindle as activity within the 11.11–16.13 Hz frequency range, the authors described a biphasic variation in the frequency of spindles, with lowest values observed during the FP (18 days before menstruation, near the mid-FP) and highest values during the late-LP [48]. Similarly, in the aforementioned study by Driver et al., which tracked sleep changes throughout an entire menstrual cycle in nine healthy women, SFA (here defined as mean power density within the 12.25–15.00 Hz frequency range) was lowest during the FP and reached peak values during the LP [49]. Maximum menstrual phase variation was observed within the 14.25–15.00 Hz band, and SWA (mean power density within the 0.75–4.50 Hz frequency range), a marker of sleep homeostasis, was unchanged across the menstrual cycle [49]. Finally, in the recent study by Baker et al., healthy women showed significantly increased SFA (12–15 Hz) during the late-LP compared to the mid-FP, with the most prominent peak again occurring in the 14.25–15.00 Hz bin specifically [55].

4.3. Summary and Future Steps. The most common sleep findings across the menstrual cycle include decreases in REM sleep, increases in stage 2 sleep and SFA, and no changes in sleep propensity and quality (SOL and SE, resp.) during the LP compared to the FP. Most studies agree with the absence

Table 2: The variation of hormonal rhythms across the menstrual cycle.

Authors [Reference]	Year	Sample size	Frequency of sampling	Hormones sampled	Menstrual phases studied	Significant effect of menstrual phase	Significant effects in PMDD (versus NC)
Steiner et al. [57]	1984	$n = 2$ healthy $n = 2$ PMS	2x/hour for 24-hours	plasma cortisol plasma PRL	FP LP	none	none
Webley and Leidenberger [58]	1986	$n = 10$ healthy	1x/4-hour for 24-hours	plasma melatonin	FP LP	↑ melatonin during LP	N/A
Brun et al. [59]	1987	$n = 9$ healthy	1x/night	urinary immunoreactive melatonin	across full cycle	↑ melatonin during LP	N/A
Brzezinski et al. [60]	1988	$n = 14$ healthy	1x/2-hour for 24-hours	Plasma melatonin plasma PRL	early-FP ovulation mid-LP	none	N/A
Berga and Yen [61]	1990	$n = 10$ healthy	1x/hour in daytime 2x/hour in nighttime	Plasma melatonin	early-FP late-FP mid-LP late-LP	none	N/A
Parry et al. [62]	1990	$n = 8$ healthy $n = 8$ PMS	2x/hour for 27-hours	plasma melatonin	early-FP late-FP mid-LP late-LP	none	↓ melatonin AUC ↓ melatonin duration melatonin phase-advanced
Ito et al. [47]	1993	$n = 4$ healthy	1x/hour for 24-hours	plasma melatonin	menses late-FP early-LP late-LP	none	N/A
Parry et al. [63]	1994	$n = 11$ healthy $n = 21$ PMDD	2x/hour for 27-hours	plasma cortisol plasma PRL plasma TSH	mid-FP late-LP	In healthy: cortisol phase-delayed in late- LP	↑ PRL amplitude at both phases ↑ PRL peak at both phases
Cagnacci et al. [35]	1996	$n = 7$ healthy	4x/hour for 24-hours	plasma melatonin	FP LP	melatonin phase-delay during LP	N/A
Parry et al. [64]	1996	$n = 18$ healthy $n = 23$ PMDD	2x/hour for 27-hours	plasma TSH plasma PRL	mid-FP late-LP	none	↑ PRL peak at both phases TSH phase-advanced at both phases
Parry et al. [65]	1997	$n = 11$ healthy $n = 21$ PMDD	2x/hour for 27-hours	plasma melatonin	mid-FP late-LP	In PMDD: ↓ AUC, ↓ amplitude, ↓ duration, delayed onset during late-LP	↓ AUC at both phases ↓ mean levels at both phases
Bloch et al. [66]	1998	$n = 10$ healthy $n = 10$ PMS	1x/day	plasma cortisol	early-FP mid-FP late-FP ovulation early-LP mid-FP late-FP	none	none

Table 2: Continued.

Authors [Reference]	Year	Sample size	Frequency of sampling	Hormones sampled	Menstrual phases studied	Significant effect of menstrual phase	Significant effects in PMDD (versus NC)
Wright and Badia [67]	1999	$n = 25$ healthy	1x/hour for 24-hours	salivary melatonin	FP LP	none	N/A
Shibui et al. [37]	2000	$n = 8$ healthy	1x/hour for 24-hours	Plasma melatonin plasma cortisol plasma TSH	FP LP	↓ melatonin AUC during LP ↓ cortisol amplitude during LP ↓ TSH amplitude during LP TSH phase-delay during LP	N/A
Parry et al. [68]	2000	$n = 15$ healthy $n = 15$ PMDD	2x/hour for 27-hours	plasma cortisol	mid-FP late-LP	In healthy: cortisol phase-advanced in LP	none

PMS: premenstrual syndrome; PMDD: premenstrual dysphoric disorder; FP: follicular phase; LP: luteal phase; PRL, prolactin; TSH: thyroid stimulating hormone; AUC: area under the curve.

of changes in homeostatic sleep mechanisms (i.e., SWS and SWA) at different menstrual cycle phases, although some inconsistencies remain (Table 1). Methodological differences between the various studies might contribute to these discrepancies. For example, menstrual phase delineation and the number of sleep recordings across the cycle is often different between studies, and menstrual phase status is not uniformly confirmed with hormonal assays. Stabilization of sleep-wake patterns before lab entry is not always done, even though it is recommended to ensure a proper alignment of sleep and circadian rhythms.

The changing sex hormone profile across the menstrual cycle may play a role in producing these LP-specific sleep alterations. Specifically, progesterone, as well as its neuroactive metabolites, can affect sleep architecture, as was illustrated by the findings that exogenous progesterone [69] or megestrol acetate, a progesterone-receptor agonist [70], reduced REM sleep in male participants. Likewise, exogenous progesterone in rats reduced REM sleep while lengthening ROL [71]. Furthermore, progesterone likely affects the sleep system through another indirect means, namely by increasing body temperature during the LP. Sleep architecture, like the timing of sleep propensity, is under a circadian regulation, with highest REM sleep occurring at times corresponding with the nadir of body temperature [72]. The finding of reduced REM sleep during the LP, when nocturnal body temperature is significantly elevated compared to the FP, is therefore interesting.

The LP-associated increase in SFA is most likely a result of the neuroactive metabolites of progesterone acting as agonistic modulators of central nervous system $GABA_A$-receptors in a benzodiazepine-like manner [49, 71]. Indeed, progesterone administration enhanced spindle activity in the rat [71] and in male participants (particularly those who experienced an early allopregnanolone peak in response to exogenous progesterone treatment) during the first two hours of sleep [69]. Like REM sleep, the temporal pattern of SFA displays a robust circadian rhythm, with the peak of low-frequency SFA (12.25–13.00 Hz range) occurring during periods of high endogenous melatonin concentration, whereas high-frequency SFA (14.25–15.50 Hz range) is minimal during these times and the greatest during periods of low circulating melatonin [73].

The functional significance of increased SFA during the LP in women is still unknown. Since sleep spindles are thought to have a sleep-protecting effect via their blockage of information processing to the cortex [74], increased SFA may be the mechanism through which sleep quality is maintained at a good level despite the changing physiological and hormonal profile associated with different menstrual cycle phases.

5. Circadian Rhythms across the Menstrual Cycle in Healthy Women

It has been proposed that the menstrual cycle could form a backdrop on which daily circadian rhythms are expressed [22], and as such, circadian physiology can be altered as a function of the changing hormone profile associated with different menstrual phases (see Table 2 for a summary). The most apparent of these alterations is CBT (see above); yet other biological and hormonal rhythms, including melatonin, cortisol, TSH, and PRL may also be affected. It was proposed that one implication of the altered circadian rhythms observed during the menstrual cycle is the production of a stable intrauterine environment [35]. Specifically, the authors point to the reduced efficacy of melatonin function during the LP, which results in a blunted nocturnal decline of CBT and reduced circadian CBT

amplitude, as a stabilizing factor which would encourage proper implantation and development of a fertilized egg [35]. However, these effects may also contribute to the increased incidence of subjective sleep complaints during the LP.

5.1. Cortisol, TSH, and PRL across the Menstrual Cycle. A small number of studies looked at rhythms of cortisol, TSH, and PRL (Table 2). The circadian variation of cortisol in healthy women was found to be phase-delayed by ~1 hour [63], phase-advanced by ~1 hour [68] or decreased in amplitude [37] during the LP compared to the FP. PRL showed either a trend for increased amplitude during the LP compared to the FP [64] or no change across the menstrual cycle [60]. Sampling throughout an ultradian sleep-wake cycle, the TSH rhythm was found to be decreased in amplitude and delayed by ~80 minutes in the LP compared to the FP [37]. Since limited number and inconsistencies once again characterize these data, it is important to replicate these studies using highly controlled experimental conditions and adequate sample sizes.

5.2. Melatonin across the Menstrual Cycle. Melatonin is known to play a role in reproductive physiology (see [75] for a review). Studying menstrual-related changes in melatonin secretion has been a topic of interest, though findings remain equivocal (Table 2). An early study sampling plasma melatonin every four hours during the FP and LP reported a significant increase in the total amount of secretion in 24 hours during the LP compared to the FP [58]. This result was supported by the finding that nocturnal urinary immunoreactive melatonin concentration (sampled nightly over an entire menstrual cycle) was significantly increased during the LP compared to the FP [59]. However, in a well-controlled study sampling every hour during the FP and LP under constant conditions, the 24-hour area under the curve (AUC) for plasma melatonin was significantly decreased during the LP, though other timing measures were unaffected [37]. On the other hand, in an important study outlining the role of melatonin on body temperature changes during the LP, Cagnacci et al. found that while AUC was unchanged between menstrual phases, there was a significant delay of ~110 minutes in the onset of nocturnal melatonin during the LP [35]. Most other studies have found no change in the patterns of melatonin secretion (including onset, offset, duration, midpoint, and AUC) across the menstrual cycle in healthy women [47, 60–62, 65, 67]. Furthermore, strengths of these studies were that they actually sampled melatonin across the menstrual cycle (i.e., at four menstrual phase [47, 61, 62, 65] as opposed to only two), or under constant conditions [67].

5.3. The Interaction between Sex Hormones and Melatonin. Evidence indicates that the pineal melatonin system and the reproductive system interact, as was illustrated by a variation in the number of cerebral and caudal arterial melatonin binding sites in the rat throughout the estrous cycle [76]. An interaction between the melatonin system and sex hormones may have an influence on sleep and body temperature rhythms across the menstrual cycle. Further support for such an interaction comes from the colocalization of melatonin receptors with estrogen and progesterone receptors throughout the brain and periphery. Specifically, considering areas involved with the reproductive cycle, melatonin binding sites were found at human [77] and rat [78, 79] granulosa cells, and melatonin was found in human ovarian follicular fluid [80]. Furthermore, various sources indicate that receptors for melatonin, progesterone, and estrogen can all be found at the SCN [81, 82], POAH [82, 83], and pineal gland [84, 85].

Evidence of a functional interaction between melatonin and sex hormones was presented by Cagnacci et al. in the aforementioned study, who illustrated that women experience a progesterone-dependent resistance to the hypothermic effects of melatonin during the LP [35]. While this appears to support a functional antagonism between melatonin and progesterone, there is also evidence for a positive relationship between the two. Exogenous synthetic progestins (in the form of oral contraceptives) have a tendency to increase melatonin secretion [58, 59, 67], and melatonin treatment can enhance human chorionic gonadotropin-stimulated progesterone production from human granulosa cells [86]. Conversely, estrogen appears to negatively influence melatonin. For example, a low-estrogen environment was associated with increased melatonin levels in menopausal women, which was suppressed after exogenous estrogen administration, and oopherectomy in premenopausal women results in a significant increase in melatonin secretion [87]. Estrogen treatment also reduced melatonin binding in the rat ovary [78] and reduced melatonin synthesis in rat pinealocytes [88].

5.4. Summary and Future Steps. Most groups have found no change in the circadian hormone profiles of melatonin, cortisol, TSH, and PRL, though phase-delays were observed for melatonin, cortisol, and TSH during the LP compared to the FP (Table 2). Interestingly, when TSH and PRL were found to change during the LP compared to the FP, the directions of these changes (i.e., decreased TSH amplitude and increased PRL amplitude) are the opposite of what occurs after a partial nocturnal sleep deprivation [89], though PSG-based estimates of sleep indicate total sleep time and SE are unchanged at different menstrual phases (see Table 1).

Most studies which sampled hormones at different menstrual phases did not do so under controlled conditions, which are advised to limit the confounding effects of environmental factors (notably ambient light exposure, posture changes, and the sleep-wake cycle), something which likely contributes to these discrepancies [90]. Again, differences in the methods of dividing the menstrual cycle as well as sampling frequency (both across 24 hours and the menstrual cycle) are likely to contribute to inconsistencies in the literature. More studies need to be conducted before definitive conclusions can be made regarding the circadian variation of different hormone secretions across the menstrual cycle.

6. Premenstrual Dysphoric Disorder

6.1. Definition and Symptoms of PMDD. PMDD is a mood disorder affecting 3%–8% of North American women [91]. As is implied by its name, the occurrence of PMDD is defined by its timing within the context of the menstrual cycle. Symptoms typically begin during the late-LP and remit after menses, with a complete absence of symptoms during the FP. The DSM-IV lists a number of core symptoms for PMDD, including depressed mood, anxiety/tension, affective lability, anger/irritability, and decreased interest, each of which must reach sufficient severity to disrupt social, academic, or professional functioning [92]. Among these mood specific symptoms, sleep disturbances (including hypersomnia or insomnia, which is reported in as much as 70% of PMDD women [92]) are often present during the symptomatic LP. Since PMDD women may suffer from altered hormone secretion and/or function (see below), endocrinological factors and their influence on the sleep-wake system are important to consider when discussing this patient population.

6.2. Proposed Causes of PMDD. While the exact causes of PMDD are still unknown, a variety of hypotheses have been proposed which implicate endocrine or other neurotransmitter systems. An altered sex hormone profile in PMDD has been reported, with lower progesterone levels found in patients compared to controls [93, 94] as well as decreased levels of the anxiolytic progesterone metabolite allopregnanolone during the LP in patients [94, 95]. Progesterone produces its anxiolytic/hypnotic effects via allopregnanolone's binding to $GABA_A$-receptors [96, 97], and some have found lower plasma GABA concentrations [98] and a decreased $GABA_A$-receptor sensitivity [99] during the LP in PMDD patients compared to controls. Results of prior drug trials have found the most effective treatment of PMDD to date to be selective serotonin reuptake inhibitors (SSRIs) and they have become the most common clinical treatment for the disorder [100]. Experimental evidence implicating the serotonergic system includes findings of reduced plasma- [101] and whole-blood [102] serotonin levels in patients compared to controls. This raises the question of whether low serotonin levels could alter the production of melatonin by the pineal gland, since serotonin is a precursor for melatonin synthesis. Interestingly, PMDD patients experience alterations in the timing and amount of nocturnal melatonin secretion (see Section 8.2 below [62, 65]), though it is unclear whether this is a cause or a characteristic of the disorder.

7. Sleep across the Menstrual Cycle in PMDD Women

7.1. Standard Polysomnographic Sleep and Qualitative Sleep EEG. Although disrupted sleep is a characteristic symptom of PMDD, results of sleep studies in these women have been limited and inconsistent (Table 1). A preliminary study comparing six healthy controls and three patients with PMS (defined as a set of emotional, physical, and behavioral symptoms that occur with similar timing, but less severity, as PMDD) failed to detect significant differences in any sleep parameter [50]. A larger study with 23 PMDD patients and 18 controls also showed no intergroup differences, though significant menstrual phase effects were noted. In both groups, ROL (min) was increased, while REM sleep (min) and stage 3 (min and %) were decreased in the LP compared to the FP [52]. In a comparison of "premenstrually symptomatic" women (defined with an increase of at least 30% in the Profile of Mood States questionnaire during the LP) with controls, women experiencing negative mood symptoms during the LP showed decreased SWS (%) at both menstrual phases as well as decreased latency to stage 1 sleep and a trend for increased stage 2 sleep (%) in the LP [46]. Another study revealed that, compared to controls, PMS patients had more stage 2 sleep (%) and less REM sleep (%), and within these patients, stage 3 sleep (min; peaks near the late-FP/early-LP) and intermittent awakenings (peaks near the late-LP) varied significantly across the menstrual cycle [45]. More recently, a study including healthy women and those with PMS found decreased SWS (%) and REM sleep (%) as well as increased stage 2 (%) during the LP in both groups [56].

To date, one study [55] investigated quantitative sleep EEG in addition to standard PSG sleep in women with PMS/PMDD. Results from this comparative study showed that women with severe PMS and healthy controls both experienced similar increases in WASO (min) and microarousals per hour during the late-LP compared to the FP. Compared to controls, PMS/PMDD women showed increased ROL (min) in both menstrual phases. Similar to what has been shown for healthy controls, PMS/PMDD women demonstrated a menstrual variation for SFA (12–15 Hz), with marked increases during the late-LP. Interestingly, compared to controls, these women showed a trend for increased EEG activity in the 12-13 Hz range [55].

7.2. Summary and Future Steps. Within-patients studies of sleep across the menstrual cycle in PMS/PMDD patients revealed reduced REM sleep during the LP compared to the FP (Table 1). A significant menstrual cycle variation of stage 3 sleep was observed, and two other studies found decreased SWS or stage 3 sleep during the LP (Table 1).

PMS/PMDD women were found to have increased WASO (min) and microarousals per hour during the LP compared to the FP, indicating more disturbed sleep during this symptomatic phase, but in that study, results were not different than healthy controls [55]. Similar to controls, PMS/PMDD women experienced a significant increase in SFA during the LP compared to the FP, though, here, a trend for increased activity in the 12-13 Hz range was observed for patients compared to controls (Table 1). Other comparisons of PMS/PMDD women and healthy control women showed patients to have increased stage 2 sleep, decreased REM sleep, or decreased SWS regardless of menstrual phase (Table 2). It remains unclear what could be causing PMDD-specific sleep changes, and further studies should address the relationships

between sleep and parameters which are known to be altered in the PMDD patients, like CBT, melatonin concentration, and circadian phase.

Increased SFA during the LP in PMDD women may serve a sleep-protective role that is similar to what is proposed for healthy women. The further increase in spindle activity within the 12–13 Hz range in PMS/PMDD, beyond what is observed in controls, may illustrate a strengthening of this effect, which is especially relevant since PMDD patients are most at risk for sleep disruptions during the LP. PMDD women also experience altered REM sleep, which is a hallmark of affective disorder [103]. Interestingly, a sleep restriction study in PMDD patients [52] (see Section 9.2) demonstrated a significant correlation between increasing REM sleep and improved mood, which implies that the reduced REM sleep sometimes observed in PMDD patients may contribute to symptom development.

Important methodological issues should be addressed in these studies as well, including (in addition to those mentioned previously) the high degree of patient heterogeneity and diagnostic criteria used in these investigations. Only one study [52] to date has addressed sleep in a singular group of women whose diagnosis reached the DSM-IV standards to be defined as PMDD.

8. Circadian Rhythms across the Menstrual Cycle in PMDD Women

8.1. Body Temperature across the Menstrual Cycle in PMDD Women. Evidence suggests that PMDD patients can experience altered biological rhythms of body temperature and hormone secretion that could contribute to symptom development and/or exacerbation. An early study showed that, compared to healthy controls, PMDD women had significantly elevated nocturnal CBT and a reduced CBT amplitude during the LP [104]. Although a later study [105] failed to replicate these results, the authors described a decreased amplitude during the LP within PMDD patients, as well as a trend for increased nocturnal CBT in PMDD women compared to controls during the LP. Finally, a nonsignificant trend for a phase-advanced temperature minimum in PMDD patients compared to controls was observed across the entire menstrual cycle [45]. Differences in experimental techniques and data collection methods are likely contributors to inconsistencies in the aforementioned studies. For example, none of these controlled for the confounding effects of ambient light exposure, posture, and sleep or by utilizing a constant routine protocol to "unmask" the endogenous rhythm of CBT. Furthermore, patient diagnostic criteria, sample size, and the frequency of temperature recordings throughout the menstrual cycle all varied between the studies. Future research should consider these methodological issues.

8.2. Hormones across the Menstrual Cycle in PMDD Women. A deficient or altered circadian rhythm of melatonin secretion (Table 2) was proposed as a mechanism causing excessive daytime sleepiness and depressed mood in PMDD. Some evidence supporting this notion, such as decreases in amplitude, AUC, and mean levels, a phase-advance, and a shorter duration of melatonin secretion in PMDD patients compared to controls were reported [62, 65]. Additionally, when comparing across the menstrual cycle within PMDD patients, onset time was delayed, off-set time was advanced, and duration of secretion was decreased in the LP compared to the FP [65].

Reports of cortisol rhythms in PMDD are inconsistent (Table 2). In one study, PMDD patients showed a tendency for a phase-advance of the cortisol rhythm during the LP compared to the FP [63], whereas in another, it was delayed by ~1 hour in the late-LP compared to the mid-FP in healthy controls but unchanged in PMDD women [68]. Three other studies failed to detect any significant differences between cortisol patterns in healthy controls and PMS/PMDD patients [57, 66, 106].

Other hormonal rhythms, such as TSH and PRL, were investigated in PMDD women, though the number of studies is limited (Table 2). The peak time and acrophase of TSH secretion was significantly phase-advanced in patients compared to controls, without any changes in concentration [64]. Throughout the menstrual cycle, amplitude and peak of PRL were higher in PMDD patients compared to controls [63, 64], with a phase-advanced acrophase also detected in these women [64]. In both of these studies, sleep patterns and light-dark exposure were controlled for and stabilized. Nevertheless, TSH and PRL profiles, both of which are affected by the sleep-wake cycle [14], were not obtained under constant conditions (including sleep deprivation); so masking effects cannot be excluded.

8.3. Summary and Future Steps. The major findings regarding altered hormone patterns in PMDD include decreased melatonin secretion (AUC and amplitude) (Table 2), which is reminiscent of findings in patients with major depressive disorder (MDD) [107]. Lending further support to the idea that PMDD women experience a phase-advance of circadian rhythms similar to what is observed in MDD [108], these women also experienced a tendency for phase-advanced CBT rhythms as well as significantly advanced melatonin and TSH when compared with controls (Table 2). Since this altered circadian physiology can contribute to an internal desynchrony, resulting in poor sleep quality and mood symptoms, more studies conducted under strict constant routine conditions are necessary. A better understanding of disturbed circadian rhythms in these women may lead to improved chronotherapeutic techniques, which, while similar to those already used in MDD and seasonal affective disorder [109], can be specialized to treat PMDD women.

9. Nonpharmaceutical PMDD Therapies Targeting Circadian Rhythms

Treatments of PMDD that target and correct circadian rhythm abnormalities may be an effective alternative to drug-based therapies and may function via a realignment of biological rhythms with the sleep-wake cycle.

9.1. Light Therapy. Since PMDD patients seem to experience a phase-advance of biological rhythms [45, 62, 64], it was hypothesized that light therapy, particularly in the evening, could have therapeutic effects. Indeed, studies have found that light therapy was effective in significantly reducing depressive symptoms in PMDD patients [110–112]. While an initial study by Parry et al. [110] found that bright evening light was more effective than morning light, a follow-up study by the same group [111] achieved similar beneficial effects of symptom alleviation in PMDD patients using bright white light in the morning, bright white light in the evening, and dim red light in the evening (a putative placebo). As the authors point out, a placebo effect cannot be excluded. A study by Lam et al. showed that compared to baseline values, bright white light in the evening was more effective than dim red light in the evening in improving symptoms [112]. This improvement may be achieved via a resynchronization or phase-shift of biological rhythms, since, compared to neutral-dim red light, bright evening light therapy was shown to delay the onset and offset of melatonin [65], increase the midpoint concentration of melatonin [65], delay cortisol acrophase [63], and increase TSH nadir [63] in PMDD patients during the LP.

9.2. Sleep Deprivation. Total [113] and partial [114] sleep deprivation (SD) was also shown to be effective in reducing depressive symptoms in PMDD patients, with as many as 80% of patients responding to this treatment [113]. In a series of studies, Parry et al. described the physiological effects of selective SD in PMDD patients [64, 68, 105]. After early-SD (sleep times: 03:00–07:00) during the LP, CBT [105], PRL [64], and TSH [64] acrophases were phase-delayed, PRL amplitude was lowered [64], and TSH amplitude was increased [64]. Late-SD (sleep times: 21:00–01:00) increased CBT amplitude [105] and advanced the acrophase of CBT [105], PRL [64], and cortisol [68], while it delayed the TSH acrophase [64]. Additionally, late-SD also resulted in a decreased PRL mesor [64] and increased TSH mesor [64]. These changes, particularly the phase-delays achieved in CBT and TSH, as well as amplitude changes produced in CBT and PRL, indicate, that like light therapy, SD might achieve its mood elevating effects by targeting and correcting abnormal circadian rhythms.

A study by Parry et al. demonstrated that, compared to baseline late-LP, both early-SD and late-SD were effective in improving sleep quality in PMDD patients during a night of recovery sleep in the LP. Reference [52] Total sleep time, SE (%), SWS (min), and REM sleep (min and %) were increased, whereas SOL (min), ROL (min), WASO, stage 1 sleep (min and %), and stage 2 sleep (%) were decreased. The authors concluded that these therapeutic effects were accomplished, at least partially, via a correction of altered circadian rhythms which affect the sleep-wake cycle. Responders in this study showed improved mood scores during the LP after early-SD, which were significantly correlated with changes in REM sleep and ROL, indicating REM parameters to be important for the therapeutic effects of SD. The therapeutic effects of SD, however, were only studied during experimental nights and at a single recovery night [52]; therefore the duration of improvement in response to such a treatment is unknown. These results are quite promising, though, so more studies should be carried out along these lines to determine the duration of such positive responses.

9.3. Summary and Future Steps. PMDD patients, like those with MDD, have responded favorably to light therapy during their symptomatic LP. Unlike MDD, however, in which morning bright light had the greatest antidepressant effects [109], two studies demonstrated the most mood improvement after evening bright light.

Studies have demonstrated that 50%–60% of MDD patients respond to SD, with greater effects on mood often observed when SD is restricted to the latter portion of the night [115]. PMDD patients responded with mood improvements after both partial and total SD, and interestingly these treatments often resulted in favorable shifts of circadian physiology. Producing changes in the proper direction to correct for altered rhythms in PMDD, early-SD delayed rhythms of CBT and TSH, and decreased PRL amplitude, while late-SD increased CBT amplitude, delayed TSH and decreased PRL; however it also advanced rhythms of CBT, PRL, and cortisol (not favorable). It should be pointed out that the human circadian system, however, is extremely sensitive to light [116, 117], and since ambient light levels during waking episodes in these experiments were kept at <100 lux, the phase shifting effects of light exposure on these rhythms cannot be excluded. Based on the single study discussed above [52], both early- and late-SD produced improvements in objective sleep parameters in PMDD patients, though future laboratory studies in this direction should address how long these improvements persist beyond a night of recovery sleep.

Preliminary results from our study investigating the effects of exogenous melatonin taken prior to nocturnal sleep periods during the LP indicate that melatonin may be beneficial in alleviating sleep disruptions in PMDD women [118]. It remains unclear whether melatonin exerts these effects on sleep via a chronobiotic/phase-shifting mechanism, its sedative/soporific properties, a direct action on hypothalamic sleep centers, or some other pathway.

10. Conclusions

Evidence from a variety of sources indicates that the menstrual cycle interacts with circadian processes to alter the expression of hormonal rhythms and sleep organization at different menstrual phases. This can lead to sleep alterations during the LP in healthy women or more specific LP-associated pathology like PMDD.

The most consistently observed menstrual cycle-related changes in the sleep profile of healthy women are a reduction of REM sleep [49, 51–53, 56], with a maintenance of homeostatic sleep mechanisms throughout the cycle [90], and a robust variation of SFA across the menstrual cycle [48, 49, 55], which increases in association with progesterone during the LP. Similarly, women with PMS/PMDD have also

shown decreases in REM sleep [52, 56] and increases in SFA [55] during the LP compared to the FP. Sleep complaints during the LP are a symptom of PMDD. PSG-based studies do not consistently demonstrate disrupted objective sleep in PMDD (see Table 1), though some have shown increased stage 2 sleep and decreases in SWS or REM sleep compared to healthy women [45, 46].

The circadian variation of CBT is altered by the menstrual cycle in both groups of women. Mean levels are increased (particularly during night time hours) [35, 36] and the circadian amplitude is reduced [35–38] during LP. Some studies have reported further nocturnal increases and phase-advanced rhythms in PMS/PMDD patients compared to healthy women [45, 104]. Generally, circadian hormone rhythms are not significantly altered across the menstrual cycle (see Table 2), though variable results including both increases [58, 59] and decreases [37] in melatonin as well as changes in the timing of hormones [35] have been described. Decreased nocturnal melatonin secretion in PMS/PMDD has also been observed [62, 65]. Finally, nonpharmacological therapies for PMDD symptoms which target the sleep-wake cycle and circadian rhythms, such as phototherapy [110–112] and sleep deprivation [52, 65, 113, 114], are often effective in improving mood and sleep quality in these patients.

Because of the persistent inconsistencies in the literature, however, it is necessary to conduct more investigations of circadian rhythm changes across the menstrual cycle. These should make efforts to assay sex hormone levels, utilize constant conditions, control for light exposure, and record sleep at numerous points throughout the menstrual and circadian cycles. In light of the present discussion, it is critical that researchers who are interested in including female participants in studies on sleep and circadian rhythms always make efforts to control for and document menstrual cycle phase. If the aim is to observe changes associated with PMDD, participants should also be studied during the symptomatic LP. When including healthy women in general sleep/circadian experiments, it appears better to study them during the mid-FP, in order to minimize interindividual variability in physiological rhythms associated with the LP. Investigations focusing on the interaction between circadian physiology, sex hormones, and the sleep-wake cycle in women across the lifespan will be important to understand the role age-related neuroendocrine changes play in the regulation of sleep and circadian rhythms.

Glossary of Abbreviations

PMDD: Premenstrual dysphoric disorder
TSH: Thyroid stimulating hormone
PRL: Prolactin
LP: Luteal phase
SWS: Slow wave sleep
SWA: Slow wave activity
SCN: Suprachiasmatic nucleus
SOL: Sleep onset latency
SE: Sleep efficiency
REM: Rapid eye movement
ROL: Rapid eye movement sleep onset latency
SFA: Spindle frequency activity
vSPZ: Ventral subparaventricular zone
DMH: Dorsomedial nucleus
TMN: Tuberomammillary nucleus
LC: Locus coeruleus
VLPO: Ventrolateral preoptic nucleus
CBT: Core body temperature
FSH: Follicle-stimulating hormone
LH: Luteinizing hormone
FP: Follicular phase
POAH: Preoptic anterior hypothalamus
PSG: Polysomnography
WASO: Wake after sleep onset
NREM: Non-REM
AUC: Area under the curve
PMS: Premenstrual syndrome
MDD: Major depressive disorder
SD: Sleep deprivation

Acknowledgment

This work was supported by the Canadian Institute of Health Research (CIHR).

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 813764, 9 pages
doi:10.1155/2010/813764

Review Article

Shift Work, Jet Lag, and Female Reproduction

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Received 22 October 2009; Accepted 2 January 2010

Academic Editor: Jessica A. Mong

Circadian rhythms and "clock gene" expression are involved in successful reproductive cycles, mating, and pregnancy. Alterations or disruptions of biological rhythms, as commonly occurs in shift work, jet lag, sleep deprivation, or clock gene knock out models, are linked to significant disruptions in reproductive function. These impairments include altered hormonal secretion patterns, reduced conception rates, increased miscarriage rates and an increased risk of breast cancer. Female health may be particularly susceptible to the impact of desynchronizing work schedules as perturbed hormonal rhythms can further influence the expression patterns of clock genes. Estrogen modifies clock gene expression in the uterus, ovaries, and suprachiasmatic nucleus, the site of the primary circadian clock mechanism. Further work investigating clock genes, light exposure, ovarian hormones, and reproductive function will be critical for indentifying how these factors interact to impact health and susceptibility to disease.

1. Introduction

In mammals, the 24-hour clock mechanism, or circadian oscillator, is critical for the function and coordination of a broad range of biological processes, from hormone secretion to locomotor activity. This biological timing system is vital for successful reproduction. Animals are more likely to gain mating opportunities if they coordinate their sexual behavior with that of their potential partners. Females benefit from synchronizing the timing of pregnancy to seasons with favorable food and weather conditions, and it is advantageous for an animal to give birth at a time of day when it is most likely to be in a safe place such as a burrow rather than out foraging. A mounting body of evidence indicates that disruptions in normally synchronized, or entrained, biological rhythms are associated with a broad range of pathologies including reproductive dysfunction in females.

This review will describe how the endogenous timing system interacts with the hypothalamic-pituitary-gonadal axis to regulate female reproductive cyclicity. I will address how disruptions in the alignment of these rhythms, as occurs in shift work or jet lag, are strongly associated with reproductive dysfunction in women. Animal models will highlight the relationship between circadian desynchrony and prevalence of disease states. I will lastly address how "clock genes", the genetic components underlying the circadian mechanism, relate to reproductive function, and how hormone secretion in turn can alter clock gene rhythmicity.

2. Shift Work and Jet Lag

The Bureau of Labor Statistics reported that in 2004 over 27 million Americans had flexible or shift work schedules. Shift work is defined as any employment after 7 pm and before 9 am. Women working non-daytime shifts equaled 12.4% or over 3 million women. Shift work is found in services such as healthcare, military, and protection (police, firefighters). Shift-workers tend to have activity, body temperature, and hormonal rhythms that are out of phase with environmental cues and often the behavioral rhythms of their family and friends. Some workers are able to adapt or synchronize their rhythms (sleep schedules, melatonin secretion patterns) to an alternative work schedule [1]. Even so, adapting to a shift work schedule can be hindered when workers have weekends off and encounter a world operating on a standard schedule [2]. A number of individuals are never able to adjust to shift work.

Jet lag is caused by shifts in the environmental light:dark cycle, or photic phase, that result in an organism's internal rhythms becoming transiently out of phase with the environment and each other [3]. Similar to shift work, jet lag also causes a myriad of physical, emotional, and psychiatric problems in humans [4–7]. It is likely that these disruptions in circadian rhythms are even more extreme for transmeridian travelers than those of shift workers. These individuals do not have a regular schedule to enable entrainment, they travel through different time zones which provide constantly changing light:dark schedules, and they experience light exposure at times when their internal clock mechanism indicates it should be night. All of these signals can continuously reset and disrupt internal circadian rhythms (e.g., sleep patterns).

Shift work, jet lag, and other forms of circadian disruption including sleep deprivation increase the risk of individuals acquiring a disease or exacerbate the symptoms of a preexisting condition. Shift-work, jet lag, and sleep deprivation have been associated with an increased risk of mood disorders, depression, cardiovascular disease, endometriosis, dysmenorrhea, as well as an increased incidence and risk of breast cancer [8–11]. Shift workers and transmeridian travelers report increased fatigue and sleep disturbances relative to individuals working daytime shifts [2]. Women with chronic sleep deprivation or insomnia are more likely to have circadian rhythm disruptions and clinical depression [11]. Sleep disturbance in late pregnancy is associated with increased labor duration and increased likelihood of requiring medical intervention such as cesarean section [12].

These relationships between work schedules and health have gained considerable attention from society and the scientific community. The American Academy of Sleep Medicine recognizes jet lag as a sleep disorder typified by excessive daytime sleepiness and associated physiological impairments [13]. In 2007, night shift work was reclassified from a possible to a probable human carcinogen (class 2A) by the International Agency for Research on Cancer. In fact, this ruling formed the basis for a recent decision by a Danish industrial injuries board to award compensation to women shift workers. These women had worked more than 20 years as a shift worker and developed cancer [14].

3. The Hypothalamus-Pituitary-Gonadal Axis and the Circadian System Regulate Reproductive Cycles

Female mammals have a cyclical change in hormone secretion and ovulation. The most-studied animal models of female reproductive cyclicity are laboratory muroid rodents (i.e., rat, hamster, mouse), which have an estrous cycle characterized by a short total duration (4-5 days), spontaneous follicular development and spontaneous ovulation. The menstrual cycles of women and the estrous cycles of these rodents have several features in common including a series of tightly orchestrated events that result in increased activity in gonadotropin releasing hormone (GnRH) neurons, a hormone surge, and ovulation (Figure 1). During the follicular phase of the cycle, maturing follicles in the ovary release increasing levels of estradiol. When estradiol concentrations reach a threshold, a surge of GnRH is released from cells in the hypothalamus into the hypophyseal portal blood system. This surge of GnRH triggers a surge of luteinizing hormone (LH) from the anterior pituitary, and this hormone acts on the ovary to induce ovulation. Following ovulation the follicles rupture then are luteinized. During this cycle stage progesterone is the dominant hormone (secreted by the corpora lutea). This luteal phase lasts for 10–16 days in women. Rats and mice have corpora lutea that function for 1–3 days but do not have a true extended luteal phase without coitus or vaginal stimulation [15].

In rodents these reproductive events occur in a cyclical and circadian manner. In rats GnRH neurons become active just before lights-off as indicated by the presence of the immediate early gene Fos within the nucleus [16]. This rhythm is endogenous, as ovariectomized rats given steroid hormones only have a rise in GnRH cell activation at one time of day, and this rhythm persists in animals housed in constant darkness [17]. The LH surge is concurrent with the GnRH cell activation and occurs just before lights-off [18]. Ovulation occurs 6–15 hours later [19]. These latter two events occur at precise circadian intervals. For example, in hamsters housed in a light:dark cycle, the estrous cycle occurs every 96 hours (4 periods of 24 hours). When animals are housed in constant conditions this rhythm continues (range 95.35–97.54 h), indicating that an endogenous circadian mechanism (rather than the environmental light:dark cycle) is regulating the estrous cycle [20]. Rodents also exhibit a daily rhythm in the timing of mating behavior; typically this occurs around the onset of their active period [21, 22].

In laboratory rodents the precise timing of this cascade of estrous cycle events is regulated by a small number of cells located in a brain region called the suprachiasmatic nucleus (SCN). The SCN contains the primary circadian mechanism and regulates the timing of central and peripheral oscillators [23]. Rats and hamsters with bilateral SCN lesions lack a rhythm in sexual behavior, the preovulatory LH surge, corticosteroid rhythms, and a consistently functional estrous cycle [24–28]. Transplants of fetal SCN tissue restore some behavioral rhythms but do not restore estrous rhythms, indicating that synaptic inputs from the circadian clock are critical for mediating these systems [28].

Women also exhibit daily rhythms in the timing of reproductive cycle events and hormone secretion patterns. The preovulatory LH surge acrophase typically occurs between midnight and 8 am [29]. A second study examining the timing of the LH surge in 155 cycles (from 35 women) found that 48% of the surges occurred between 4 and 8 am and 37% of the surges occurred between midnight and 4 am [30]. In women, the precise timing of ovulation has not been determined but is estimated to occur 24–40 h later [19, 30, 31]. In humans, the LH surge occurs before the active period (daytime) as is the case for other day-active or diurnal species [32]. In nocturnal rodents, these events also occur just before their active period at the time of lights-off [21].

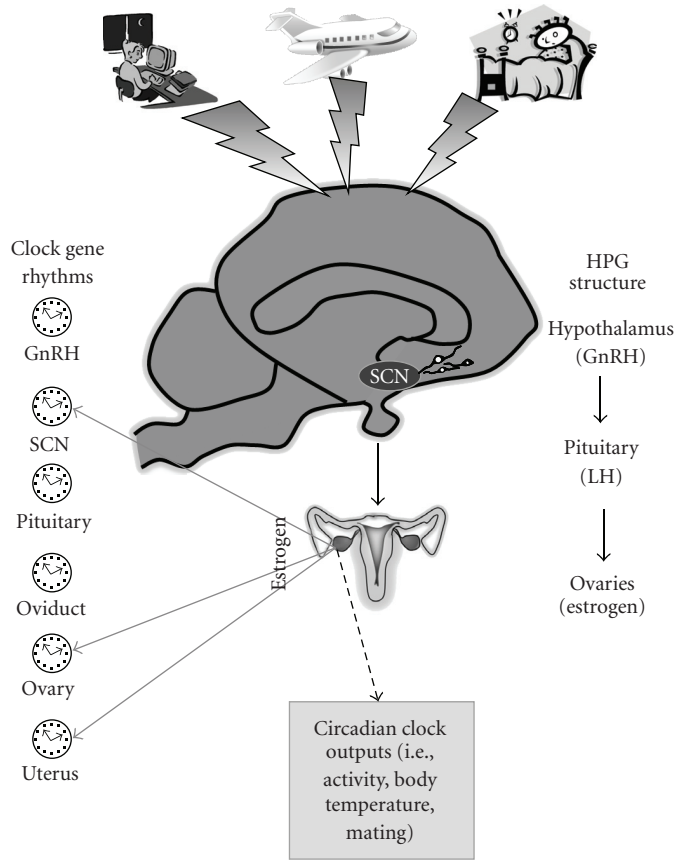

Figure 1: The hypothalamus-pituitary-gonadal axis regulates reproductive cycles in female mammals. Increasing levels of estrogens released from the ovaries feedback onto the hypothalamus. When estrogen stimulation reaches a threshold, gonadotropin releasing hormone (GnRH) neurons release their product into the blood stream. GnRH acts on the pituitary to trigger a surge of luteinizing hormone (LH) which then induces ovulation. In rodents, the suprachiasmatic nucleus (SCN) of the hypothalamus provides an additional signal which regulates the timing of reproductive events. Shift work schedules, jet lag, and sleep deprivation can perturb the daily (circadian) rhythms in reproduction and "clock gene" expression. Clock gene expression has been detected in the SCN, GnRH neurons and female reproductive tissues. Estrogen can influence the pattern of expression of gene expression in some of these tissues (solid arrows). Estrogen also influences the rhythmic expression of clock-controlled outputs such as activity and body temperature (dashed arrow).

Women express other daily rhythms related to reproduction. There is diurnal variation in the pattern of pulsatile LH secretion; this rhythm of peaks and troughs remains evident even in the reduction or absence of ovarian hormones, as is seen in hypogonadal women [33]. The timing of the onset of labor and the timing of birth also exhibit strong diurnal rhythmicity with respect to time of day. The rupture of membranes is reported to occur between midnight and 4 am [34]. A study of over 17,000 term singleton deliveries found the majority of women going into labor between midnight and 8 am with 01:45 AM as the peak time of labor onset [35]. In a second study of over 15,000 women, the onset of labor had a 24-hour rhythm, with a nadir in the middle of the day and peaks around dawn and dusk [36]. The timing of birth typically occurs in the middle of the afternoon. In two retrospective studies (6608 and 15,000 women, resp.), the majority of births following a spontaneous onset of labor occurred between 1 and 2 pm [36, 37]. Interestingly, multiparous women were more likely to deliver babies earlier in the morning, between 8 and 11 am when compared to nulliparous mothers, the authors speculated this difference may be related to the timing of fetal and maternal hormone secretions [37]. A clinical study was conducted to determine if this diurnal rhythm in the onset of labor was also important to women in whom labor was induced. Women which had labor induced in the morning required less uterine stimulation (i.e., oxytocin), had a shorter interval from induction to birth, and were less likely to require operative assistance with the delivery when compared to women that had their labor induced in the evening hours [38].

These reproductive events in women occur with a diurnal rhythmicity; however, it remains possible that the circadian system does not control the timing of reproductive events in humans as tightly as it does in rodents. For example, humans and primates are able to copulate throughout the ovarian cycle and are not limited to a particular time of day or specific duration of exposure to steroid hormones [39]. In

primates a surge in LH can be induced at any time of day with the proper strength and interval of steroid hormone treatment [40]. This does not eliminate the possibility that appropriate and successful reproduction in women is regulated by the light:dark cycle and/or a circadian timing mechanism. Nearly all of the available data indicate that alteration of the phase relationship between an animal, human or otherwise, and the light:dark cycle has adverse effects on the physiology of the affected organism. In support of this hypothesis, alterations or disruptions in the daily (and potentially circadian) rhythms of women are linked to significant disruptions in reproductive function.

4. Disruption of Diurnal Rhythms Is Associated with Reproductive Dysfunction

Women working an evening shift, night shift, or have irregularly scheduled shifts (such as days-off or flexible schedules) report altered menstrual cycle length (both increases and decreases), increased menstrual pain, and changes in the duration and amount of menstrual bleeding [41, 42]. These symptoms are accompanied by changes in patterns of ovarian and pituitary hormone secretion, such as an increase in follicular stage length and changes in follicular stimulating hormone (FSH) concentrations [8, 10, 42, 43]. These effects are apparent even when the studies controlled for health, lifestyle, or job environment (i.e., stress) [43].

Pregnancy outcomes are also affected by the working environment. Female shift workers have a higher risk of producing premature and/or low birth weight babies, spontaneous abortion and subfecundity [10, 44]. Flight attendants who worked while they were pregnant were twice as likely to have a spontaneous abortion when compared to flight attendants who did not work during their pregnancy [45]. Some studies on pregnancy outcomes in flight attendants indicate that this risk of miscarriage is moderate compared to the general population of women [45, 46]. In a mouse model of shift work, there was a significant reduction in the percent of animals that mated when they were housed in a 22 hours (11 h light : 11 h dark) or 26 hours (13 h light : 13 h dark) light-dark cycles for 2 or more weeks prior to mating [47]. Interestingly, if pregnant animals were taken from a 24 hours light:dark cycle and moved to a 22 or 26 hours light:dark cycle there was very little effect on the pregnancy outcomes. Entrainment to the light:dark cycle in women and rodents may be essential for successful copulation and conception, however, once pregnancy is achieved, female hormonal secretion patterns may be less sensitive to environmental changes [47].

Shift work and jet lag may exert their effects on health and physiology by reducing the total amount of sleep for an individual. Women working the night shift or experiencing transmeridian travel report a decrease in the amount of sleep and an increase in fatigue and insomnia [13, 41]. This reduction in sleep duration is not trivial as it has an effect on hormone secretion patterns. For example women with less than 8 hours of sleep secrete 20% less FSH compared to women with longer sleep durations [48]. Total or partial sleep deprivation increases LH amplitude, estradiol and FSH concentrations in normal cycling women [49]. Increased estrogen is associated with an increased risk of breast cancer (discussed below). It is possible that the altered menstrual cycle physiology associated with circadian misalignment is due to a direct effect of sleep state on ovarian and pituitary hormone secretion. It remains to be eluciated if circadian disruption, while significant to emotional well being and other physiological aspects, is a critical mechanism underlying the reproductive dysfunctions [41].

5. Breast Cancer and Biological Rhythms

In the last decade there has been a strong link between shift work and incidence of breast cancer. As a number of recent reviews discuss this issue in depth, this topic will only be highlighted here [50, 51]. There is a substantial literature which links light exposure at night, shift work or transmeridian travel, and an increased risk of breast cancer [9, 51–54]. One report examining over 85,000 women enrolled in the Nurses' Health Study found that a woman's relative risk of getting breast cancer was amplified if she worked the night shift or had rotating shifts [52, 55]. Similar risk levels have been determined for female flight attendants [53]. Animal cancer models indicate that altered circadian function exacerbates cancer symptomology. In a series of elegant studies, Filipski et al. disrupted circadian rhythms in mice either through SCN ablation or jet-lag schedules (repeated advances of the light:dark cycle). Mice experiencing this desynchrony had significantly accelerated growth of inoculated tumor cells [56–58].

One hypothesis which addresses the mechanism underlying this risk of breast cancer in shift workers is the "light at night theory" [51]. This postulates that the increased exposure to light during evening working hours decreases melatonin secretion. Melatonin is a pineal hormone that is secreted during the dark phase of the light:dark cycle and is suppressed when an individual is exposed to light including artificial light. Melatonin concentration, diurnal pattern of melatonin secretion, and the relationship of this pineal hormone rhythm to other physiological rhythms are altered in shift workers compared to daytime employees [13]. When compared to day-shift workers, women working the second or third shift have altered melatonin rhythms as measured by the urinary melatonin breakdown product 6-hydroxymelatonin sulfate [2]. This hormone has a protective effect against cancer, and can inhibit the growth of metastatic cells. In in vitro studies melatonin can suppress the growth of malignant breast cancer cells (reviewed in [59]).

Melatonin-rich blood (collected at night from healthy women) suppresses tumor growth in immunodeficient rats carrying a human breast cancer xenograft. When these animals were given the melatonin rich blood and a melatonin receptor inhibitor, or blood collected during the day, the tumor suppressive effects were eliminated [50].

There is a strong link between light at night, melatonin, and breast cancer risk However, shift work or sleep deprivation may not be the direct cause of cancer. Rather the exposure to light at night suppresses the oncostatic hormone melatonin and accelerates the development of cancer symptoms. Additionally, as mentioned above, sleep deprivation can alter gonadal and pituitary hormone secretion patterns which may influence tumor cell growth. It is clear that shift work, jet lag, and sleep disturbances put a woman at increased risk for acquiring this pathology and this will require additional research to determine the causal relationships.

6. Clock Genes and Reproduction

The link between circadian rhythms and reproductive function also functions at the molecular level. In the last decade a family of "clock" gene and protein transcription and translation feedback loops have been identified. These clock genes play a role in an individual's rhythmicity, entrainment and responsiveness to light [60–62]. In mammals, the proteins CLOCK and BMAL1 form heterodimers. This complex then activates the transcription of thee *Period* genes known as *Per1, Per2, and Per3*. This CLOCK/BMAL1 heterodimer also turns on the transcription of two *cryptochome* genes known as *Cry1* and *Cry2*. The protein products of the *Per* and *Cry* genes heterodimerize, then act as repressors and turn off the transcription of *Clock* and *Bmal1*. A second protein, NPAS2 also forms heterodimers with BMAL and this protein complex also initiates *Per* and *Cry* transcription [63].

The initial identification of rhythmic expression of clock gene transcription and translation was within individual cells of the SCN. These molecular rhythms have also been found in peripheral organs including female reproductive tissues such as the ovary [64, 65], uterus [66–68], and oviducts [69] (Figure 1).

Daily rhythms in clock gene expression have been found in an additional component of the HPG system; the GnRH neurons themselves. In cell cultures of GnRH GT1-7 cells, mRNA of *Clock, Bmal1, Per1* and *Per2,* and the protein BMAL1 have a diurnal pattern of expression [70, 71]. Transfecting these cells with an altered CLOCK protein ($Clock^{\Delta 19}$) or the addition of the CRY protein to the culture alters the amplitude and frequency of GnRH pulsatility [70]. The exact role of the molecular clock within these neuroendocrine cells has not been determined. It is possible that this is a mechanism which alters cellular activity of GnRH neurons, or modifies their sensitivity to estradiol [72].

Further evidence that clock gene rhythmicity is critical for reproductive function is seen in knock out or transgenic animal models. Disruptions in known circadian clock genes disrupts reproductive processes in female rodents; several detailed reviews have been published recently [19, 73]. In knock-out mice missing either the *Per1* or *Per2* gene, estrous cycles are irregular or absent, and animals have decreased fertility. This reduced fertility is more pronounced in "middle aged" mice compared to young mice, suggesting that mutations in this gene accelerate ageing at least with respect to reproductive function [74]. *Bmal1* knock-out female mice are able to mate but are not able to produce young [75]. Mice expressing a homozygous genotype of a mutated CLOCK protein ($Clock^{\Delta 19/\Delta 19}$) have a dampened LH surge, disrupted and irregular estrous cycles and difficulties with pregnancy [76]. Not all clock genes have an equal effect on reproduction as mice lacking, *Per3, Cry1, or Cry2* (or combinations of these genes) are able to breed and reproduce [19].

Fertility and reproductive cyclicity may depend upon the precise phase relationship between the "master" clock contained in the SCN and the clocks contained within reproductive tissues and GnRH neurons. Clock gene rhythms within the SCN and peripheral tissues have a phase relationship. The peak expression of *Bmal1* in the rat ovary is about 4 hours delayed relative to the acrophase of *Bmal1* mRNA in the SCN. Similarly, the *Per2* rhythm in the ovary peaks 4 hours after lights off, whereas it peaks 6 hours earlier in the SCN [65]. If a female experiences a shift in the light:dark cycle, it is unknown how long it takes the circadian clock genes in the SCN, ovary and uterus to resynchronize to one another. It is known that in mice experiencing a phase advance, *Per1* mRNA rhythms in the SCN rapidly readjust to the new light:dark cycle but the peripheral organs (liver, lung, muscle) take nearly 6 times as long as the SCN to recover [77]. Rhythms in clock gene expression thus adjust to jet lag at different rates relative to one another, and relative to the peripheral organs. It is this mismatch of rhythms within the body that may underlie the reproductive deficits experienced by women experiencing disrupted biological rhythms [77, 78].

The relationship between clock genes and female health has not yet been examined closely in women; however, several studies have correlated circadian clock gene polymorphisms with reproductive disorders. The expression of three different polymorphisms of the NPAS2 gene was examined in control ($n = 476$) and breast cancer cases ($n = 431$). This gene is part of the transcription-translation loop of clock genes. A significant association was found between breast cancer risk and one of the heterozygous gene polymorphisms (compared to homozygous genotype) [63]. This same research group also found a 1.7 fold increased risk of breast cancer in women with a heterozygous genotype for a *Per3* length polymorphism compared to women with a homozygous genotype [79]. In contrast no link was found between endometriosis, shift work, and the expression of a polymorphism of the *Clock* gene (hT3111C) in humans. This gene is correlated with mood disorders and in *Clock* mutant mice estrous cyclicity is impaired [76, 80]. Despite these data, the authors did find that women working the night shift had a nearly doubled increase in risk of endometriosis and this was further increased if women had altered sleep rhythms on their days off. Circadian gene markers may provide a valuable tool for identifying individuals in shift work environments that may be particularly susceptible to developing diseases. These markers may also help identify those individuals that may be better able to adapt to or accommodate a changing work schedule.

7. Interaction between Circadian Timing Mechanisms and Ovarian Hormones

A reciprocal interaction exists between the circadian timing mechanisms and gonadal hormones. As described above, the timing of estrus-related events including hormone secretion is regulated in part by the SCN and circadian system. Ovarian hormones in turn influence the behavioral and molecular circadian rhythms [81, 82]. On the day of sexual receptivity (estrus), female rats, hamsters, and degus (*Octodon degus,* an hystricomorph rodent*)* advance the onset of their daily activity rhythms [83–85]. Ovariectomized female hamsters and rats have given a capsule containing estrogen similarly advance the onset of their activity rhythms and have a shorter free running period when compared to control animals [86, 87].

Ovarian hormones appear to have a similar effect in women as diurnal and circadian rhythms including sleep-wake cycles and endocrine rhythms (cortisol, melatonin) change between the follicular and luteal phases of the reproductive cycle [88–90]. There are relatively few studies that have examined these rhythms in a controlled environment but one generalization is that ovarian hormones modify the amplitude but not the phase of various physiological rhythms. For example, humans have a daily rhythm in the fluctuation of body temperature, the nadir occurs after lights-off, and the temperature remains relatively low until the time of lights-on. In females, this general pattern remains consistent across the menstrual cycle but the amplitude of the rhythm is reduced during the luteal compared to follicular phase [91]. Similarly, when women were studied in an ultra-short sleep-wake protocol (which separates the endogenous rhythms from the influence of the environmental cues) the daily rhythm in cortisol was blunted during the luteal compared to follicular phase [90].

Ovarian hormones also influence the expression of circadian clock genes both within and outside of the SCN. Importantly, the effects of estrogen on the rhythm of clock gene expression are both tissue and gene specific. In ovariectomized female rats, chronic estrogen treatment significantly phase advances the acrophase of *Per2* mRNA expression, but not that of *Per1,* in the SCN [67]. An injection with estrogen significantly decreases the amount of *Cry2* mRNA within the SCN, but does not change the amount of *Cry1* mRNA [92]. In the uterus, estradiol treatment results in bimodal *Per1* and *Per2* expression whereas control animals had a single peak and estrogen shortens the period of *Per2* expression [67, 93]. On the day of proestrus (high estradiol), *Bmal1* mRNA levels are increased relative to diestrus [65]. Data on clock gene expression in reproductive tissue of women is limited; breast and endometrial cancer lines and tissue from breast cancer patients express clock genes and their protein products [94, 95]. Additionally, *Per2* expression inhibits the expression of estrogen receptors in breast cancer cell lines [94]. Lastly, it is possible for estrogen to have a direct effect on the circadian timing system as estrogen receptors have been detected in the human SCN [96].

In rodent studies, changing concentrations of estradiol, either though the endogenous estrous cycle, or though disrupted ovarian function can phase shift or desynchronize circadian genes in both a tissue specific and clock gene specific manner [67]. This perturbation in the steroid hormone signal can lead to a change in the expression of circadian clock genes both within the SCN and in peripheral tissues including female reproductive organs. It will be important to determine if these factors also play a role in human reproductive health and disease.

8. Conclusions

The general mechanisms by which the SCN and circadian system regulate the physiological rhythms are still being elucidated. The investigation of specific central (SCN) or peripheral oscillators that regulate rhythms in the well-described hypothalamic-pituitary-gonadal system will provide a more general understanding of how the circadian clock mechanism regulates rhythmic outputs. Future work will also clarify the relationship between the circadian timing system and the contribution of other factors that impact women's reproductive health. Life or work stressors, sleep deprivation and fatigue, smoking habits, age, weight, and environmental conditions such as exposure to solvents all impact female reproductive function [97].

The circadian timing system and SCN regulate the onset of the preovulatory LH surge, ovulation, and mating behavior in rodents. Rhythmic clock gene expression within the SCN and peripheral reproductive tissues in females, and the relationship of these rhythms to one another, may be critical for successful reproduction. I hypothesize those disruptions in the endogenous circadian timing mechanism underlie reproductive deficits. In animal models, disruptions in these rhythms, as seen in transgenic and knockout mice, SCN lesioned animals, or individuals experiencing changes in the light:dark cycle, lead to changes in estrous cyclicity and altered patterns of hormonal secretion. The desynchrony of gene expression within a tissue and between central and peripheral tissues may also impact upon an individual's ability to establish phase relationships to environmental cues. In women, perturbations in daily rhythms, as occurs in shift work, jet lag, and sleep deprivation is associated with an increased menstrual cycle irregularity, increased risk of miscarriage, difficulty in conceiving, and a higher risk of breast cancer. Females' health and physiology may be particularly vulnerable to circadian disruption as the resulting changes in steroid hormones secretion patterns can further alter clock gene rhythms. Further investigations are needed to examine how reproductive cycles are regulated in women, the impact of disturbed biological rhythms on reproductive physiology, and how to reduce the health risks associated with altered rhythms.

Acknowledgment

The author would like to thank J. Mohawk, M. Hagenauer, and J. Koch for reviews of earlier drafts of this manuscript.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 270832, 12 pages
doi:10.1155/2010/270832

Review Article

Sleep and Metabolism: An Overview

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Received 29 September 2009; Revised 2 February 2010; Accepted 28 April 2010

Academic Editor: Jessica A. Mong

Sleep and its disorders are increasingly becoming important in our sleep deprived society. Sleep is intricately connected to various hormonal and metabolic processes in the body and is important in maintaining metabolic homeostasis. Research shows that sleep deprivation and sleep disorders may have profound metabolic and cardiovascular implications. Sleep deprivation, sleep disordered breathing, and circadian misalignment are believed to cause metabolic dysregulation through myriad pathways involving sympathetic overstimulation, hormonal imbalance, and subclinical inflammation. This paper reviews sleep and metabolism, and how sleep deprivation and sleep disorders may be altering human metabolism.

1. Introduction

Consequences of sleep deprivation and fragmentation are being increasingly recognized. We are a sleep deprived society with evidence showing that we sleep on an average 6.8 hours as opposed to 9 hours a century ago. Around 30% of adults report sleeping less than 6 hours per night [1–3]. The 24/7 economy and its subsequent impact on sleep patterns may be testing the bodies limits to maintain metabolic and hormonal equilibrium. Prevalence of both diabetes and obesity has increased to acquire pandemic proportions. Though other factors such as diet and reduced physical activity have contributed to the obesity epidemic the impact of sleep dysregulation on causing metabolic derangements is being increasingly recognized. Considering only a small percentage of people can maintain a healthy weight over a long period on diet and exercise alone, the impact of sleep on weight has opened a new venue for potential intervention.

Understanding this topic is important as both sleep and metabolic dysregulation are common and growing problems. There are many unresolved issues including cause and effect, pathogenesis and potential implications to therapy.

2. Metabolism in Normal Sleep

Human sleep comprises of nonrapid eye movement sleep (NREM) and REM sleep. NREM is further comprised of three stages (stages N1, N2, and N3). N3, also referred to as slow wave sleep, is considered deep sleep with the body being least metabolically active during this period. REM sleep is characterized by vivid dreams, loss of muscle tone, and rapid eye movements. The EEG pattern of REM sleep closely mimics that of wakefulness marked by a high-frequency and low-voltage wave pattern. NREM and REM sleep occur alternatively in cycles of around 90 minutes throughout the night [4]. The first half of the night is predominantly NREM, and the second half is predominantly REM sleep. Sleep architecture, though, is heavily influenced by genetic and environmental factors including sex, race, socioeconomic status and culture among others. Sleep duration in mammals generally depends on the size of the animal [5]. Elephants require only 3 hours of sleep while rats and cats can spend up to 18 hours in sleep. It is postulated that this may be due to differences in metabolism. Smaller animals have higher metabolic rate and higher body and brain temperatures compared to larger animals.

Metabolism is defined as the whole range of biochemical processes that occur within a living organism. It constitutes the two processes of anabolism (build up) and catabolism (break down). In simpler terms, metabolism is the amount of energy (calories) the body burns to maintain itself. Metabolism in general is associated with cell injury due to the release of free radicals [6]. The lower metabolic rate and

brain temperature occurring during non-REM sleep seem to provide an opportunity to deal with the damage done during awake and metabolically active period. Siegel and his group from University of California at Los Angeles (UCLA) have shown brain damage in sleep-deprived rats [7]. Most data available and referred to in this review deals with glucose utilization and energy expenditure.

It is believed that during normal sleep the metabolic rate reduces by around 15% and reaches a minimum in the morning in a standard circadian pattern [8, 9]. Only a 15% reduction in metabolic rate appears counter-intuitive considering the prolonged state of physical inactivity. However, the basal metabolic rate constitutes 80% of the metabolism needed to maintain all cellular processes in the body. Glucose utilization in normal subjects is highest during wakeful state and lowest in NREM sleep and intermediate in REM sleep [10].

Growth hormone and cortisol are two hormones that have an impact on glucose regulation. Growth hormone is typically elevated at onset of sleep with highest levels during slow wave sleep (SWS) while cortisol levels are greatly increased during the second half of the sleep, predominantly in REM sleep [11, 12]. Studies on normal subjects with constant glucose infusion during sleep (to suppress endogenous glucose production) have revealed that a fall in brain glucose metabolism contributed to a two-thirds fall in systemic glucose utilization during sleep despite increase in glucose and insulin levels. Reduced muscle tone and anti-insulin like effect of growth hormone surge during the first half of sleep contributes to the rest of fall in glucose utilization [13]. Hence there is a relative state of insulin resistance during early phases of sleep.

During the latter part of sleep the glucose and insulin levels fall despite continuous infusion of glucose. Other studies have shown similar findings suggesting increased glucose utilization during REM phase of the sleep and increased glucose levels in the evening with reduced insulin sensitivity [13]. In addition, studies have shown an increase in cortisol levels in evening after just one night of sleep deprivation contributes to glucose dysregulation [14].

3. Consequences of Sleep Deprivation

Although impact of sleep on glucose regulation has been known and studied for some time, metabolic dysregulation with sleep loss has only recently been understood. Prior research models had focused on acute sleep deprivation. Studies done by Hampton et al. revealed that when subjects were made to simulate shift work it resulted in alterations in postprandial glucose and lipid metabolism [15]. This response was noted with 9-hour phase advance. The same group later showed that it takes at least 2 days to adapt to eating meals on a simulated night shift [16]. Since the body has good rebound capacity, the metabolic derangements, if any, were readily corrected in acute sleep loss model. The more practical model to study is recurrent prolonged partial sleep deprivation, which mirrors real life scenarios. In fact, studies have shown that both slow wave sleep (SWS) and growth hormone (GH) rebound after acute sleep loss, but no such spike is seen in SWS and GH during recurrent partial sleep restriction [17, 18]. For these reasons, chronic sleep deprivation models are more relevant in terms of clinical significance and subject of our focus.

Though a previous study has shown reduced insulin sensitivity to oral glucose administration it was limited to one night of sleep deprivation [19]. The first detailed study to examine the impact of partial sleep deprivation on glucose tolerance was performed by Cauter et al. at the University of Chicago. Eleven healthy young men were subjected to 4 hours in bed for 6 nights followed by 12 hours for 7 nights to recover from sleep debt. Intravenous glucose tolerance test was performed on the sixth day. Sleep deprivation resulted in reduced glucose tolerance (rate of glucose clearance) by 40%. Glucose effectiveness, a measure of noninsulin dependent glucose disposal, was 30% reduced along with a reduction in insulin response to glucose [20]. A subsequent study with a randomized crossover design by the same group confirmed the findings [21]. The conclusion from these laboratory based studies is that a week of sleep deprivation can result in a significant alteration in metabolic and endocrine function.

The mechanism of sleep deprivation causing metabolic dysregulation may be multifactorial. Changes in hormonal secretion profile as discussed above may have profound effect on glucose regulation [13].

Sympathetic stimulation has been shown to occur with sleep deprivation [22] and might contribute in the metabolic dysregulation. The third possible mechanism is inflammation. Experimental sleep deprivation has been found to alter immune response and increase proinflammatory markers such as IL-6, TNF-α , and CRP [23–25].

4. Sleep Duration and Risk of Diabetes

It is projected that by 2010, 221 million people would be affected by diabetes globally [26]. It is important we understand the role of sleep in glucose metabolism and potential directions for new research and therapy.

Epidemiological data increasingly suggests that short sleep duration or chronic partial sleep deprivation may increase the risk of type II diabetes. In a large cohort of nurses (Nurse Health Study with more than 70,000 respondents), self-reported short (5 hours or less) and long duration of sleep (9 hours or more) was associated with symptomatic diabetes with a relative risk of 1.34 for short [1.04–1.72]) and long 1.35 for long [1.04–1.75]) sleepers [27]. A Swedish study with more than 2000 people followed for over 10 years revealed that short duration of sleep (< 5 hours) and difficulty initiating and maintaining sleep were associated with higher incidence of diabetes in men (but not in women) even after adjusting for confounding factors like age, BMI, snoring, depression, and hypertension [28]. In another study by Yaggi and colleagues, a large cohort of men from the Massachusetts Male Aging Study (MMAS), without diabetes at baseline was followed for more than 15 years in a longitudinal study. Subjects who self-reported less than 6 hours of sleep were twice as likely to develop diabetes.

Subjects sleeping longer than 8 hours were three times more likely to develop diabetes. This elevated risk remained after adjusting for HTN, age, waist circumference, smoking, and education [29].

Although epidemiological studies do not establish causality, these studies are consistent with the physiological data discussed earlier.

In summary, the laboratory data seem to be supported by large epidemiological studies (including longitudinal) that short sleep duration might play an important role in altering glucose metabolism. However, these results appear to be more applicable to men than women for reasons not fully understood. The relationship between increased sleep duration and risk for diabetes is not fully understood.

5. Sleep Loss and Appetite

5.1. Leptin and Ghrelin. The appetite center is believed to be located in the arcuate nucleus of the hypothalamus, which in turn is influenced and regulated by peripheral hormones such as leptin and ghrelin. Leptin is an appetite suppressant hormone produced by adipose tissue, and ghrelin is released from the stomach primarily in response to fasting and promotes the feeling of hunger [30]. Leptin has been shown to rapidly increase or decrease in response to caloric shortage or surplus [31]. In human studies, a marked rise in leptin and ghrelin are noted during sleep, though the levels of ghrelin tend to fall during latter part of night despite maintenance of fasting conditions [32, 33]. It is believed that leptin levels stay elevated due to melatonin-influenced insulin-triggered leptin production [34]. This suggests the effects of the rising ghrelin levels during the early part of night might be blunted by leptin, preventing arousal during sleep due to hunger. Spiegel and colleagues work on healthy humans have also shown that sleep deprivation lowered leptin levels by 19% compared to sleep extension [35]. They further observed that sleep deprivation blunted the diurnal variation normally seen without sleep deprivation. These findings were confirmed by the same group in a randomized crossover trial of sleep restriction in normal human subjects. Subjects were sleep restricted for 2 nights (4 hours/night) followed by 2 nights of sleep compensation (10 hours/night) while receiving continuous glucose infusion. Significant reduction in leptin levels (18%) were noted with a concomitant 28% increase in ghrelin levels [36]. A 24% increase in hunger rating and 23% increase in appetite rating were also noted. Reduction of leptin level was a significant predictor of magnitude of hunger observed. Further analysis of appetite rating revealed that subjects tended to show more preference to high carbohydrate foods (sweets, salty food and starchy foods), that is, Craving for salty food increased by 45% ($P = .02$). This suggests that sleep deprivation may affect eating behavior favoring nonhomeostatic food intake (food intake driven by emotional/psychological need rather than caloric need of the body) [36]. Acute sleep deprivation of single night in young healthy men increases ghrelin levels but not leptin levels [37]. Sleep deprivation may also affect the circadian profile of leptin. Healthy men subjected to 88 hours of sustained wakefulness have been shown to have reduced diurnal amplitude of leptin, with return to normal rhythm on sleep recovery [38]. Recent study by Penev et al. revealed that short, partial sleep deprivation (< 5.5 hours/day) in normal subjects resulted in increased consumption of calories from snacks but no increase in total energy consumption. This study did not show any significant changes in leptin or ghrelin levels. The authors hypothesized that the higher carbohydrate intake due to sleep restriction may be due to prolonged exposure to more palatable food [39].

A population based study of 1024 patients (derived from the Wisconsin sleep cohort study, a large longitudinal population based study on sleep disorders) that revealed similar alteration in leptin and ghrelin levels based on total sleep time as measured by overnight polysomnography [40]. The study also revealed that chronic sleep deprivation (sleep less than 8 hours) was associated with increase in BMI.

Leptin has been found to be elevated in obese individuals and patients with obstructive sleep apnea. It is believed that the elevated CRP levels in obesity and obstructive sleep apnea bind to leptin resulting in elevated serum levels [41]. This is believed to be accompanied by leptin resistance due to down-regulation of leptin receptors. This leads to impairment in weight regulation and may contribute to weight gain [42].

The fact that relationship between sleep and leptin may be bidirectional is evident by animal studies by Laposky et al. Leptin deficient mice have been shown to have more disrupted sleep architecture, increased time spent in NREM sleep and increased total sleep time [43]. The same authors also showed that leptin signaling exerts a role in sleep-wake regulation. Obese/diabetic mouse with mutation of leptin receptors exhibited sleep fragmentation, decreased compensatory response to sleep deprivation and decrease locomotor response [44].

In summary, leptin may represent an important link between, sleep, circadian rhythm and metabolism.

5.2. Orexins. Discovery of excitatory neuropeptide hormones orexins A and B (hypocretins) expressed from neurons located in perifornical region of the hypothalamus, [45] has significantly added to our knowledge. Energy homeostasis, as determined by the balance between calorie intake and energy expenditure, is regulated by hypothalamus [46]. Orexins neurons are located in the hypothalamus and from them project throughout the brain, including paraventricular nucleus of the thalamus, the arcuate nucleus and, most notably, the locus coeruleus, dorsal, and tuberomammillary nucleus (areas involved in wakefulness) but not the cerebellum [47, 48]. Orexins have been found to be influenced by peripheral metabolic cues like leptin, ghrelin, and glucose which indicated that orexins may provide an important link between sleep and metabolism [49] and play a key role in metabolism. Administration of orexins increases food intake and stimulates wakefulness and energy expenditure [50, 51]. Narcolepsy, a sleep disorder caused by orexin deficiency is accompanied by decreased energy intake, increased BMI, and increased incidence of type 2

diabetes [52, 53]. Orexin knockout mice also demonstrate late onset weight gain [54]. The fact that orexin deficient mice display reduced energy expenditure independent of sleep duration and wake durations suggests that orexin-induced increased metabolism is not simply due to its wake promoting action and subsequent more exposure to food [55]. Recently investigators, working on glucose metabolism in orexin knockout mice, found that orexin is essential for maintenance of normal insulin sensitivity with increasing age [56]. In conclusion, these findings suggest that sleep deprivation may blunt and upset the finely tuned signaling response of hormones to body's caloric needs not only leading to increase in appetite but also a propensity for psychological eating (nonhomeostatic food intake).

6. Sleep Deprivation and Weight

More than two dozen epidemiological studies from around the globe looking at sleep deprivation and BMI in humans have shown association between decreased obesity and an increase in sleep duration. These studies however do not establish a causal relationship. Few studies revealed a U-shaped curve with lowest mean BMI associated with 7.7 hours/night [40, 57, 58]. NHANES study revealed (using a normal benchmark of 7 hours/night) odds ratio for obesity as 2.35 for 2–4 hours/night, 1.60 for 5 hours/night, and 1.27 for 6 hours/night of sleep. This association was observed in both obese and nonobese subjects and adjustment for sex, age, and population size though the relationship appeared to wane with age [40, 57, 59–62]. These findings are supported by studies conducted in children [63–65]. The impact of short sleep appeared to be greatest in children and young adults as compared to older adults [61–69].

A major limitation of epidemiological studies looking at sleep duration and BMI has been self-reporting of sleep time as opposed to objective measurement. However recent studies [56, 70–72] have looked at objectively measuring sleep via actigraphy (device worn like a watch with ability to record gross motor movements) and overnight polysomnography. The CARDIA study [70] used a large cohort of subjects and obtained 3 nights of actigraphy. Mean sleep duration was found to be 6.1 hours with variation among different race-sex groups (mean sleep duration of 6.7 hours in white females to 5.1 hours in African-American males). This study also found moderate correlation between subjective and objective sleep time duration though participants overreported their sleep duration by about 0.8 hours (measured sleep duration was 6 hours versus a self-reported time of 6.8 hours). The Danish revealed that sleeping less than 5 hours was associated with higher BMI in elderly population. Sleep fragmentation was also found to be strongly associated with increased BMI in this study [71]. In another recent study with over 3000 patients where the sleep duration was again objectively recorded by actigraphy, researchers found that older men and women with reduced amounts of sleep (less than 5 hours) as measured by actigraphy had an elevated BMI. Sleeping 5 or fewer hours per night was associated with 3.7-fold greater odds of obesity among men and 2.3-fold increase among women compared to those sleeping 7-8 hours per night Patel et al. [73]. Apart from cross sectional studies, there have been 9 prospective/longitudinal studies in adults and children, 8 of which have shown similar findings of sleep deprivation and a higher prevalence of obesity [61, 62, 65, 74–76].

Data regarding impact of sleep deprivation on weight loss is conflicting in animals and humans. Sleep deprivation in rodent models causes weight loss despite hyperphagia [63–68]. These differences in rodents and humans may be explained by increased brown fat in rodents (rarely present in adult humans), which is metabolically more active and has been shown to increase thermogenesis and total energy expenditure [67]. In conclusion, epidemiological data is suggestive of weight gain with sleep deprivation though a few studies have also noted weight gain with prolonged sleep. Based on data on sleep duration and weight, sleep hygiene counseling could form an important tool in management of obesity.

7. Obstructive Sleep Apnea and Type II Diabetes

Obstructive sleep apnea (OSA) is a highly prevalent disorder affecting 2%–4% of the population. It is characterized by intermittent but repetitive cessation of breathing accompanied by hypoxemia or reduced level of oxygen in blood. OSA has significant affect on sleep architecture including sleep fragmentation and reduction in stage REM and slow wave sleep (SWS) [77].

Data from a recent national survey shows that as many as one in four adults are at risk of having OSA [78]. More than 50% of patients with type II diabetes have obstructive sleep apnea [79]. Studies as early as 1985 had noted an association between snoring, diabetes, and abnormal glucose tolerance [80, 81]. A Swedish study with longitudinal design and over 2600 subjects revealed habitual snoring as an independent risk factor for diabetes at 10 year followup [82]. Several studies since then have supported the findings of snoring associated with increased prevalence of type II diabetes, with habitual snorers being at twice the risk for having diabetes [83, 84].

Cross-sectional studies using polysomnography confirmed OSA have similarly shown increased insulin resistance, glucose intolerance and an increase in HgA1C [85–88]. Importantly, the severity of OSA appears to be proportional to the severity of metabolic dysfunction. This association stood after adjustment to age, sex, and adiposity. However, a longitudinal study by Wisconsin sleep cohort group failed to show an independent relationship between OSA and incidence of diabetes at 4-year followup. These conflicting results may be due to short duration of the study [89].

Clinic-based studies have demonstrated similar trends favoring an association between OSA and diabetes. In a study of patients with OSA compared to obese patients without OSA were found to have higher fasting glucose, higher insulin levels, and higher systemic inflammatory markers [90]. In a subsequent larger study by Punjabi and colleagues, 150 mildly obese but otherwise healthy men

underwent polysomnography, oral glucose tolerance test, and determination of body fat. In this study, the prevalence of OSA (defined as AHI > 10/hrour) was more than 45%. After adjusting for BMI, OSA was associated with increased risk of having impaired glucose tolerance (Odds ratio of 2.15) and related to degree of oxygen desaturation [85]. Studies on a large Asian cohort done by Ip et al. also found OSA to be independently associated with insulin resistance as measured by HOMA-IR (homeostasis model assessment of insulin resistance) [86]. Similarly a large European study (595 patients) revealed that type II diabetes was present in 30% of patients with OSA [91] and a Japanese study (213 patients) found increased insulin resistance in patients with OSA [92]. Though most studies looked at BMI, few studies looked at visceral obesity and waist to hip ratio, which more closely relates to insulin resistance than BMI [92, 93]. Though most studies have supported an association between OSA and diabetes/glucose dysregulation, a few studies have been negative [94, 95]. This is not surprising as obesity is a huge confounding factor in all studies dealing with OSA. These data simply indicate an association between OSA and type II diabetes and does not however establish causality or direction of causality.

If it is true that OSA causes diabetes, then treatment of OSA should mitigate the metabolic dysregulation. However, treatment by CPAP (continuous positive airway pressure therapy), which is currently the most accepted therapeutic intervention for OSA has shown inconsistent results. Several studies have shown improvement in insulin sensitivity after varying periods of CPAP therapy in patients with diabetics and nondiabetics [96–98], including a study showing a reduction in HbA1C [99]. A German study using the hyperinsulinemic euglycemic clamp technique (the gold standard for measuring insulin sensitivity) evaluated 40 patients with moderate to severe obstructive sleep apnea and found improved insulin sensitivity after only 2 days of CPAP therapy, which persisted during a 3 month followup [100]. This rapid improvement suggests that the resolution of sympathetic drive might play an important role in the pathogenesis of metabolic dysregulation seen in patients with obstructive sleep apnea. However, the debate on the impact of CPAP therapy in mitigating metabolic dysregulation is far from resolved. Equal numbers of studies have shown no impact of therapy on diabetes or glucose metabolism [101–104]. A uniform problem with these studies has been small number of patients and no controls. Recently, two randomized controlled trials have been conducted. A study by Coughlin et al. took 34 patients with severe sleep apnea and metabolic syndrome and randomized them to receive CPAP therapy versus sham CPAP followed by a crossover after 6 weeks. The study failed to show any improvement in insulin sensitivity or metabolic profile despite improvement in blood pressure [105]. West et al. evaluated 42 patients with OSA and diabetes and randomized them to 3 months of treatment versus sham treatment. The study did not show any significant improvement in glycosylated hemoglobin or insulin resistance measured by euglycemic clamp and HOMA [106]. The compliance in this study was however suboptimal (3.6 hours/night) and may have affected the outcome. Whether this had any impact is debatable. One major confounding factor in these studies is obesity. Harsh and colleagues showed that the improvement in insulin sensitivity in patients with BMI > 30 kg/m^2 is minimal [100] but improved after 3 months [107]. Future studies are required to define the correct patient profile, time duration and impact of compliance, to get better understanding of the role of CPAP therapy in improving diabetes.

It is believed that obstructive sleep apnea may cause metabolic dysregulation through several pathways. Sympathetic surge is known to occur with each apnea event. Sympathetic activation has been shown to increase levels of circulating free fatty acids because of the stimulation of lipolysis, which promotes insulin resistance [86]. Elevated catecholamine levels were found in people with more wake time after sleep onset [108]. Additionally, sleep fragmentation, recurrent hypoxemia, and triggering of inflammatory cytokines on a nightly basis may all contribute to higher propensity to metabolic syndrome and type II diabetes. The relative contribution of any of the above pathways is not known. Some of these pathways may overlap with suggested pathophysiological pathways of sleep deprivation and circadian misalignment (Figure 1).

In summary while there is growing evidence of an association between OSA and metabolic dysregulation the direction of causality and decoupling of major confounding factor of adiposity has not been clearly stated. Data on interventional studies is also conflicting and marred by small sample sizes, inadequate power, and observational design.

8. Metabolic Consequences of Shift Work Disorder

Sleep is controlled by two powerful processes: circadian and homeostatic [109]. During waking hours, the sleep drive gradually increases until it reaches a critical threshold. This drive is referred to as homeostatic. Circadian rhythm, on the other hand, is a signal generated by the master clock, the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. Circadian rhythm, derived from the Latin term "*circa diem*" which literally means "approximately one day" is the body's internal clock. This clock is set at slightly over 24 hours. It controls sleep as well as most biological processes, including hormone production, metabolism, core body temperature variations, and cell regeneration among others [110]. This clock is normally highly synchronized to environmental cues (Zeitgebers, German for "time giver"), the strongest of them being the light-dark cycle. In most humans the alertness pattern shows a biphasic distribution, with a mid-day decrease in alertness around 2–4 pm, followed by an increased alertness during mid to late evening, and finally declining to its lowest levels during the night [109, 111]. Almost all physiological systems in humans run slightly over a 24 hour cycle. Disturbance of this well-regulated circadian rhythm and homeostatic drive (circadian misalignment) can lead to various sleep disorders collectively known as circadian rhythm sleep disorders. Shift work disorder is one of the circadian rhythm disorders which have

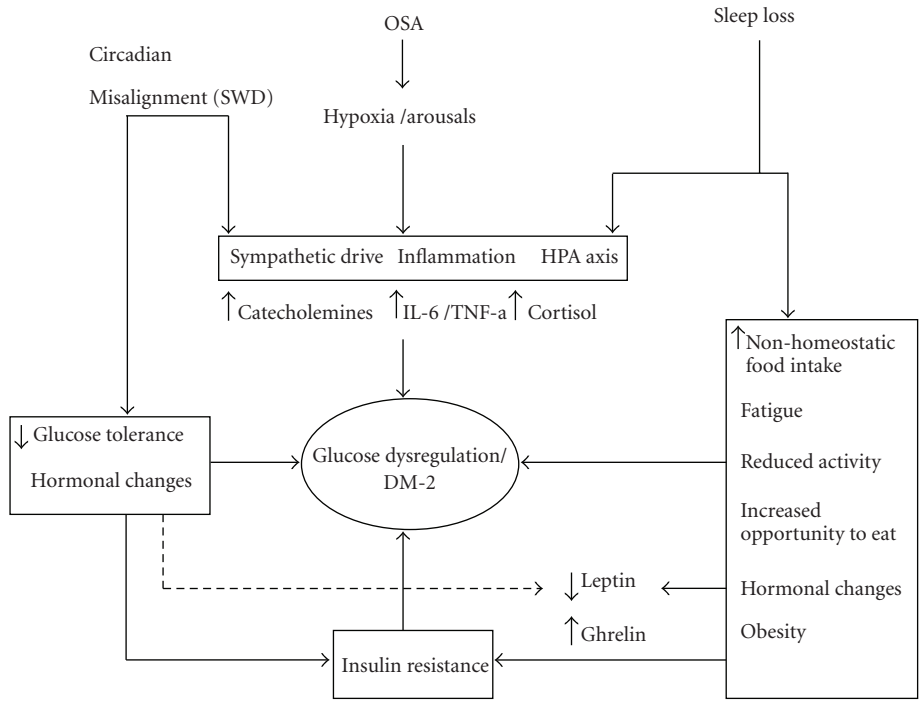

Figure 1: Schematic diagram of potential mechanism of glucose dysregulation/diabetes pathogenesis, secondary to sleep loss, sleep apnea, and circadian misalignment. The three main sleep disorders are listed at the top. Arrows point to possible pathophysiological alteration the disorders may induce. Some of the pathways are common to all the disorders and are listed together, that is, sympathetic drive, inflammation, and alteration of HPA axis. Sleep loss may in addition lead to changes like hormonal imbalance and reduced activity (listed on the box to the right of the diagram). Similarly circadian alteration may also cause insulin resistance and hormonal imbalance (shown in the box to the left). All these pathophysiological alterations eventually may lead to type II diabetes which is shown in the center. SWD: Shift work disorder.

been a focus of large epidemiological studies for its potential implications on health.

People involved in some form of shift work are increasing globally. U.S. Bureau of Labor statistics indicate that 8.6 million people were shift workers in 2004 in the United States alone [112]. Circadian misalignment due to shift work or jet lag has been associated with obesity, diabetes, and cardiovascular diseases. A Swedish study followed shift workers for 15 years and reported increased relative risk for ischemic heart disease (RR = 2.8) as compared to daytime workers independent of smoking and age with similar socioeconomic background [113]. More recent studies have suggested that shift work is the most significant source of ischemic heart disease accounting for over 10% of mortality in men and over 5% in women [114]. Another prospective study found increased risk of circulatory diseases in shift workers after controlling for confounding factors [115]. In a large cohort of subjects followed prospectively in the Nurse Health Study II investigators found increased risk of type II diabetes in young and middle age nurses working in rotating night shift work [116]. Cross-sectional data also suggests higher triglyceride levels, lower HDL levels, and more obesity in the shift workers than daytime workers [117, 118]. Another recent study emulating shift work for short duration (10 days) revealed decreased leptin, increased glucose, and reversed cortisol rhythm. Circadian misalignment caused 3 of the 8 subjects to exhibit postprandial glucose responses in the range typical of a prediabetic state [119].

Mechanistic pathways by which shift work can cause metabolic dysregulation are not clear but appear to involve hormonal alterations and increased sympathetic drive leading to decreased insulin sensitivity and insufficient beta-cell compensation. Possibility of altered melatonin profile during circadian misalignment contributing is another potential pathway as there is some evidence that melatonin may inhibit glucose-induced insulin release [120]. Additionally, animal models subjected to circadian alterations simulating shift-work have resulted in premature death [121].

In conclusion, the limited data regarding circadian misalignment suggests its role, albeit unclear, in metabolic dysregulation. Since sleep deprivation is commonly associated with shift work disorder further prospective trials adjusting for sleep deprivation are required to establish role of circadian misalignment as opposed to indirect effect of sleep deprivation on metabolic dysregulation.

9. Energy Expenditure in Sleep and Sleep Disorders

Several studies have looked at the relationship of body energy expenditure in sleep and sleep disorders (mainly OSA). The

energy expenditure of human body appears to reduce and is lowest during sleep [122–125]. This reduction in energy expenditure may be influenced by circadian rhythm [122, 126], changes in body temperature [127], and reduction in muscle activity [128, 129], not to mention the depth and duration of sleep and physical activity [8, 129–132]. Energy expenditure has also been reported to vary depending on the stage of sleep [8, 133]. Race also seems to play a role as African-Americans appear to have a lower sleep metabolic rate (SMR) and increased propensity for weight gain as compared to Caucasians [134]. Also SMR decreases during sleep as a function of BMI and the decrease rate in SMR is larger as BMI increases [134].

Acute sleep loss results in small increase in SMR [122, 133, 134]. A similarly small increase in SMR has been recorded in chronic sleep deprivation [135].

Limited studies looking at energy expenditure in patients with obstructive sleep apnea have revealed mixed results. Stenlof et al. found higher total energy expenditure (TEE) and SMR with reduction in energy expenditure upon treatment with continuous positive pressure therapy (CPAP). A study by Lin et al. found increase in SMR but not morning BMR in patients with OSA. Patients in this study who underwent laser-assisted uvulopalatoplasty demonstrated a reduction in SMR. However, Hins et al. found no relationship between OSA and TEE or SMR. Similar mixed results have been noted in children [136–138].

In summary, energy expenditure is reduced during sleep. Sleep deprivation appears to increase energy expenditure. Data in impact of sleep apnea on energy expenditure is equivocal. Studies in patients with OSA are also limited by small size and lack of body composition data which significantly impacts energy expenditure. It is also important to point out that most of these studies have utilized indirect calorimetry technique instead of the gold standard metabolic chamber (direct calorimetry). Larger studies utilizing direct calorimetric techniques are needed to understand the impact of sleep apnea on energy expenditure.

10. Conclusions

Sleep disorders and diabetes are rapidly growing problems with grave public health implications. There is growing interest and evidence that sleep loss and sleep disorders have a significant impact on metabolism. Laboratory studies have clearly shown that sleep deprivation can alter the glucose metabolism and hormones involved in regulating metabolism, that is, decreased leptin levels and increased ghrelin levels. A majority of large epidemiological studies have suggested that chronic partial sleep deprivation is associated with an increased risk of obesity and diabetes. However, there are several areas where the data conflicts. The role of gender is not entirely clear. Ayas et al. and Mallon et al. have shown that while sleep duration does predict diabetes in women, the significance is lost once corrected for risk factors like BMI. The relationship of sleep duration to metabolic dysregulation is also found to be U-shaped in many studies (nurse health study, sleep heart health study, and Massachusetts male health study) suggesting that not only short duration but also longer duration may have the potential to disturb the metabolic equilibrium of the body. Paradoxically a similar U-shaped relation is also noted in several studies looking at the relationship between sleep and weight, with both short and long sleep leading to weight gain [62, 139]. Most epidemiological studies have relied on subjective self-reported measures of sleep duration.

Further studies are needed to clearly elucidate the role of gender, sleep duration, and metabolism with more objective measurements of sleep. Also needing to be clarified is the difference between sleep deprivations due to voluntary sleep loss versus Insomnia. A model of nonobese patients with OSA may help decouple the impact of adiposity on diabetes. Differences exist between human and animal response to sleep deprivation on weight. Mechanism explaining the complex interaction between sleep and metabolism need to be further explored if we hope to derive more clinical mileage with sleep becoming an important tool to fight the obesity pandemic.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 726071, 8 pages
doi:10.1155/2010/726071

Research Article

Gender Differences in the Association between Sleep Duration and Body Composition: The Cardia Study

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Received 25 June 2009; Accepted 14 October 2009

Academic Editor: Jessica A. Mong

Sleep duration has been inversely associated with body mass index (BMI). We examined the relationship between self-reported sleep duration and BMI, waist circumference, and percent body fat in Black and White individuals from the CARDIA study. Box-Tidwell regression models were adjusted for age and race (Model 1), additional lifestyle and demographic variables (Model 2), and physical activity (Model 3). There were significant interactions between sleep and gender for the main outcome variables. In men, there was a trend for an inverse relationship between reported sleep duration and BMI in Model 2 ($\beta = -0.20, P = .053$) but not model 3 ($\beta = -0.139, P = .191$). In women, inverse relationships were observed between sleep duration and BMI ($\beta = -0.294, P = .005$) and waist circumference ($\beta = -0.442, P = .059$), in Model 2. These associations became nonsignificant in model 3 (BMI: $\beta = -0.172, P = .084$; waist circumference: $\beta = -0.161, P = .474$). Our results are consistent with previous findings that sleep is associated with BMI and other body composition variables. However, the relationship between self-reported sleep duration and body composition may be stronger in women than in men.

1. Introduction

Physical activity and dietary patterns have received much attention in attempts to explain the rise in obesity of past decades; however, many other factors have been identified that may have contributed to the obesity epidemic that we observe today [1]. One contributor receiving much interest recently is sleep debt. In a 2004 survey, approximately 63% of adults reported sleeping 7-8 h/night and almost 30% averaged less than 6 h/night [2]. In the Sleep Heart Health Study, mean sleep duration was reportedly slightly over 7 h/night in both men and women [3]. In the Coronary Artery Risk Development in Young Adults (CARDIAs) study, young adults were getting approximately 6 hours of sleep/night [4] with Black men and women sleeping, on average, about 1 h/night less than White men and women (about 5.5 versus 6.4 h/night).

Such short reported sleeping times may be of concern in the context of an obesity epidemic since several studies have found that sleep duration is inversely associated with body mass index (BMI, in kg/m^2) [5–8]. Data from the National Health and Nutrition Examination Survey I (NHANES I) showed that young adults getting <7 hours of sleep/night had higher BMI and were more likely to be obese than those sleeping 7 h/night or more [9]. Similar findings are observed in children and adolescents [10–13]. Furthermore,

data from the Nurses' Health Study show greater weight gain in women sleeping less than 7 h/night compared with those sleeping at least 7 h/night [14]. Women sleeping 7-8 h/night also had the lowest risk for major weight gain (≥15 kg over 16 years) and sleeping ≥7 h/night was not associated with an increased risk of developing obesity in normal weight women whereas sleeping 5 or 6 h/night was. Similarly, in the Quebec Family Study, those who reported sleeping 5-6 h/night gained approximately 2 kg more over a 6-year follow-up period than those who reported sleeping 7-8 h/night [15].

Despite the large number of epidemiological studies linking obesity and short sleep duration [16], there is a paucity of data carefully examining the relationship between body composition and sleep duration in adults. Strengths of our cohort study include the presence of waist circumference, and percent body fat data from dual energy X-ray absorptiometry (DXA) as well as the inclusion of both Black and White individuals. Waist circumference contributes independently to the prediction of visceral adipose tissue [17] and it is therefore of interest to assess its relationship with sleep duration. The main objective of this study was to examine relationships between self-reported sleep duration and BMI, waist circumference, and percent body fat in the CARDIA cohort. We hypothesized that short sleep duration would be associated with higher BMI, waist circumference and percent body fat. Secondary objectives were to determine whether body composition also showed similar relationships with sleep duration between Black and White adults and between men and women. This study is important since it is one of the few studies to examine the impact of sleep duration on body composition indices in both Black and White men and women. It is interesting to note that Black individuals tend to be more overweight and obese than Whites [18] and also tend to sleep less [4]. It is possible that sleep duration may have a greater impact on obesity status in Blacks than Whites, yet this has not been examined. Similarly, gender differences in the impact of sleep duration on obesity status have been noted in children but not extensively studied in adults [19].

2. Methods

Data for the analyses reported here are from the CARDIA Study, a cohort study established to examine the determinants and evolution of cardiovascular disease risk factors in young Black and White adults. A total of 5115 men and women, aged 18–30 years, were recruited from 4 centers in 1985-1986: Birmingham, AL (University of Alabama at Birmingham), Chicago, IL (Northwestern University), Minneapolis, MN (University of Minnesota), and Oakland, CA (Kaiser Permanente Oakland). Subjects were examined at baseline and years 2, 5, 7, 10, and 15. At the time of preparation of this manuscript, year 20 data were not available and only cross-sectional analyses are reported here. Furthermore, sleep was assessed only at examination Year 15, preventing us from assessing longitudinal relationships with body composition data from prior examination years. All subjects provided written informed consent at each visit and study protocols were approved by the Institutional Review Board of each institution. Details of the recruitment and study procedures are reported elsewhere [20]. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

For the present study, we examined the relationship between sleep duration and indices of body composition from examination at year 15, when subjects were 33–45 years of age. Of the initial cohort of 5115 subjects, 3672 (72%) returned for the year 15 visit. We excluded subjects who had low (<18.5) and extremely high (>45) BMI, implausible sleep data (≥15 h/night), those who reported drinking more than 3 standard deviations above the mean alcoholic beverage consumption (>30 drinks per week), women who were pregnant or breastfeeding, and subjects with missing data. Our final sample size was 3473 subjects for the anthropometric analyses (BMI and waist circumference). DXA was only done at the Birmingham and Oakland sites on a subsample of the study population, allowing analyses examining the relationship between sleep duration and body fat in 320 participants [21].

2.1. Demographics and Lifestyle Information. Demographic characteristics, age, sex, race, education level, and income level, were self-reported on standardized questionnaires. The information used in this study was collected at the year 15 examination. Education level was determined by obtaining the highest grade or year of regular school completed and was included in the models as a continuous variable (range 1–20+ years). Income level was categorized as total combined family income for the past 12 months and coded ordinally (1 = < \$5000, 2 = \$5000–11 999, 3 = \$12 000–15 999, 4 = \$16 000–24 999, 5 = \$25 000–34 999, 6 = \$35 000–49 999, 7 = \$50 000–74 999, 8 = \$75 000–99 999, and 9 = ≥ \$100 000). Data are presented with groups 1–4 combined (< \$25 000), 5–7 combined (\$25 000–74 999), and 8-9 combined (≥ \$75 000). Leisure-time physical activity and work-related physical activity were assessed using a validated interview-administered questionnaire.

2.2. Body Composition Measurements. Weight (to the nearest 0.2 kg) and height (to the nearest 0.5 cm) were recorded with subjects wearing light clothing and without shoes. BMI was calculated as weight in kg divided by the square of height in meters. Waist circumference was measured at the level of minimal abdominal girth (to the nearest 0.5 cm) and recorded as the average of 2 measurements. Body composition was measured using DXA QDR-2000 scanner (Hologic, Inc., Waltham, MA). Daily phantom scanning was done to ensure consistent data acquisition throughout the study.

2.3. Sleep Questionnaire. A standardized sleep questionnaire was administered at 15 years of followup. The questionnaire included the question: "During the past month, how many hours of actual sleep did you get at night? (this may be

different than the number of hours you spend in bed)." The answer to this question was used to determine self-reported sleep duration.

2.4. Statistical Analyses. Descriptive statistics consisted of frequencies, percentages, means, and standard deviations. The relationship between continuous predictors and anthropometric outcomes was assessed with regression models and for categorical variables with the Cochran-Armitage trend test.

To initially assess the association of sleep with body composition variables, Box-Tidwell regressions were conducted [22]. Nonlinear relationships were noted for both sleep duration and age with the four dependent variables (weight, BMI, waist, and percent body fat). The Box-Tidwell procedure was utilized to identify an appropriate power transformation of the independent and dependent variables to linearize relationships. To adjust for the nonlinear relationship, all four dependent variables were log-transformed. Once the transformations were selected in the Box-Tidwell regressions, the new transformed variables were included in ordinary multiple linear regressions. The transformed variables were rescaled by linear transformation to their original mean and variance for ease of interpretation and presentation. Table 1 shows the respective transformations used for sleep and age by gender. There was a significant interaction between gender and sleep for the main outcome variables and therefore the models were stratified by gender.

The appropriate transformed variables were used in three regression models for each dependent variable. In Model 1, the impact of sleep on the dependent variable was adjusted for age and race. Model 2 was further adjusted for lifestyle (smoking, alcohol intake) and demographic (education level, income) factors. These lifestyle variables are routinely included in models assessing the impact of one behavior on body composition [14]. Factors that did not significantly impact the dependent variable for both men and women were removed for the analyses. Model 3 was additionally adjusted for physical activity level. The beta (β) coefficients reported are unstandardized estimated regression coefficients calculated using predictor variables after they have been transformed (as described above) and then rescaled via linear transformations to their original mean and variance to ease interpretation. For instance, a 1-hour increase in sleep changes the dependent variable by β units. All models were tested for interactions between race and sleep and no significant interactions were found. Therefore the estimates reflect the combined racial groupings. A two-tailed α level of 0.05 was considered statistically significant. Data were analyzed using SAS software for Windows version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

A total of 1585 men and 1888 women were included in the main analyses. For the analyses using data from DXA measurements, the sample included 159 men and 161 women. Table 2 shows subject characteristics by gender and race for the main analyses. Most comparisons were statistically significant. In general, women were older than men, weighed less, had higher percent body fat, drank less alcohol and smoked less, reported sleeping longer, and were more inactive than men. Generally, Blacks were younger, heavier, had lower education and income level, reported sleeping less, were less physically active, and smoked more than Whites.

Sleep duration tended to be inversely associated with BMI in men in Model 1 ($\beta = -0.20$, $P = .053$) and after controlling for other lifestyle and physiologic variables in Model 2 ($\beta = -0.198$, $P = .068$) (Table 3). In Model 3, after including physical activity, sleep was not significantly associated with BMI in men ($\beta = -0.139$, $P = .191$). In model 3, race, smoking, alcohol intake, education level, family income, and physical activity level were all significantly associated with BMI. In women, the inverse association between sleep duration and BMI was significant after controlling for age and race ($\beta = -0.332$, $P = .002$) and other lifestyle and physiologic variables ($\beta = -0.294$, $P = .005$). However, after physical activity was added to the model, the association between sleep and BMI became nonsignificant ($\beta = -0.172$, $P = .084$). In women, in model 3, age, race, education level, family income, working full time, and physical activity level were all significantly associated with BMI.

There was no statistically significant association between sleep duration and waist circumference in men, although the magnitude and direction of the sample slope was similar to that observed in women (Table 4). In women, waist circumference was significantly inversely associated with sleep duration in model 1 ($\beta = -0.543$, $P = .022$). This relationship was no longer statistically significant when we further controlled for other lifestyle and demographic variables, but was similar in magnitude and nearly statistically significant in model 2 ($\beta = -0.442$, $P = .059$) but not in model 3 ($\beta = -0.161$, $P = .474$). Percent body fat was not significantly associated with sleep duration in neither men nor women.

4. Discussion

This is one of the few studies to examine the relationship between sleep and body composition variables beyond body weight and BMI in adults. Furthermore, it is the only study to date to examine the relationship between sleep and body composition in a bi-racial population of Blacks and Whites. As such, this is the first study to examine whether sleep duration is related to waist circumference and percent body fat in Black and White adults.

Few studies to date have examined the relationship between waist circumference and sleep in adults. In the Better Health for Better Hong Kong campaign, waist circumference was inversely related to sleep duration [5], in agreement with our data in women. In men, although the association was not statistically significant, the magnitude and direction of the association between waist circumference and sleep duration was similar to that observed in women. However, in a sample

Table 1: Transformations for sleep and age by gender.

Dependent Variable	Men		Women	
	Sleep	Age	Sleep	Age
BMI	0.25 power	Square root	Square root	0.25 power
Waist circumference	Log	Log	Log	0.75 power
Percent Body Fat	Square root	None	Log	0.25 power

Table 2: Participant characteristics by gender and race.

Characteristic	White men ($n = 897$)	Black men ($n = 688$)	White women ($n = 962$)	Black women ($n = 926$)
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Age (years)	40.67 (3.36)	39.47 (3.73)*	40.79 (3.36)	39.67 (3.84)*
Weight (lbs)	193.95 (34.21)	199.85 (41.49)*	158.0 (35.20)	183.14 (39.99)*
BMI (kg/m^2)	27.65 (4.34)	28.59 (5.24)*	26.23 (5.57)	30.66 (6.26)*
Waist circumference (cm)	93.67 (11.59)	92.88 (12.55)	80.76 (12.85)	88.74 (13.49)*
Body fat (%)[1]	26.88 (6.26)	24.40 (7.82)*	38.25 (9.70)	43.81 (7.46)*
Education level (years)	15.69 (2.66)	13.71 (2.21)*	15.82 (2.40)	14.09 (2.19)*
Alcohol intake (drinks/wk)	4.92 (6.20)	4.69 (6.91)	3.16 (4.84)	1.90 (4.08)*
Sleep duration (h/night)	6.65 (1.00)	6.26 (1.37)*	6.84 (1.09)	6.28 (1.48)*
	N (%)	N (%)	N (%)	N (%)
Family income				
< $5000-$24 999	61 (6.8)	145 (21.6)*	75 (7.9)	246 (27.1)*
$25 000-$74 999	361 (40.3)	345 (51.7)	431 (45.0)	478 (52.6)
$75 000- ≥ $100 000	474 (52.9)	178 (26.7)	450 (47.1)	186 (20.3)
Full-time work				
Yes	801 (89.3)	539 (78.7)*	559 (58.1)	695 (75.5)*
No	96 (10.7)	146 (21.3)	403 (41.9)	226 (24.5)
Difficulty paying for basics				
Very hard	12 (1.3)	20 (2.9)*	20 (2.1)	40 (4.4)*
Hard	13 (1.5)	24 (3.5)	28 (2.9)	35 (3.8)
Somewhat hard	84 (9.4)	99 (14.5)	108 (11.2)	176 (19.2)
Not very hard	787 (87.8)	541 (79.1)	806 (83.8)	667 (72.6)
Physical activity				
Inactive	34 (3.8)	25 (3.6)*	47 (4.9)	94 (10.2)*
	144 (16.1)	69 (10.0)	177 (18.4)	184 (20.0)
Moderately active	391 (43.7)	298 (43.3)	419 (43.6)	430 (46.7)
	205 (22.9)	125 (18.2)	191 (19.9)	100 (10.9)
Very active	120 (13.5)	171 (24.9)	127 (13.2)	112 (12.2)
Current smoking				
Yes	155 (17.3)	228 (33.3)*	150 (15.6)	233 (25.2)*
No	741 (82.7)	458 (66.7)	811 (84.4)	691 (74.8)
Sleep quality				
Very bad	5(0.6)*	19 (2.8)	12 (1.3)	24 (2.6)
Fairly bad	127 (14.2)	70 (10.2)	138 (14.4)	150 (16.3)
good	268 (30.0)	241 (35.1)	289 (30.1)	296 (32.2)
Fairly good	319 (35.7)	219 (31.9)	326 (34.0)	287 (31.3)
Very good	174 (19.5)	137 (20.0)	195 (20.2)	161 (17.6)

[1] $n = 320$

*$P < .05$ for comparison between race, within gender category.

Table 3: Multivariate models for predictors of body mass index in the CARDIA study stratified by gender (β, 95% CI)[1].

Variable	Men			Women		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Sleep (h)	−0.20	−0.20	−0.14	−0.33	−0.29	−0.17
	(−0.40, 0.002)	(−0.41, 0.01)	(−0.34, 0.07)	(−0.53, −0.13)*	(−0.50, −0.09)*	(−0.37, 0.02)
Age (yrs)	0.003	0.004	−0.02	0.12	0.13	0.12
	(−0.06, 0.07)	(−0.07, 0.07)	(−0.09, 0.05)	(0.05, 0.20)*	(0.06, 0.20)*	(0.05, 0.19)*
Race	−0.72	−1.17	−1.40	−4.49	−3.28	−3.14
(White versus Black)	(−1.23, −0.22)*	(−1.72, −0.62)*	(−1.94, −0.86)	(−5.03, −3.94)*	(−3.88, −2.68)*	(−3.72, −2.57)*
Current smoker		−1.54	−1.54		−0.47	−0.50
(Yes versus No)		(−2.18, −0.89)*	(−2.17, −0.91)*		(−1.17, 0.23)	(−1.17, 0.18)
Number		−0.06	−0.06		−0.09	−0.06
drinks/week		(−0.10, −0.03)*	(−0.09, −0.02)*		(−0.15, −0.03)*	(−0.11, 0.0005)
Education (yrs)		−0.12	−0.15		−0.32	−0.30
		(−0.23, −0.009)*	(−0.26, −0.04)*		(−0.44, −0.19)*	(−0.42, −0.18)*
Income		0.20	0.21		−0.33	−0.25
(ordinal 1–9)		(0.04, 0.35)*	(0.06, 0.36)		(−0.47, −0.18)*	(−0.40, −0.11)*
Work full-time		−0.06	0.18		0.65	0.71
(Yes versus No)		(−0.83, 0.71)	(−0.57, 0.93)		(0.08, 1.21)*	(0.17, 1.25)
Physical activity			−1.04			−1.57
			(−1.27, −0.81)*			(−1.80, −1.33)*

[1]Beta (β) coefficients reported are unstandardized estimated regression coefficients calculated using predictor variables after they have been transformed and then rescaled via linear transformations to their original mean and variance.
*$P < .05$.

Table 4: Multivariate models for predictors of waist circumference in the CARDIA study stratified by gender (β, 95% CI)[1].

Variable	Men			Women		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Sleep (h)	−0.40	−0.35	−0.15	−0.54	−0.44	−0.16
	(−0.90, 0.11)	(−0.89, −0.18)	(−0.67, 0.36)	(−1.01, −0.07)*	(−0.90, 0.02)	(−0.60, 0.28)
Age (yrs)	0.22	0.24	0.17	0.38	0.40	0.36
	(0.05, 0.38)*	(0.08, 0.41)*	(0.008, 0.33)	(0.21, 0.54)*	(0.24, 0.56)*	(0.21, 0.52)
Race	0.98	0.39	−0.36	−8.31	−5.69	−5.39
(White versus Black)	(−0.22, 2.18)	(−0.93, 1.72)	(−1.63, 0.91)	(−9.53, −7.09)*	(−7.01, −4.37)*	(−6.65, −4.13)
Current smoker		−2.93	−2.91		0.25	0.18
(Yes versus No)		(−4.48, −1.39)*	(−4.39, −1.43)*		(−1.32, 1.83)	(−1.32, 1.69)
Number		−0.10	−0.07		−0.16	−0.08
drinks/week		(−0.19, −0.006)*	(−0.16, 0.02)		(−0.29, −0.03)	(−0.21, 0.04)
Education (yrs)		−0.43	−0.51		−0.72	−0.68
		(−0.70, −0.16)*	(−0.77, −0.25)*		(−1.00, −0.45)*	(−0.95, −0.42)
Income		0.35	0.45		−0.79	−0.62
(ordinal 1–9)		(< 0.001, 0.70)*	(0.12, 0.79)		(−1.11, −0.46)*	(−0.93, 0.30)
Physical activity			−3.33			−3.58
			(−3.88, −2.78)			(−4.11, −3.06)*

[1]Beta (β) coefficients reported are unstandardized estimated regression coefficients calculated using predictor variables after they have been transformed and then rescaled via linear transformations to their original mean and variance.

of older Spanish adults, waist circumference was not related to sleep duration [23]. Results from the Quebec Family Study also showed larger waist circumference in men and women who reported sleeping <7 h/night compared to those who reported sleeping 7-8 h/night [24]. It is possible that the age difference between the Spanish cohort and our young adult cohort is responsible for the different results. This relationship between waist circumference and sleep duration is of importance since well-known metabolic disturbances are associated with increased waist circumference [25].

In our study, BMI and waist circumference were inversely associated with sleep duration in women before including physical activity in our model. In men, associations tended to be in the same direction and of similar magnitude, but were not statistically significant. This gender difference has not been consistently reported in adults. In fact, no gender effect on the association of sleep and BMI was observed in an elderly Spanish cohort [23], a primary care U.S. sample [26], or the Quebec Family Study [24]. However, in a sample of Southern France, sleep duration was found to be related to BMI in women but not men [27]. Gangswisch et al. [9] have previously reported that BMI was higher in men and women who slept less than 7 hours compared to those who slept 7 hours or more only in individuals age 32–49. This age group includes the age group of our cohort (33–45 years). In the NHANES data, gender differences were also observed in the association between BMI and sleep duration, with women being progressively more likely to be obese as sleep duration was reduced below 7 h/night whereas men were more likely to be obese with 6 or fewer hours of sleep/night. In our study, the association between BMI and sleep duration was significant in women but a trend in men. Our data add to the body of literature suggesting that sleep may have a slightly greater impact on body composition in adult women than in men. This potential gender difference in the relationship between sleep and adiposity deserves further exploration, especially since discordant data have also been observed in children and adolescents [10, 11, 28, 29]. Previous metabolic studies have been conducted in young men only [30, 31] or in a study with few women [32]. Future metabolic studies should be done in women to determine if they have a different hormonal response to short sleep duration than men.

Our finding that percent body fat was not significantly associated with sleep duration is novel. One previous study has examined the relationship between this body composition measure and sleep duration in adults [24]. In our cohort, we did not find any significant association between these two variables. In the Quebec Family Study, Chaput et al. [33] found lower percent body fat in men and women who reported sleeping 7-8 h/night compared to those reporting 5-6 hours of sleep per night. It is possible that our sample size was not sufficient to detect an association. In fact, only 320 subjects participated in the DXA measurement, leaving few participants within each race-gender category. In comparison, the Quebec Family Study had more than twice our sample size with only one racial group.

In this study, adding physical activity to our models attenuated or abolished the relationship between sleep duration and body composition. We can speculate that sleep may in part act on body composition via changes in physical activity. It is possible that adults who sleep less are too tired to be physically active or those who sleep very long have too little time to be physically active. In fact, in our data, physical activity tended to increase with increasing sleep duration in women (data not shown). Moreover, being physically active can improve sleep quality and duration [34, 35] such that physical activity and sleep can be positively related.

Conservation of energy is a well-known principle that applies to obesity research. In this principle, energy is neither created nor lost. Therefore, in order to lose weight, one must expend more energy than is consumed or consume less energy than is expended; to gain weight, one must expend less energy than is consumed or consume more energy than is expended. It thus follows that our hypothesis explaining the relationship between sleep duration and body composition must (short of variations in energy partitioning) be due to an effect of sleep on energy expenditure or energy intake. If one controls for energy intake (food consumption) and energy expenditure (not equivalent, but closely related to physical activity), much of the variance in body composition variables is accounted for. This was the case when we added physical activity level to our models. In addition, food intake may be increased in those who sleep less. An increase in food intake with shorter sleep duration may result from various factors; longer hours awake create more time for eating, and hunger may increase with shorter sleep duration. Increased hunger ratings have been reported with short sleep duration and these have been related to reduced leptin and increased ghrelin levels [33]. Furthermore, in a recent report from the Quebec Family Study, the relationship between sleep duration and adiposity measures disappeared after controlling for leptin levels [24]. In fact, 88% of short sleepers had low leptin levels, confirming a previous clinical study showing that short sleep decreases leptin concentrations [33]. Dietary information was not taken at Y15 in the CARDIA study and we could not include this variable in our models.

Our study has several limitations. First, our sleep data are self-reported. Sleep was objectively measured in a subsample of our cohort [38]. In that study it was shown that the correlation between self-reported sleep duration and actigraph-measured sleep duration was 0.47. Furthermore, there was a systematic overestimation of sleep duration that was greater in short sleepers than in those sleeping more than 7 h/night. Also, self-reported sleep duration by obese individuals tended to be more closely related to actigraph-measured sleep duration than lean individuals, who tended to overestimate their sleep duration in self-reports relative to the actigraph measurement. Thus, obese individuals may provide more accurate self-reports of their sleep duration than nonobese individuals and nonobese individuals over-report their sleep times. These data suggest that longer sleep hours would falsely include a greater proportion of lean individuals than obese individuals. This might then lead one to erroneously conclude that BMI decreases with increasing sleep duration even if this were not actually the case. In fact, Knutson and Lauderdale [36] have reported that the odds

ratio for overweight in adolescents using time-diary sleep times was not significantly affected by sleep duration whereas the odds ratio for overweight was significantly increased with reduced sleep duration when sleep duration was self-reported. On the other hand, Nixon et al. [37] found a significant inverse association between actigraphy-measured sleep duration and overweight/obesity in 7-year old children. Similarly, Taheri et al. [7] found a significant U-shaped relationship between sleep duration and BMI when sleep was measured using polysomnography. More research is needed to determine the degree of error introduced by biased sleep reporting into the association of sleep duration and obesity.

Finally, our data show that the relationship between sleep duration and body composition is not affected by race but rather differs according to gender. In fact, women show a more consistent effect of sleep duration on body composition than men. Our data thus suggest that short sleep duration may be a risk factor for overall and abdominal obesity in young Black and White women. However, our overall small sample size, self-reported measures of sleep, and the cross-sectional nature of our data do not allow us to make definitive conclusions on the impact of gender on the relationship between sleep duration and obesity. More studies are needed to examine the gender difference on the relationship between sleep and obesity and consideration must be given to objectively-measured sleep duration.

Acknowledgment

Work on this manuscript was supported in part by contracts to the University of Alabama at Birmingham (Coordinating Center, N01-HC-95095; Field Center N01-HC-48047); the University Minnesota (Field Center, N01-HC-48048); Northwestern University (Field Center, N01-HC-48049); Kaiser Foundation Research Institute (N01-HC-48050) from the National Heart, Lung, and Blood Institute; and NIH grant P30DK056336. The opinions expressed herein are those of the authors and do not necessarily reflect those of the NIH or any other organization with which the authors are affiliated. None of the authors have any conflict of interest to disclose.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 474518, 11 pages
doi:10.1155/2010/474518

Review Article

Neuroendocrine Alterations in Obese Patients with Sleep Apnea Syndrome

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Received 31 August 2009; Revised 8 December 2009; Accepted 17 December 2009

Academic Editor: Deborah Suchecki

Obstructive sleep apnea syndrome (OSAS) is a serious, prevalent condition that has significant morbidity and mortality when untreated. It is strongly associated with obesity and is characterized by changes in the serum levels or secretory patterns of several hormones. Obese patients with OSAS show a reduction of both spontaneous and stimulated growth hormone (GH) secretion coupled to reduced insulin-like growth factor-I (IGF-I) concentrations and impaired peripheral sensitivity to GH. Hypoxemia and chronic sleep fragmentation could affect the sleep-entrained prolactin (PRL) rhythm. A disrupted Hypothalamus-Pituitary-Adrenal (HPA) axis activity has been described in OSAS. Some derangement in Thyroid-Stimulating Hormone (TSH) secretion has been demonstrated by some authors, whereas a normal thyroid activity has been described by others. Changes of gonadal axis are common in patients with OSAS, who frequently show a hypogonadotropic hypogonadism. Altogether, hormonal abnormalities may be considered as adaptive changes which indicate how a local upper airway dysfunction induces systemic consequences. The understanding of the complex interactions between hormones and OSAS may allow a multi-disciplinary approach to obese patients with this disturbance and lead to an effective management that improves quality of life and prevents associated morbidity or death.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is an emerging public health problem and is characterized by repetitive upper airway occlusion episodes leading to apnea and asphyxia, typically occurring 100–600 times per night, with arousal being required to reestablish airway patency [1–3].

The most important epidemiological risk factors for sleep apnea are obesity and male gender [2, 4, 5]. OSAS is estimated to affect up to 7% of the adult male population, and its prevalence increases with advancing age, although the clinical severity of apnea decreases [4–6]. The increased risk of sleep apnea in male subjects may be due to differences in airway anatomy, pharyngeal dilator muscle function, and ventilatory control mechanisms [4, 5].

The pathophysiology of OSAS is complex and incompletely understood but is mainly based on an imbalance between the collapsing forces of the upper airway during inspiration and the counteracting forces of the upper airway dilating muscles [7, 8].

The sequence of events in an episode of apnea consists of upper airway constriction, progressive hypoxemia secondary to asphyxia, autonomic and EEG arousal sufficient to prompt one to open and clear the airway to reverse the asphyxia, followed by successive relaxation of the airway, upper airway constriction, and so forth. As the cycle repeats itself throughout the night, the patient's sleep is fragmented [8, 9]. Daytime sleepiness results, along with decreased cognitive performance, decreased quality of life and an increased risk of industrial and motor vehicle accidents [2, 4, 5]. Moreover, OSAS may increase the risk of developing some of the features of the metabolic syndrome, including hypertension, insulin resistance, and type 2 diabetes, leading to adverse cardiovascular consequences such as myocardial infarction and stroke [8, 10–13]. Thus, more than a local abnormality, OSAS should be considered a systemic disease [13].

Because the treatment of OSAS provides many benefits to patients and society, it is very important to obtain an early diagnosis. The diagnosis of OSAS is based on the combination of clinical features and compatible findings on instrumental tests in which multiple physiologic signals are monitored simultaneously during a night of sleep. Polysomnography is routinely indicated for measuring sleep stages and sleep-disordered breathing, for detection of OSAS [14–16]. The severity of OSAS is commonly expressed as the apnea/hypopnea index (AHI), which indicates the frequency of the apnea/hypopnea episodes per hour of sleep [2, 3, 17].

Nasal continuous positive airway pressure (nCPAP) is the initial treatment of choice for most patients because of its noninvasive approach and technical efficacy. It is worn on a nightly basis and acts like a constant pressure air splint to prevent collapse of the upper airway during sleep. nCPAP provides immediate relief of symptoms and has only minor side effects [18]. Nevertheless, an alternative treatment is needed if nCPAP is not feasible for medical or psychological reasons. Removable oral appliances that advance the mandible when fitted to the teeth during sleep also improve nocturnal breathing disturbances, symptoms, quality of life, and vigilance in OSAS patients. However, their long-term effectiveness and side effects require further study [19]. In morbidly obese patients suffering from OSAS bariatric surgery should be considered as a treatment that reduces obesity and at the same time improves OSAS [20]. In selected patients including those with adeno-tonsillar hypertrophy, and craniofacial malformations various surgical techniques that enlarge the upper airway may be a treatment option for OSAS, although the effectiveness in improving OSAS and snoring has been inconsistent and unpredictable [19, 21, 22].

An accumulating body of evidence shows that OSAS induces changes in the serum levels or secretory patterns of several hormones. These changes are not only related to obesity but may be due also to sleep fragmentation induced by apnea and hypopnea, to frequent arousals leading to an increase in stress hormone levels [23], to direct effects of hypoxia on central neurotransmitters with alterations in the hypothalamus-pituitary axes and in the secretion of the peripheral endocrine glands [24], and to the effects of hypercapnia which may increase levels of adrenocorticotropic hormone (ACTH) and adrenal hormones [9, 25]. Finally, the sleep pattern disruption, sleep loss, and naps cause an alteration of hormonal circadian rhythms.

In this review the neuroendocrine changes associated to OSAS in obesity will be revised. Namely, alterations of the growth hormone (GH)/insulin-like growth factor-I (IGF-I), adrenal, thyroid, and gonadal axes will be discussed.

2. Obstructive Sleep Apnea Syndrome and Obesity

Several clinical and epidemiological studies have demonstrated the strict association existing between OSAS and obesity. The incidence of OSAS among morbidly obese patients is 12- to 30-fold higher than in the general population [26]. Body mass index (BMI) has been shown to be the most important risk factor for OSAS, preceding age and male gender. In particular, the android-central type of obesity is strictly associated to OSAS. Neck circumference is the most important predictor of OSAS among obese subjects [4].

Several mechanisms are involved in the association of obesity and OSAS. These include upper airway alterations such as an increased collapsibility of the peripharyngeal tissues. The accumulation of adipose tissue in the neck and also in the pharyngeal structures induces an airway restriction and collapse during inspiration [19, 27]. Abnormalities in the chest wall dynamics, a reduced respiratory compliance, and an impaired respiratory muscle function contribute to the pulmonary dysfunction of severely obese patients [28].

Noteworthy, OSAS itself may predispose individuals to worsening obesity because of sleep deprivation, daytime somnolence, and disrupted metabolism [12, 18].

Weight reduction has been proven effective in reducing the severity of the sleep disturbance, probably through an influence on the upper airways structure and function [20, 29].

It is well known that simple obesity is associated with coronary heart disease (CHD) and is an established marker of cardiovascular risk. Obstructive sleep apnea is an independent risk factor for hypertension [10, 30] and is thought to be a cause of premature death, ischaemic heart disease, and stroke [13]. Moreover, OSAS is connoted by a specific worsening in endocrine and metabolic abnormalities which can account for a further increase in cerebro- and cardiovascular risk [13].

It is also well established that sleep deprivation has an impact on glucose metabolism [8, 11–13, 31]. A growing body of epidemiological evidence supports an association between chronic partial sleep deprivation and the risk for obesity, insulin resistance, and diabetes [31]. Because OSAS is associated with sleep fragmentation, effectively sleep loss, and daytime sleepiness, the insulin sensitivity in patients has been assessed and indeed insulin resistance has been reported [11, 32, 33] (Table 1). That OSAS is an independent risk factor for increased insulin resistance can be learned from improvement in insulin sensitivity after 3 months of treatment with nCPAP [34].

Recently, adipocytokines, adipocyte-specific secreted proteins, have been considered to play an important role in the progression of atherosclerotic disease in obesity and in OSAS. Of all adipocytokines, leptin and adiponectin have received the most attention. Despite the antiobesity effect of leptin, obese subjects often have increased serum leptin levels [35]. In contrast, adiponectin levels are decreased in obese individuals and are associated with insulin resistance and hyperinsulinemia [36, 37] (Table 1).

Serum leptin levels have been shown to be positively correlated with the severity of OSAS in obese subjects [37–39], suggesting that leptin is a hormonal factor affected by OSAS. However, Barceló et al. [40] did not observe a leptin decrease in obese OSAS during prolonged nCPAP treatment and recorded only a slight reduction in nonobese OSAS, speculating that the increased leptin levels described so far in patients with OSAS are mostly associated with obesity and not with the disease itself. Similarly, a correlation

between adiponectin concentrations and the severity of OSAS have been described by some [41, 42] but not by other authors [37] and nCPAP failed to increase adiponectin concentrations in obese patients with OSAS [43] (Table 1).

Interestingly, apart its antiobesity effects, leptin exerts important physiological effects on the control of respiration and has been suggested to be a better predictor than percent body fat for the presence of hypercapnia in patients with obesity-hypoventilation syndrome [44].

Ghrelin is a hormone that influences appetite and fat accumulation and its physiological effects are opposite to those of leptin. No clear relation has been found between ghrelin and OSAS (Table 1). In a study of 30 obese OSAS patients, plasma ghrelin levels were significantly higher in OSAS patients than in controls and rapidly decreased with nCPAP therapy, suggesting that the elevated ghrelin levels could not have been determined by obesity alone [45]. The appetite stimulating effects of ghrelin may contribute to increased caloric intake and weight gain in patients with OSAS [8]. In a study of 30 untreated obese patients with moderate-severe OSAS, significantly higher levels of serum leptin were found in OSAS patients than in controls, but ghrelin levels presented no such difference [39]. Thus, the relation between OSAS and ghrelin is still an unresolved issue.

3. Neuroendocrine Disturbances in Obstructive Sleep Apnea Syndrome

3.1. GH/IGF-I Axis. OSAS is connoted by a reduced spontaneous GH secretion, which seems to be due to the sleep respiratory disturbance and is restored by nCPAP treatment. Saini et al. [46] have shown that a single night nCPAP treatment is able to increase the duration of slow wave sleep and to normalize GH levels in obese subjects with OSAS. The treatment increases the amplitude but not the frequency of GH secretory bursts. These authors underlined the tight connection between sleep fragmentation and low circulating GH levels in untreated OSAS patients. Since no modification of the concomitant hyperinsulinemia was recorded after nCPAP treatment, they concluded that insulin did not play a role in the pathogenesis of GH reduction in these patients.

Cooper et al. [47] confirmed the effects of nCPAP treatment on GH secretion in obese patients with OSAS and demonstrated an increase of FFA concentrations indicating an increase of GH peripheral lipolytic action.

Reduced IGF-I levels have also been described in obese patients with OSAS [49]. This reduction is greater than in obese subjects without OSAS and is independent of BMI and age. These authors outlined the role of hypoxemia rather than sleep fragmentation in the pathogenesis of hormonal alterations and documented a significant increase in IGF-I levels three months after the initiation of nCPAP treatment.

Ursavas et al. [50] recently demonstrated that the low circulating IGF-I levels in patients with OSAS were negatively correlated with AHI, duration of apnea-hypopnea, arousal index, average desaturation, and oxygen saturation index. These authors have also hypothesized that the negative correlation between obesity and IGF-I levels that was found in previous studies can be related to the presence of OSAS in the majority of obese patients.

We have demonstrated that obese patients with OSAS show an impairment of both basal and stimulated GH secretion [48]. In fact, in obese patients with OSAS we have found basal GH levels similar to those recorded in patients with simple obesity and lower than in normal subjects, with a deeper reduction of the GH response to a provocative test as potent and reproducible as GHRH plus arginine [72]. Interestingly, this impairment occurred in the presence of basal IGF-I levels significantly lower than in simple obesity and not responsive to the short-term administration of a very low recombinant human GH dose. These data support the hypothesis that OSAS per se may impair GH/IGF-I axis activity, independently of adiposity. Accordingly, the reduction of nocturnal GH secretion of overweight patients with OSAS is reversed by nCPAP, before any significant variation in body weight occurs [46, 47]. Moreover, nCPAP has been found able to restore IGF-I levels in OSAS patients independently of body weight variations [49].

The mechanisms controlling sleep and GH secretion are tightly associated [73], and the amplification of somatotroph secretion during sleep, for example, III-IV stages, is well known [74]. Qualitative and quantitative sleep alterations in OSAS have been clearly demonstrated [75] and are improved by nCPAP treatment, together with GH and IGF-I secretion [46, 49]. In particular, slow-wave sleep is specifically and markedly reduced or absent in OSAS [76]. Thus, sleep-related alterations of the neuroendocrine control of GH secretion could also contribute to the peculiar impairment of GH release in obese patients with OSAS.

Insulin resistance can be also proposed to explain the impairment of GH/IGF-I axis activity in OSAS. In fact, insulin is able to inhibit GH synthesis and secretion [77] and to enhance GH-induced hepatic IGF-I production [78] (Figure 1).

Finally, hypoxia itself might impair both somatotroph function and the peripheral sensitivity to GH. In fact, animal studies have shown that acute as well as prolonged hypoxia reduces GH synthesis and release [71]. Moreover, hypoxia reduces IGF-I mRNA expression in endothelial cells in vitro [79], and low IGF-I levels have been shown in patients with ischemic dilated cardiomyopathy [80].

In conclusion, obese patients with OSAS show a peculiar reduction of both spontaneous and stimulated GH secretion coupled to reduced IGF-I concentrations and impaired peripheral sensitivity to GH. These endocrine abnormalities can be responsible for metabolic alterations, which are common in OSAS and increase the risk of cardiovascular events as well as mortality.

3.2. Prolactin. Plasma prolactin (PRL) concentrations exhibit a sleep-dependent pattern, with highest levels during sleep and lowest levels during the waking period. In human physiology, outside pregnancy, PRL secretion is altered by increasing body weight in both children and adults [81]. PRL in this circumstance appears to be a marker

Table 1: Main hormonal changes in obesity and obstructive sleep apnea syndrome (OSAS).

	OBESITY without OSAS	OBESITY with OSAS	Reference
GH	↓	↓↓	[46–48]
IGF-1	n or ↓	↓↓	[48–50]
PRL	↓	n or ↑	[49, 51–53]
ACTH	↑	↑	[51, 54, 55]
Cortisol	↑	n or ↑	[49, 53–60]
Aldosterone	↑	↑	[61, 62]
fT_3	n	n	[51]
fT_4	n	n	[49, 51]
TSH	n	n or ↓	[49, 51, 56, 63]
LH	n or ↓	n or ↓	[49, 56, 64]
FSH	n or ↓	n or ↓	[49]
Testosterone in ♂	↓	↓	[49, 65–68]
Free Testosterone in ♂	n or ↓	↓	[49]
Testosterone in ♀	↑	?	[69, 70]
SHBG	↓	↓	[49]
Insulin	↑	↑↑	[11, 31–33]
Leptin	↑	↑↑	[35, 37–40]
Adiponectin	↓	↓↓	[36, 37, 42, 43, 71]
Ghrelin	↓	?	[39, 45]

n: normal; ↑: increased levels; ↓: reduced levels.

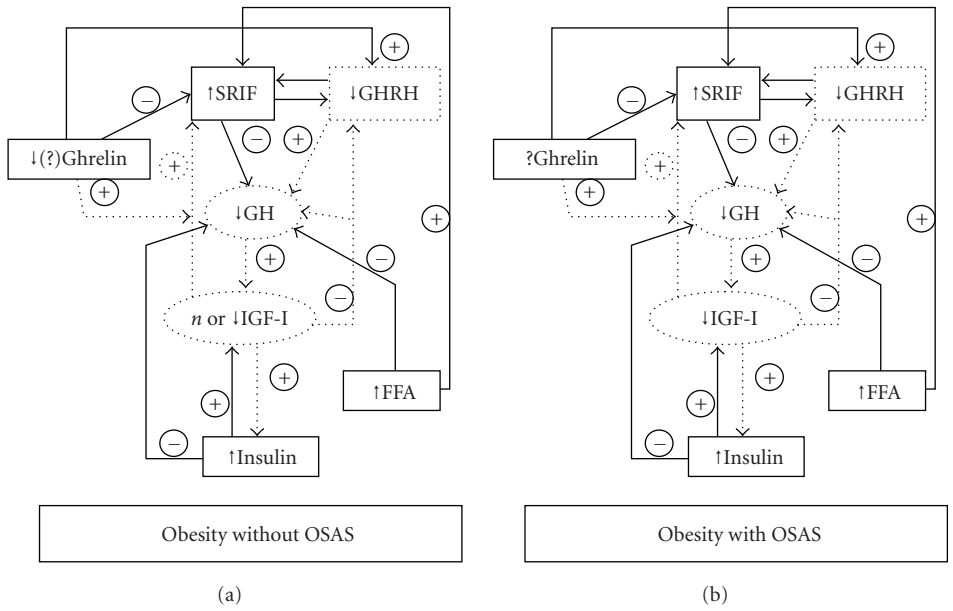

Figure 1: Regulation of GH secretion in obese patients without OSAS and obese patients with OSAS.

of hypothalamus-pituitary function: the PRL response to insulin-hypoglycaemia, Thyrotropin-Releasing Hormone (TRH) stimulation, and other stimulatory factors may be diminished [81–83]. In addition, obesity alters the 24 hour spontaneous release of PRL with a generalised dampening of release. These alterations seem to be due to obesity per se with its hyperinsulinaemic state as well as an interplay between PRL and leptin concentrations. Weight reduction, with accompanying decrease in plasma insulin levels, leads to a normalization of PRL responses in most, but not all, circumstances [81].

Studies on PRL secretion axis in OSAS provided conflicting results [49, 51, 84]. Hypoxemia and chronic sleep fragmentation in OSAS could affect the sleep-entrained PRL rhythm [52]. PRL secretion is reversibly elevated in an hypoxic stress response and can be a useful marker of acute, severe, illness-induced stress [53]. No correlation of PRL levels with OSAS severity and no changes induced by nCPAP

treatment have been described by Grunstein et al. [49] and by Meston et al. [53]. We have found similar basal PRL concentrations as well as PRL response to TRH in obese subjects with OSAS, in obese subjects without OSAS, and in normal lean controls [51]. On the other hand, Spiegel et al. [52] have described a lower PRL pulse frequency in untreated OSAS patients as compared to treated patients and have indicated that nCPAP treatment immediately restores a normal sleep structure and normalizes PRL release by restoring pulse frequency to values similar to those observed in normal subjects.

3.3. Adrenal Axis. A disrupted Hypothalamus-Pituitary-Adrenal (HPA) axis activity has been described in OSAS. Nocturnal awakenings are associated with pulsatile cortisol release [23] and autonomic activation. The latter leads to increased catecholamine release as well as Corticotropin-Releasing Hormone (CRH) and cortisol release. Sleep deprivation itself is associated with HPA axis hyperactivity [85].

The literature varies regarding the effects of OSAS on the HPA system. An enhanced cortisol secretion in patients with OSAS has been reported by some [54, 56, 57] but not by other authors [49, 53, 58, 59]. In a group of obese male patients with OSAS we have found normal adrenocorticotropic hormone (ACTH) and cortisol levels but an ACTH hyper-responsiveness to CRH that, in fact, was even more remarkable than that occurring in nonapneic obese patients [51]. This peculiar ACTH response pattern in obese OSAS patients indicates that factors other than obesity per se have a role in this clinical condition. In fact, a disrupted HPA axis function has been described in patients with abdominal obesity, including both neuroendocrine and peripheral alterations leading to inappropriately higher than normal exposure to cortisol of peripheral tissues, particularly the visceral adipose tissue. The disregulation of the HPA axis in abdominal obesity has been demonstrated also by many dynamic studies showing both a high cortisol secretion after laboratory stress test and a hyper-responsiveness after various provocative stimuli [86]. Altered HPA axis activity in obesity may also derive from a dysruption of the catecholaminergic regulation in the central nervous system, particularly during acute and chronic stress challenges [87].

Hypoxia is likely to directly or indirectly play a critical role in the alteration of the HPA axis activity in OSAS, since it has been shown able to induce HPA axis activation both in animals and in humans [88, 89]. In fact, an hypoxic state is likely to represent a stressful condition that, in turn, could well trigger the HPA axis. Moreover, sleep-related alterations of the neuroendocrine control of anterior pituitary function could contribute to the peculiar alteration of ACTH secretion in obese patients with OSAS.

Several studies have primarily focused on the effects of nCPAP on cortisol. Some authors have reported that nCPAP does not reduce cortisol levels [49] or that acute withdrawal of nCPAP therapy does not result in an increase in cortisol levels [90]. In contrast, other studies have reported that nCPAP does reverse hypercortisolemia [91], particularly with prolonged use [56]. Noteworthy, several of these studies were limited in that cortisol was measured at a single time point, and consequently they do not measure potential clinically important HPA axis and rhythm changes. Vgontzas et al. [55] have demonstrated that sleep apnea in obese men is associated with increased cortisol levels during the night, compared with nonapneic obese controls, which is corrected after the use of nCPAP for 3 months. The correction of the increased cortisol appears to be related to the elimination, through nCPAP, of the stress of repetitive respiratory pausing and sleep fragmentation and/or better oxygen saturation [55]. Finally, Carneiro et al. [60] have recently indicated that men with OSAS present a blunted response of cortisol suppression after dexamethasone, which is recovered after 3 months of nCPAP therapy.

When untreated, this HPA axis hyperactivity in OSAS may be a risk factor for the metabolic syndrome, and also for insomnia and depression, which are both associated with hypercortisolemic states. Similar sleep EEG changes were found in depression and Cushing's disease, and a role for obstructive sleep apnea has been suggested [92].

Several components of the renin-angiotensin-aldosterone system (RAAS) are elevated in obese humans [61] and play an important role in the etiology of obesity hypertension [93]. In addition, plasma renin activity declines with weight loss and is correlated with the reduction in blood pressure [94, 95].

To our knowledge, there is a lack of data on the effects of OSAS on the mineralocorticoid axis, although hypertension is common in OSAS patients and may result from prolonged repetitive stimulation of the renin-aldosterone axis [96]. Moreover, it is well recognized that renin is elevated in response to systemic illness [97]. However, Meston et al. [53] did not find a relationship between OSAS severity and aldosterone or renin levels in overweight and obese OSAS patients. A recent report demonstrated that elevated aldosterone is a cause of hypertension in OSAS, but the cause of hyperaldosteronism was unknown [62]. Since ACTH stimulates both aldosterone and cortisol synthesis and secretion, it has been hypothesized that the HPA axis hyperactivity from OSAS may increase aldosterone and thereby contribute to hypertension [9]. This same mechanism has been proposed for explaining hypertension in depression [98].

3.4. Thyroid Axis. A link between OSAS and hypothyroidism is suggested by the high prevalence of sleep apnea among hypothyroid patients, particularly in rare myxoedematous patients [99, 100]. The increased prevalence of OSAS appears to be related to obesity and male sex rather than to hypothyroidism per se [101]. However, decreased ventilatory responses [102], extravasation of albumin and mucopolysaccharides in the tissues of the upper airway [103, 104], and hypothyroid myopathy [99] have been suggested as possible contributing factors for OSAS in hypothyroidism.

In patients with OSAS, the prevalence of hypothyroidism is 1%–3% [100, 105], which is not different from that in the general population.

In a group of obese patients with OSAS we have not found an impaired thyroid activity in basal conditions nor

an altered TSH response to TRH challenge test [51], in agreement with some but not other studies. In fact, some derangement in TSH secretion in obesity with or without OSAS has been demonstrated [49, 56, 106].

As with other forms of systemic illness, suppression of thyroid responsiveness occurs during the development of OSAS with reversal of these changes during treatment [63]. Bratel et al. [56] have reported a more pronounced reduction of serum TSH in OSAS patients with the most severe nocturnal hypoxemia, with a normal TSH response to TRH before and after nCPAP treatment. However, TSH levels decreased even further after 7 months of nCPAP therapy [56]. In 101 overweight and obese male patients, Meston et al. [53] have described a small significant inverse correlation between OSAS and free T4 levels but not TSH, with no apparent association between obesity and either hormone. One-month nCPAP treatment compared to placebo resulted in a significant reduction in TSH without elevation in free T4 levels, consistent with the pattern of recovery from non-thyroidal illness.

Biochemical screening for hypothyroidism in patients with OSAS is not considered necessary by many authors unless the patient is symptomatic or belongs to a risk group [105, 107, 108]. However, given the overlap in clinical presentation of primary OSAS and hypothyroidism, some authors indicate that screening for hypothyroidism is required to prevent misdiagnosis and that it is a cost-effective component of the investigation of sleep apnea [109].

Contrasting data are available concerning the efficacy of thyroid replacement therapy in improving sleep apnea in patients with clinical hypothyroidism. Some authors describe a prompt reversal of symptoms, sleep-disordered breathing, and nocturnal hypoxia [109] while little or no improvement in sleep apnea is reported by others [108].

3.5. Gonadal Axis. Among endocrine disturbances, changes of gonadal axis are common in patients with OSAS, who frequently show a hypogonadotropic hypogonadism likely due to alterations of the hypothalamic-pituitary control of gonadotropin synthesis and release. In particular, decreased morning and nocturnal testosterone concentrations have been found in lean and obese male patients with OSAS [49, 64–66] with an increase after uvulopalatal resection [65] or normalization after nCPAP treatment [49, 67]. Changes in sleep efficiency and architecture have been associated with alteration in pituitary-gonadal function in healthy older men [110, 111]. In young adults, the sleep-related rise in testosterone has been linked with the first rapid eye movement (REM) sleep episode and has been shown to be dependent on the integrity of the sleep process [112].

Gonadotropin levels have been found reduced both basally and after gonadotropin-releasing hormone (GnRH) stimulation but only partially reverted by hypoxia correction [49, 53]. Reduced Sex Hormone-Binding Globulin (SHBG) concentrations coupled to low testosterone levels and correlating to OSAS severity support a diagnosis of secondary hypogonadism [49, 53]. SHBG levels have been reported to rise during active nCPAP treatment [49, 53].

A significant correlation between LH/testosterone profiles and the severity of OSAS is described, thus suggesting that sleep fragmentation and hypoxia in addition to the degree of obesity may be responsible for the central suppression of testosterone in these patients. Moreover, testosterone concentrations fall with prolonged physical stress, sleep deprivation, and sleep fragmentation in normal young and elderly males [111–113]. Finally, hypoxia decreases LH and testosterone levels and alters circadian rhythm of testosterone secretion [24, 68, 114]. It has also been hypothesized that decreased testosterone levels may be part of an adaptive homeostatic mechanism to reduce sleep disordered breathing assuming that testosterone aggravates it [49, 115]. In fact, androgen levels can directly influence the prevalence and severity of sleep-disordered breathing and some reports have demonstrated that administration of exogenous androgens to both men and women can induce or precipitate apnea [116, 117]. However, few studies have systematically evaluated the effects of exogenous androgen replacement therapy on OSAS. Testosterone replacement therapy induced OSAS in one of five males and aggravated a preexisting sleep disordered breathing in another [117]. In 11 hypogonadal males, testosterone replacement increased apneic events but only in three subjects was the increase considered statistically significant [118]. In a placebo-controlled study of 17 overweight elderly males with partial androgen deficiency, testosterone replacement therapy decreased total sleep time and sleep efficiency and aggravated sleep apnea [119].

The few available data from females with sleep disordered breathing support the link with androgens. Irrespective of the menopausal state, obese females have higher androgen levels than nonobese females [69, 70]. In a lean, 70-year-old woman, a testosterone producing tumour caused sleep apnea, which disappeared after removal of the tumour [120].

Female hormones are thought to protect women from OSAS until menopause [121]. In clinical studies, male : female ratio of OSAS is $\sim 10 : 1$ [4, 122]. Among females referred to a sleep clinic, 47% of the postmenopausal and 21% of the premenopausal females had sleep apnea [123]. In a large community-based study, 1.9% of postmenopausal females and 0.6% of premenopausal females had OSAS, defined as AHI ≥ 10 and occurrence of daytime symptoms [6].

Menopause-related changes in body fat distribution, from gynoid phenotype to android features, may include deposition of fat around the upper airway [124]. The effect of menopause on body fat distribution is ascribed to declining levels of estrogen and progesterone and appears to be reversed or attenuated by the use of replacement hormones [125]. Declining levels of these hormones might also predispose some women to sleep-disordered breathing by lowering the ventilatory drive to the upper airway, leading to an imbalance between the collapsing forces of the upper airway during inspiration and the counteracting forces of the upper airway dilating muscles.

4. Conclusions

OSAS is a serious, prevalent condition which is strongly associated with obesity and has significant mortality and morbidity when untreated. Sleep fragmentation and hypoxia are likely to play a prevalent role in causing cardiovascular alterations that increase morbidity and mortality in comparison with simple obesity. The same factors can also be responsible for the endocrine abnormalities in OSAS that are frequently more marked than those in nonapneic obese patients. These abnormalities may be considered as adaptive changes which indicate how a local upper airway dysfunction induces systemic consequences. On the other hand, the same abnormalities can also contribute to the maintenance or progression of OSAS itself.

The recognition and understanding of the complex interactions between hormones and OSAS may allow a multidisciplinary approach to obese patients with this disturbance. Effective assessment and management of OSAS in obesity may correct endocrine changes, improve quality of life, and prevent associated morbidity or death.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 759509, 9 pages
doi:10.1155/2010/759509

Review Article

Sleep and Diabetes

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Received 28 July 2009; Accepted 2 January 2010

Academic Editor: Jessica A. Mong

Sleep apnea is clinically recognized as a heterogeneous group of disorders characterized by recurrent apnea and/or hypopnea. Its prevalence ranges from 4% to 24%. It has been implicated as an independent risk factor for several conditions such as hypertension, stroke, arrhythmia, and myocardial infarction. Recently data has been emerging which suggests an independent association of obstructive sleep apnea with several components of the metabolic syndrome, particularly insulin resistance and abnormalities in lipid metabolism. We hereby review the salient features of the association between sleep and diabetes.

1. Introduction

Sleep apnea is clinically recognized as a heterogeneous group of disorders characterized by recurrent apneas (complete cessation of breathing) and/or hypopnea (decrease in airflow with desaturation of 4%) [1]. It is estimated that obstructive sleep apnea may affect at least 2%–4% of the general population, with prevalence estimates that may be much higher based on demographic variables such as age, sex, and body mass index (BMI) [2]. The apnea-hypopnea index (AHI) was defined as the total number of obstructive apneas (cessation of airflow for at least 10 seconds) and hypopneas (decrease of the airflow signal amplitude by at least 50% accompanied by oxyhemoglobin desaturation of at least 4% or by an arousal) per hour of sleep [3]. An AHI of 10 or higher and excessive day-time somnolence has also been used to define obstructive sleep apnea (OSA), finding similar figures in a large cohort of male subjects [4]. Data from Sleep in America poll by The National Sleep Foundation showed that approximately 25% of adults and 57% of obese individuals are at high risk for obstructive sleep apnea (OSA) [5]. Sleep apnea has been implicated as an independent risk factor for hypertension, myocardial infarction, and stroke [6].

Diabetes Mellitus is a well-established risk factor for cardiovascular disease. Data from the Third National Health and Nutrition Examination survey indicate that 5.1% of adults in the United States have physician diagnosed Diabetes Mellitus and an additional 2.7% meet the criteria of diabetes but remain undiagnosed [7]. Given the pandemic of obesity, the prevalence of Type 2 Diabetes Mellitus(DM) and metabolic syndrome has also increased dramatically over the last decade [8–12]. DM affects approximately 6% of adults in the United States [13]. There have been several studies which have suggested an independent association of obstructive sleep apnea with several components of metabolic syndrome, particularly insulin resistance and abnormalities in lipid metabolism [14–17].

There has been data that long-term intermittent hypoxia and sleep fragmentation increase sympathetic activity, which in turn lead to disorders of glucose metabolism [18]. Alternatively some studies have suggested that insulin resistance and chronic hypoxemia may in turn lead to development of sleep apnea syndrome [19].

The Sleep Heart Health Study found that subjects with DM had increased sleep disordered breathing and more severe hypoxemia [20]. Factors influencing and increasing the risk of sleep apnea include male sex [1, 21, 22], obesity [23, 24], age [4, 25], and race [25, 26]. Studies done to look at the association of DM as an etiologic factor for sleep apnea have suggested that autonomic neuropathy may be a responsible for dysfunction of central respiratory control

of the diaphragm and decreased upper airway tone. Somers et al. found that sleep disturbance negatively affects glucose metabolism and endocrine function. After six nights of four hour sleep, sympathetic nervous activity has increased ($P < .02$) [27]. Findings from epidemiological studies indicate that sleep apnea is independently associated with hypertension [28] and cardiovascular disease [29]. A growing body of literature suggests that sleep apnea is associated with fasting hyperglycemia, insulin resistance, and DM [30].

Several factors have been associated with diabetes in sleep from obesity to altered glucose metabolism. Insulin resistance, glucose intolerance, REM sleep and diabetes, and the effect of sleep apnea treatment on diabetes have been implicated as causation factors. We will try to summarize this complex subject in as simple a form as possible.

2. Obesity, OSA, and Diabetes

Obesity is generally regarded as a risk factor for both OSA and Insulin resistance [31, 32]. During the past 20 years, the prevalence of obesity and DM in the United States has increased consistently [33]. Obesity, in particular central obesity, is the strongest risk factor for sleep apnea [34–41]. OSA is prevalent particularly among middle-aged, obese men, although its existence in women and lean individuals is being increasingly recognized.

There is an alarming rise in the prevalence of DM that may be largely attributed to the epidemic of obesity [42]. The strongest risk factor for both DM and OSA is obesity with a high visceral (central) fat distribution [43, 44]. Approximately two thirds of all patients with OSA are obese, and the effect of obesity as a predictor of OSA is 4 times greater than the influence of age and twice as great as the influence of male gender [44].

Obesity, macroangiopathy, hypertension, and dyslipidemia often coexist both in OSA and in NIDDM. However, factors other than obesity appear to play a significant role in the development of insulin resistance and metabolic disturbances in patients with OSA [45–50] including sleep fragmentation, increased sympathetic activity, and intermittent hypoxia [27, 51–54].

3. Obesity and Insulin Resistance

The prevalence of overweight and obesity in the United States and other industrialized countries is rapidly increasing. Over the last 40 years, the average body mass index (BMI) in men and women aged 20–74 yrs has increased from just over 25 Kg/M^2 to almost 28 Kg/m^2 [55–57].

It is also recognized that many subjects with OSA have central obesity and other features of metabolic syndrome [39], which is most widely accepted as being comprised of hyperinsulinemia, glucose intolerance, dyslipidemia, central obesity, and hypertension [58]. Insulin resistance is increased with increasing levels of obesity, but the reasons for this are not completely clear. As weight increases, the risk to develop complications such as hypertension, insulin resistance, diabetes mellitus, sleep disordered breathing, and obstructive sleep apnea syndrome increases [59].

The relationship of OSA with insulin resistance [47] may be the pathway that leads to increased risk for the development of cardiovascular disease in some patients. It has been observed that OSA patients have increased leptin [60] and C-reactive protein(CRP) [61], indicating a possible role in the pathogenesis of cardiovascular morbidity. Punjabi et al. [62] found that CRP is associated with nocturnal hypoxia. Thus, obesity is strongly associated with OSA [63], insulin resistance [64], leptin [65], and CRP [66] levels and may be the major confounding factor in the relationship of OSA to insulin resistance and cardiovascular morbidity.

4. OSA and Insulin Resistance

Several studies have tried to establish the association between OSA and diabetes [67–70]. Van Cauter et al. have shown that experimentally induced acute sleep deprivation can cause a state of glucose intolerance [71]. OSA can affect the metabolism indirectly, by decreasing the quantity and/or quality of sleep [5]. Insulin resistance has been induced among healthy volunteers by sleep restriction. Sleep restriction on the other hand has also resulted in an increase in evening cortisol level and sympathetic activation [72].

A number of studies have also examined the cross-sectional relationship between OSA, as assessed by overnight polysomnography, and metabolic abnormalities [31, 39, 48–50, 67–69, 73–75]. Most of the studies suggest that OSA is related to impaired glucose tolerance and insulin resistance. Recent studies also confirm the high prevalence of habitual snoring in DM [73], or higher prevalence of metabolic syndrome in habitual snorers [74]. Over the past decade there has been increasing clinical and experimental evidence of the association between insulin resistance and OSA in non obese diabetic patients with autonomic neuropathy [75]. A laboratory-based investigation showed that diabetic patients with autonomic neuropathy are more likely to have OSA and central apnea than diabetic patients without autonomic neuropathy [76, 77].

Frequent snoring was associated with reduced glucose tolerance, as assessed by abnormal oral glucose tolerance tests (OGTTs) results and higher levels of HbA1c [78]. Another study done in the United States with a sample size of 150 healthy men reported that AHI and the degree of nocturnal desaturation were associated with glucose intolerance and insulin resistance independent of obesity [31].

Finally, concrete evidence came from the Sleep Heart Health Study [47]. In a community sample of 2656 subjects, the AHI and average oxygen saturation during sleep were associated with elevated fasting and 2-hour glucose levels during an oral glucose tolerance test. Sleep apnea severity was also associated with the degree of insulin resistance independent of BMI and waist circumference, amongst other confounders.

Thus, there is a strong evidence which indicates that OSA and the risk of type 2 diabetes are associated, but the evidence supporting a role for OSA in the development of type 2 diabetes is still fairly limited. The reverse direction of causality (i.e., that diabetes may be a cause for breathing

abnormalities during sleep) is also possible, as autonomic neuropathy could indeed disturb the control of respiration.

Meslier et al. [79] studied 595 men who were referred to a sleep laboratory for suspected OSA. The cross-sectional data from polysomnography and 2-hour oral glucose tolerance tests (OGTTs) revealed that DM was present in 30.1% of OSA patients and 13.9% of nonapneic snorers.

Studies in humans at high altitude [80] have indicated that sustained hypoxia adversely affects glucose tolerance and insulin sensitivity. Excessive daytime sleepiness (EDS) is a frequent, but not universal, symptom in patients with OSA [81] and recent evidence suggests that EDS may be an independent risk factor for diabetes [82]. In this study, it was hypothesized that EDS was associated with insulin resistance in OSA (independent of obesity), and that continuous positive airway pressure (CPAP) therapy improves both conditions, and our results confirm this hypothesis. The fact that EDS is also a marker of blood pressure response to CPAP therapy in patients with OSA [81–83] suggests that EDS is a potentially relevant clinical marker of several clinical manifestations of OSA.

Vgontzas et al. [19] suggested that insulin resistance was a risk factor stronger than BMI and testosterone plasma levels for OSA and daytime sleepiness in premenopausal women suffering from polycystic ovarian syndrome. More recently, Punjabi et al. [84] found in 150 healthy mildly obese men that the severity of OSA correlated with levels of insulin 2 hours after an oral glucose load and reported a twofold increase in insulin resistance in subjects with an AHI 65, after controlling for BMI and percent body fat. Manzella et al. [75] observed that in 185 subjects with OSA, after adjusting for obesity, both AHI and minimum oxygen saturation were independent determinants of insulin resistance (the degree of insulin resistance increased by 0.5% for every single hourly increase in the AHI).

Ficker et al. [85] assessed the presence of OSA (AHI 610) in a group of diabetic patients with and without diabetic autonomic neuropathy (DAN). They found a prevalence of Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) amounting to 26% in diabetics with DAN; whereas none of the diabetics without DAN met the criteria for OSAHS. Neumann et al. [77] demonstrated a close correlation between nocturnal oxygen desaturation and the presence of DAN in a population of diabetic patients. In humans, as mentioned, several studies have shown increased sympathetic nervous system activity and increased catecholamine which in turn results in hyperinsulinemia [27, 72, 86–88]. Figure 1 illustrates the relationship between OSA, insulin resistance, and DM.

5. OSA and Endocrine

It is reported that the morbidity of acromegaly, diabetes, and thyroid disorders may, to a large extent, be ascribed to an altered sleep function [89].

Hypoxia mediated enhanced activation of the sympathoadrenergic system increasing plasma insulin despite the glycemic level was demonstrated in a study by Elmarsy et al. [48]. Sympathetic hyperactivity can influence glucose homeostasis by increasing glycogen breakdown and gluconeogenesis. Further, predisposition toward metabolic dysfunction in sleep apnea may also occur through its effects on the hypothalmic-pituitary-adrenal (HPA) axis. Experimental partial or total sleep deprivation has been shown to increase plasma cortisol level by 37% and 45%, respectively [90]. OSA to insulin resistance in humans has not been fully elucidated. Several plausible explanations can be proposed. Leproult et al. [91] hypothesized that the pathway between OSA and glucose intolerance was stimulation of the HPA axis due to hypoxias and fragmented sleep and leading to an increase in cortisol with corresponding hyperglycemia. For example, physical inactivity (due to day time somnolence) and sleep deprivation may be important contributing factors. OSA is also characterized by a proinflammatory state and elevated cytokine levels (e.g., tumor necrosis factor-alpha) which may lead to insulin resistance [52–54, 92]. TNF-α is usually elevated in individuals with obesity-induced insulin resistance. Studies have suggested that subjects with OSA had higher concentrations of IL-6 and TNF-α than obese subject without OSA [93].

Insulin resistance is also caused by increased lipolysis and fatty acid availability [93–95]. OSA may act through this mechanism by virtue of its association with central obesity and sympathetic activation [27]. Sympathetic activation rises circulating free fatty acids via stimulation of lipolysis and promotes insulin resistance [96].

Leptin, IL-6, and inflammatory mediators have also been implicated in the pathogenesis of insulin resistance and other features of metabolic syndrome [97, 98]. There have been several studies which have suggested an independent association of obstructive sleep apnea with several components of metabolic syndrome, particularly insulin resistance and abnormalities in lipid metabolism [14–17].

On the other hand, there is increasing evidence that Non Insulin Dependent Diabetes Mellitus (NIDDM) and OSA may be directly related throughout sleep disordered breathing-(SDB-) induced insulin resistance. Indeed, sleep fragmentation due to repetitive apneas may increase the plasma catecholamine and cortisol levels. These counter regulatory hormones induce glycogenolysis, gluconeogenesis, lipolysis with increased free fatty acid portal levels, and glucagon secretion, thus predisposing to hyperinsulinemia. However, other factors, including hypercarbia and recurrent arousals from sleep, can also increase autonomic output [27, 99, 100].

6. Diabetes and REM Sleep

Blood glucose homeostasis is subject to tight control exerted by the endocrine system [101]; nonetheless, both ultradian factors and different stages of sleep influence insulin secretion, concentration, and resistance [102, 103].

Insulin resistance increases towards the middle of the night with a subsequent decrease; as nonrapid eye movement (NREM) sleep is more frequent and longer in the first half of the night and rapid eye movement (REM) sleep in the second half of the night, sleep patterns may be implicated [104]. REM sleep is a physiologic and repetitive behavioral state

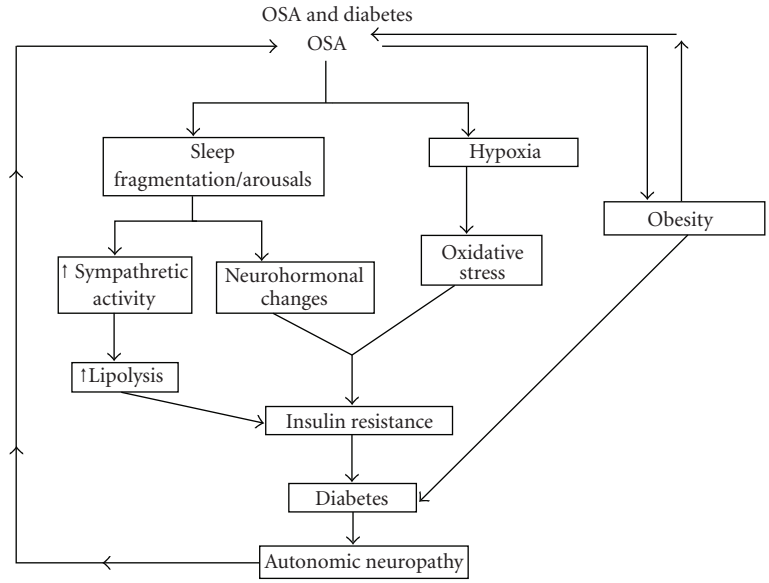

Figure 1: It illustrates the relationship of Obstructive Sleep Apnea and Diabetes.

in which high cerebral energy requirements correspond to a sustained neuronal activity [105]. REM sleep is accompanied by increased cerebral glucose utilization and cerebral blood flow [106, 107]. A decreased concentration of insulin and glucagon has been observed in REM sleep [102].

The higher prevalence of diabetes in OSA patients who have worse REM related respiratory events may be related to the unique neuroendocrine aspects of REM sleep, and their possible disruption as a consequence of sleep-disordered breathing. A decreased concentration of insulin and glucagon has been observed in REM sleep [108]. Hypoxemia is an important stimulus for altering autonomic activity, with larger desaturation causing greater increase in sympathetic activity [109, 110]. REM sleep is known to be associated with increased sympathetic activity [111]. REM sleep (and loss of muscle tone) triggers marked increases in sympathetic-nerve activity involving muscle blood vessels. REM-sleep twitches result in surges in blood pressure, and despite evidence of increased vasoconstriction in animals, we found a suppression of sympathetic-nerve activity in our subjects [111]. Thus, REM sleep is found to be associated not only with insulin resistance and diabetes but it also results in hypoxaemia due to sympathetic hyperactivity as well as a variable blood pressure surge which eventually increases the severity of diabetes and its risks. The study by Surani et al. [112] showed a very high prevalence of diabetes in an unselected cohort of Hispanic patients with obstructive sleep apnea compared to Caucasian. A REM apnea-hypopnea index of >20 was significantly associated with an increase prevalence of diabetes in Hispanic population. The brain, which constitutes 2% of body mass, depends entirely on glucose metabolism and utilizes approximately 50% of total body glucose [113]; it extracts about 10% of blood glucose without the need of insulin to cross the blood-brain barrier due to facilitated glucose transport [114]. In numerous physiological respects, REM is a distinctive sleep phase, with brain activation reflected by a 30% larger blood flow compared with quiet wakefulness, which relates to augmented glucose consumption [115].

7. OSA Treatment (CPAP) and Insulin Resistance

The effect of CPAP treatment on glucose metabolism has been evaluated in multiple studies [93, 116–129]. Trenell et al. reported that CPAP treatment for 2 days rapidly improved the insulin sensitivity in nondiabetic patients and the effect of CPAP persisted for approximately 3 months after treatment [123].

Brooks et al. found that obese patients with DM often complained of excessive daytime sleepiness, fatigue, and tiredness. In their study, patients with OSA were treated with CPAP. After four months of treatment, the insulin responsiveness had significantly improved [130]. Several other studies about successful treatment of OSA with CPAP have been shown to produce improvement in insulin sensitivity [59, 110, 119, 121, 122, 130–132]. Interestingly, most of the studies suggest that the lower the BMI, the better response in the insulin sensitivity improvement after CPAP treatment [59]. When OSA is timely and properly treated the results seen are not only a decrease in daytime excessive sleepiness, but also a decrease in cardiovascular risk, and in improvement of insulin resistance [1, 22]. In a study by Babu et al. [122], subjects who used CPAP for more than four hours per day had a significant reduction in HbA1c level. Recent studies have linked untreated sleep disordered breathing to hypertension, insulin resistance, coronary disease, congestive heart failure, stroke, obesity, and gastro esophageal reflux [59].

More recently, in a population-based sample, Lindberg et al. [133] showed reductions in fasting insulin levels and insulin resistance (estimated by HOMA) after 3 weeks

of CPAP treatment in 28 men with OSA compared with matched nonapneic (AHI, ˍ 10) control subjects followed over the same time period without CPAP therapy. Czupryniak et al. [121] also suggested that in non-diabetic patients, increased blood glucose was seen after one night of CPAP therapy, with a tendency to higher fasting insulin and insulin resistance after CPAP. This was felt to be secondary to a CPAP-related increase in growth hormone. A few studies reported decrease in visceral fat after CPAP use [131] while another study found no change [134]. Three independent preliminary studies presented in abstract form have suggested a positive response to CPAP therapy with improvements in insulin sensitivity [135], fasting, [136], and nocturnal [137] glucose levels in both diabetic and nondiabetic patients with OSA. However, the effect of CPAP therapy on metabolic syndrome is controversial. The author feels that recent studies have increasingly been favoring the role of CPAP therapy in enhancing insulin sensitivity. Several studies are currently ongoing which we hope can help to resolve the issue.

8. Conclusion

Diabetes Mellitus and Obstructive Sleep Apnea are extremely common medical conditions that are prevalent in our population. There is mounting evidence which links sleep deprivation, obesity, and sleep-related breathing to diabetes. Studies have established the association of OSA with diabetes as well as the importance of timely CPAP therapy in decreasing the insulin resistance in patients. However, despite the availability of convincing evidence and abundant cross-sectional studies, there is clearly a substantial requirement for a well-designed prospective study to clearly address these issues in depth. It is imperative for physicians to have a high degree of suspicion regarding the reciprocal prevalence of diabetes mellitus and obstructive sleep apnea. Moreover, there is lot to be done in educating Family physicians regarding the association of OSA and diabetes.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 108641, 7 pages
doi:10.1155/2010/108641

Research Article

Prolonged Sleep Restriction Affects Glucose Metabolism in Healthy Young Men

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Received 31 July 2009; Revised 13 November 2009; Accepted 10 February 2010

Academic Editor: Deborah Suchecki

This study identifies the effects of sleep restriction and subsequent recovery sleep on glucose homeostasis, serum leptin levels, and feelings of subjective satiety. Twenty-three healthy young men were allocated to a control group (CON) or an experimental (EXP) group. After two nights of 8 h in bed (baseline, BL), EXP spent 4 h in bed for five days (sleep restriction, SR), followed by two nights of 8 h (recovery, REC). CON spent 8 h in bed throughout the study. Blood samples were taken after the BL, SR, and REC period. In EXP, insulin and insulin-to-glucose ratio increased after SR. IGF-1 levels increased after REC. Leptin levels were elevated after both SR and REC; subjective satiety remained unaffected. No changes were observed in CON. The observed increase of serum IGF-1 and insulin-to-glucose ratio indicates that sleep restriction may result in an increased risk to develop type 2 diabetes.

1. Introduction

Sleep is considered to be a restorative process with beneficial effects on many bodily systems, including the digestive system, the immune system, and the cardiovascular system. Yet in modern industrialized societies, voluntary restriction of sleep is getting increasingly common due to, for instance, increasing work demands and atypical working hours [1]. Moreover, partial loss of sleep is common among people who experience environmental or psychological stress, who have psychiatric or physical disorders or who participate in shift work [2]. The consequences of this chronic deficiency of sleep are numerous and include increasing amounts of accidents, both in traffic and at work, increased prevalence of certain diseases, and even increased mortality [2]. It is important to understand and elucidate the mechanisms through which sleep and health are related if we are to find ways to manage people with chronically restricted sleep.

Sufficient sleep is a key component in the regulation of energy metabolism. Several epidemiological studies have shown that habitual short sleep duration is correlated with an increased risk of developing obesity and diabetes [3, 4]. Controlled laboratory studies, investigating the effects of prolonged sleep restriction on energy metabolism, are more scarce. Glucose tolerance has been shown to be impaired after six days of sleep restricted to four hours per night, compared to a condition in which participants were allowed twelve hours in bed per night for six days [5], which might contribute to the risk of developing type 2 diabetes. Furthermore, it has been shown that two nights of sleep restricted to four hours, compared to two nights of ten hours in bed, results in a reduction of the satiety hormone leptin, accompanied by increased hunger and increased serum concentrations of the orexigenic factor ghrelin [6], which might add to the risk of developing obesity.

Rodent studies on energy metabolism have mainly applied either a total sleep deprivation or a selective REM sleep deprivation design, which are both difficult to compare to a sleep restriction design. Everson and Crowley showed, in rats, that 15 days of sleep restriction suppress concentrations

of IGF-1 and leptin [7], which was, interestingly, accompanied by weight loss. Bodosi and colleagues have shown, on the other hand, that 5 h sleep deprivation does not affect leptin concentrations but increases ghrelin concentrations [8].

In the present study, we simulated accumulating sleep restriction during five working days followed by two days of weekend recovery sleep and measured the changes in several metabolic parameters that occurred during this period, including glucose metabolism, serum leptin concentrations, and feelings of satiety.

2. Materials and Methods

2.1. Participants. Twenty-three healthy men, aged 19–29 (mean ± SD 23.1 ± 2.5), participated in this study and were recruited by advertisements in local newspapers during a two-year time span. First, volunteers were screened during a telephone interview, followed by a thorough physical examination, blood tests (triglycerides, cholesterol, haemoglobin, creatinine, leukocytes, erythrocytes, haematocrit, TSH, ASAT, ALAT, MCV, MCH, and MCHC), and screening polysomnography. Participants' final eligibility was evaluated according to preset inclusion and exclusion criteria. Volunteers were excluded from participation for any of the following: an irregular sleep-wake schedule, regular naps, having either advanced or delayed sleep phase syndrome, insomnia or other sleep problems, loud snoring >5 nights/week, repeating apneas, excessive daytime sleepiness (Epworth Sleepiness Scale >8), restless legs at least once a month, a disorder that might become worse because of prolonged wakefulness (such as a severe mental disorder, epilepsy, and cardiac arrhythmia), excessive caffeine consumption (>5 cups of coffee/day), excessive alcohol consumption (>15 units/week; 1 unit = 11 g or 13.9 mL of alcohol), smoking, medication affecting the central nervous system during the last two weeks, any clinically relevant abnormality on blood tests, any other reason that health may be harmed because of if participating, apnea-hypopnea index >20, periodic limb movement index >25, epileptiform activity on the EEG, abnormal urinary drug screening, and having experienced a significant recent life event that could disturb sleep. In addition, volunteers were only included when fulfilling all of the following criteria: male aged 19–29, sleep latency in the evening <20–30 minutes, uninterrupted nocturnal sleep and if awakened no problem to fall asleep again, no chronic disease or symptom affecting sleep, no continuous medication, and willing and able to participate.

All participants reported habitual sleep duration of 7–9 hours and a regular sleep-wake schedule. For at least one week prior to the experiment they completed sleep diaries and carried actigraphs in order to verify adherence to a regular sleep-wake schedule. One week prior to the start of the experiment, participants had an adaptation night in the sleep laboratory. The prestudy mean (±SD) sleep duration was 6.88 (±0.58) h in the control group and 7.05 (±0.80) h in the experimental group. Participant's prestudy mean (±SD) body mass index (BMI) was 23.24 (±2.39) in the control group and 23.25 (±2.70) in the experimental group.

2.2. Experimental Protocol. The protocol was approved by the ethical committee of the University Hospital of Helsinki District, and written confirmed consent was obtained from all participants. A 10-day experimental schedule (Figure 1) was executed at the Brain and Work Research Centre of the Finnish Institute of Occupational Health (FIOH). Altogether, participants spent ten consecutive nights in the sleep laboratory. Fifteen participants were randomly allocated to the experimental group (EXP), spent the first two nights 8 h in bed (baseline, BL; from 23:00 h to 07:00 h), followed by five nights of 4 h in bed (sleep restriction, SR; from 03:00 h to 07:00 h) and, finally, again three nights of 8 h in bed (recovery, REC). Eight participants were randomly allocated to the control group (CON) and spent 8 h in bed every night. Sleep during the daytime was not allowed, which was monitored by EEG recordings and a continuously present investigator. During waking, participants took part in a bigger experiment of our sleep laboratory involving the simulation of a workweek by a variety of cognitive and psychological tasks. Their main activities during the day included the repeated assessment of the psychomotor vigilance task (PVT), the Brain@Work Multitask, a saccade test, and the training and testing of memory and motor tasks. Moreover, saliva samples were provided ten times per day and blood pressure was assessed eight times a day.

Participants ate standardized meals at fixed times throughout the experiment: breakfast at 08:00 h (600 kcal), lunch at 12:30 h (800 kcal), dinner at 18:30 h (700 kcal); snacks at 15:30 h (300 kcal) and 21:30 h (200 kcal). In addition, participants in EXP ate a piece of fruit (apple or orange) at 00:30 h (50 kcal). Participants were not allowed to leave the building but could, during regular short breaks, leave the sleep and test room and visit a relax room with television and PC. Illuminance in the sleep and test room ranged from 150 to 400 lux, and in the relax room from 350 to 600 lux, the temperature in the rooms ranged from 19 to 23 degrees Celsius. Polygraphy and ECG were continuously measured.

2.3. Hormonal Measurements. Hormonal levels were assessed from blood samples that were taken before breakfast at 07:30 h after the second BL night, the fifth SR night, and the second REC night in EXP and corresponding nights in CON. Samples were analyzed by Medix Laboratories, Espoo, Finland for glucose, insulin, IGF1, and leptin. Before blood sampling, subjects were asked to rate their feeling of hungriness on a 1 to 5 scale (1 = very hungry, 5 = very satiated). The saliva samples described above were analyzed for cortisol levels using a commercial kit assay (Salivary Cortisol, LIA, IBL, Hamburg, Germany).

2.4. Statistical Analysis. For both CON and EXP, mean values ± SD were calculated for each experimental day, BL, SR, and REC. In addition, SR and REC values were expressed as percentages of each individual participant's BL value, that is, normalized. We have compared SR and REC values to BL values by applying paired t-tests for normally distributed differences and Wilcoxon signed ranks

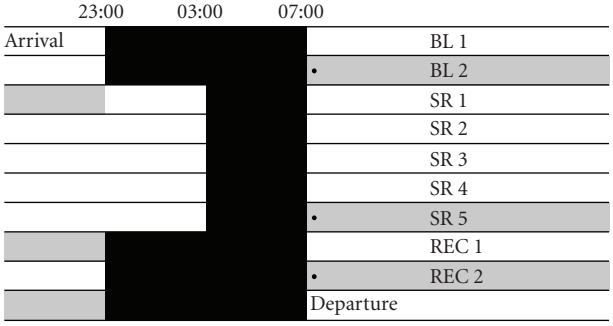

Figure 1: The experimental protocol. After two nights of 8 h sleep (baseline BL), sleep is restricted to 4 h per night for 5 subsequent days (sleep restriction, SR), followed by three nights of 8 h recovery sleep (REC). Profile days are shaded in grey. Bullet points indicate the taking of blood samples and rating of subjective satiety.

tests for differences that were not normally distributed. The normality of differences was checked using Kolmogorov-Smirnov goodness of fit test. A P-value <.05 was considered to be statistically significant. All statistical analyses were carried out using SPSS version 15 (SPSS Inc., Chicago, USA).

3. Results

3.1. Total Sleep Duration and Cortisol Profile. In CON, the mean total sleep duration (±SD) remained unaffected throughout the experiment, whereas in EXP, the mean sleep duration, as expected, strongly reduced during the SR period (Table 1). In EXP, the peak in cortisol levels was delayed with 16.2 ± 5.5 min. after SR compared to BL ($P < .05$; Table 1). After REC, the cortisol profile was similar to BL again. In CON, the cortisol profile remained unaffected throughout the experiment (Table 1).

3.2. Glucose, Insulin, and IGF-1. Mean glucose, insulin, and IGF-1 levels throughout the experiment in both groups are described in Table 2. Glucose levels showed a tendency for a decrease after SR and its levels were significantly decreased after REC to 65.5% ± 1.3% of BL levels ($P < .05$; Figure 2). In CON, glucose levels remained at BL level throughout the experiment (Figure 2).

Insulin levels were increased after SR to 159.9% ± 25.6% of BL levels ($P < .05$; Figure 2) and returned back to BL levels after recovery (114.5% ± 10.1% of BL levels). In CON, insulin levels remained at BL level throughout the experiment (Figure 2).

The insulin-to-glucose ratio was significantly increased after SR to 160.8% ± 25.4% of BL levels ($P < .05$; Figure 2), returning back to BL levels after subsequent REC (118.2% ± 9.9% of BL levels). In CON, the insulin-to-glucose ratio remained at BL level throughout the experiment (Figure 2).

IGF-1 levels showed a tendency for an increase after SR and its levels were significantly elevated after REC to 111.7% ± 3.6% of BL levels ($P < .01$). In CON, IGF-1 levels remained at BL level throughout the experiment (Figure 2).

3.3. Leptin and Subjective Satiety. Mean leptin levels and feelings of subjective satiety throughout the experiment in both groups are described in Table 2. Leptin levels were increased after SR to 163.3% ± 42.4% of BL levels ($P < .01$) and were still significantly elevated after REC (123.1% ± 7.0% of BL levels; $P < .01$; Figure 2). In CON, leptin levels remained at BL level throughout the experiment (Figure 2).

Feelings of satiety remained unaffected throughout the experiment in both groups (Figure 2).

4. Discussion

Chronic sleep deprivation is becoming an increasingly common phenomenon in modern 24 h societies due to, for instance, voluntary sleep restriction and increasing work demands [1, 9]. Restricted sleep does not only result in sleepiness and impaired cognitive performance, it also adversely affects general health [10]. Several widespread disorders have been shown to be epidemiologically associated with habitual short sleep duration, including cardiovascular diseases [11, 12], type 2 diabetes [13], and obesity [14, 15].

In the present study, serum glucose levels declined during the course of sleep restriction and subsequent recovery sleep, whereas serum insulin levels increased. Hence, the insulin-to-glucose ratio was significantly elevated after sleep restriction but returned to baseline values after subsequent recovery sleep. Elevating insulin levels that are not accompanied by elevations in glucose levels indicate a reduced sensitivity to insulin, which may ultimately increase the risk of developing noninsulin-dependent diabetes (i.e., type 2 diabetes). Taken together with a previous study showing that prolonged sleep restriction significantly lowers glucose tolerance [5], the experimental support for a causative connection between insufficient sleep and type 2 diabetes is gradually accumulating and supports the already present epidemiological evidence [13, 16, 17].

Under normal physiological conditions, blood glucose concentrations are tightly regulated within narrow limits. A well-known condition in which blood glucose levels rise due to deficits in insulin signaling is diabetes, but no common conditions are known in which blood glucose levels decline. Blood glucose is the most important energy supply to the brain and, therefore, the observed decrease in glucose after recovery as compared to baseline is as puzzling as it is alarming, since the most important adverse effect of chronically decreased blood glucose levels is brain dysfunction and in extreme cases even damage [18]. Moreover, low levels of fasting blood glucose are associated with an increased mortality risk [19].

In addition to insulin, insulin-like growth factor-1 (IGF-1) is another substance that lowers serum levels of glucose in both rats and humans [20, 21] and has even the capability of doing so in patients with severe insulin resistance [22]. The present study has indeed shown that, after recovery, IGF-1 levels were increased while glucose levels were decreased. Interestingly, in addition to lowering serum glucose levels, IGF-1 has also been shown to decrease serum insulin levels in

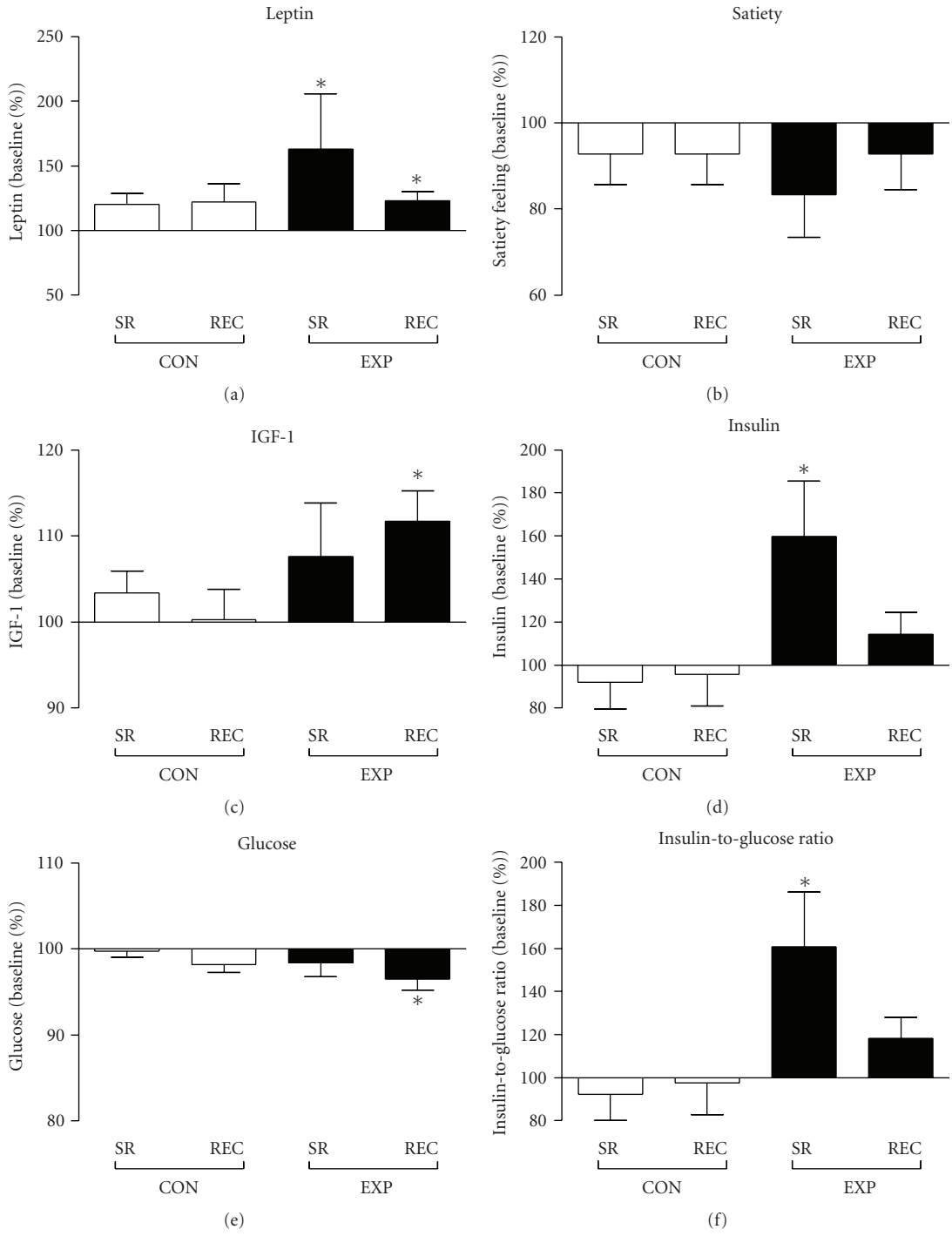

Figure 2: Changes in serum concentrations of leptin, IGF-1, insulin, and glucose, and changes in insulin-to-glucose ratio and subjective satiety after sleep restriction (SR) and recovery (REC) in the control group (CON) and experimental group (EXP). Data are expressed as percentages of participant's individual baseline values (mean ± SEM) ($^*P < .05$).

both rats and humans [23, 24]. It has been hypothesized that, by lowering insulin levels, IGF-1 reduces insulin resistance and might thus be of therapeutical importance in physiological states that are associated with insulin resistance, such as type 2 diabetes. Hence, the observed elevations in IGF-1 after recovery in the present study might be viewed as a compensatory reaction to the increased insulin levels after sleep restriction.

The rapidly expanding global incidence of obesity has a great impact on public health [25], for instance, by increasing the risk of developing cardiovascular diseases. Not only has this trend been paralleled by a trend of a gradual reduction

Table 1: Sleep duration and cortisol.

Variable	Group	Day		
		BL	SR	REC
		Mean (±SD)	Mean (±SD)	Mean (±SD)
Total sleep duration (min.)	CON	440 (±23)	442 (±16)	429 (±27)
	EXP	439 (±20)	232 (±5)	458 (±13)
Cortisol peak (clock time)	CON	07:48 (±0:15)	07:33 (±0:19)	07:33 (±0:10)
	EXP	07:39 (±0:14)	07:55 (±0:11)	07:36 (±0:13)

Table 2: Descriptives of the data.

Variable	Group	Day		
		BL	SR	REC
		Mean (±SD)	Mean (±SD)	Mean (±SD)
Glucose (mmol/L)	CON	5.14 (±0.50)	5.13 (±0.49)	5.04 (±0.41)
	EXP	4.91 (±0.24)	4.83 (±0.24)	4.74 (±0.17)
Insulin (mU/L)	CON	8.27 (±2.62)	7.33 (±2.84)	7.50 (±2.82)
	EXP	6.02 (±2.90)	8.59 (±6.99)	6.25 (±2.36)
Insulin-to-glucose ratio	CON	1.65 (±0.65)	1.49 (±0.73)	1.52 (±0.67)
	EXP	1.22 (±0.57)	1.75 (±1.33)	1.31 (±0.46)
IGF-1 (nmol/L)	CON	33.81 (±11.15)	34.84 (±10.99)	34.03 (±11.63)
	EXP	26.35 (±6.29)	27.64 (±5.39)	28.93 (±5.23)
Leptin (μg/L)	CON	3.44 (±3.09)	3.79 (±2.92)	3.70 (±2.80)
	EXP	6.25 (±4.55)	7.59 (±5.00)	6.93 (±4.07)
Satiety (1 to 5 scale)	CON	2.71 (±0.76)	2.57 (±0.98)	2.57 (±0.98)
	EXP	2.21 (±0.43)	1.79 (±0.70)	2.00 (±0.55)

in self-reported sleep duration, many epidemiological studies have linked those trends and observed a correlation between short sleep and obesity [26]. Recently, however, several groups have questioned the clinical relevance of this link [27, 28]. Expanding the current literature with experimental investigations might attribute to resolving those heated debates, editorials, and news reports.

Leptin and ghrelin are peripheral hormones believed to contribute to the central regulation of food intake [29]. Ghrelin, predominantly released by the stomach, stimulates appetite whereas leptin, mainly produced by adipocytes, stimulates feelings of satiety. Therefore, chronic elevations of ghrelin levels and/or reductions of leptin levels may attribute to the development of obesity. Obesity is indeed associated with leptin resistance and obese subjects show highly elevated serum concentrations of leptin [30]. Hitherto, only two experimental studies have investigated the effects of prolonged sleep restriction on serum ghrelin and leptin levels and observed decreased leptin and increased ghrelin levels, accompanied by increased feelings of hunger and appetite after a period of 4 h sleep compared to a period of 10 h sleep [6] and 12 h sleep [31]. In addition, prolonged sleep restriction in rats has been shown to result in decreased leptin levels that were associated with a reduction in body weight despite an increase in food intake [7]. Our observations, interestingly, contradict those findings in not having found any changes in feelings of hunger and having found an increase rather than a decrease in serum leptin levels.

Several factors are known to regulate serum leptin concentrations. Taheri and colleagues have shown that sleep duration is correlated to leptin levels [32]. Hence, long-sleepers have higher serum leptin concentrations than short-sleepers. We are, however, the first to show in a within-subject design that experimental restriction of participant's habitual sleep duration does not have a similar effect and that it is even increasing serum leptin concentrations. The only previous experimental studies compared sleep restriction against sleep extension and have found that after sleep restriction, leptin levels are lower than after sleep extension but unaffected as compared to participant's habitual sleep duration [6, 31].

Serum leptin concentrations are known to exhibit a circadian rhythm, with minimum values during daytime and a nocturnal rise [33]. This rhythm is not entrained to the circadian clock, but to meal patterns [34]. However, it does not acutely change in response to single meals [35]: a substantial meal of 1000 kcal did not alter leptin levels for the next three hours after administration [36]. In our study, there was only a modest (16 minute) delay in the endogenous circadian rhythm of salivary cortisol in the experimental group. However, meal timing was kept constant throughout the experiment, except for an additional apple or orange that participants in the experimental group received at 00:30 h during the days of restricted sleep. We find it unlikely that this small addition of about 50 kcal for a period of five days to the habitual meal pattern would have increased leptin

levels with 63%. How abolishing oral meals completely by replacing them with intravenous glucose infusion affects serum leptin concentrations [6] is not known.

Physical activity is inversely related to fasting plasma leptin levels [37]. Physical exercise has indeed been shown to result in decreased concentrations of serum leptin, both acutely and over the entire 24 h time span [38, 39]. In the present study, however, we did not aim to keep physical activity constant. Hence, participants in the experimental group were not restricted in their physical activity during the period of prolonged wakefulness. Therefore, physical activity was slightly elevated during this period when compared to the baseline and recovery periods. This could, in theory, have decreased leptin levels.

Leptin has for a long time been considered to be purely a satiety signal and previous sleep restriction studies have indeed found that lower leptin levels were associated with increased feelings of hunger [6]. In the present study, however, elevated leptin levels were not accompanied by any changes in hunger feelings. This may suggest that leptin plays additional physiological roles apart from regulating food intake, such as a proinflammatory role [40, 41].

An alternative explanation for the observed epidemiological correlation between short sleep and obesity might have little to do with the homeostatic control of sleeping and feeding behavior. As Saper and colleagues have pointed out, both the regulation of feeding and sleeping have a strong hedonic component [42, 43]. That is, both can be very satisfying at times when their physiological need is not that strong. It may be that, under the unpleasant experience of restricted sleep, a search for pleasure begins and excessive food is being consumed. Indeed, it has been shown that sleep restricted subjects—in a setting of ad libitum access to palatable food—consume excessive amounts of calories from snacks [44].

5. Conclusions

We showed that prolonged sleep restriction in a situation that mimics a working week changes glucose metabolism and may lead to an increased risk of developing type 2 diabetes. Two nights of normal sleep, however, restored this effect. In addition, we showed that five nights of sleep restriction does not affect hunger feelings and results in elevated leptin levels. This suggests that sleep restriction per se as it would occur during a typical working week may not increase the risk of developing obesity. Therefore, the previously observed epidemiological associations between short sleep and obesity might be due to a common underlying factor rather than a direct causation between short sleep and obesity. In addition, the excessive consumption of calories from snacks rather than from meals during a period of restricted sleep may contribute to the development of weight gain and/or obesity [44].

Acknowledgments

This study was supported by the European Union Framework 6 (MCRTN-CT-2004-512362) and the Finnish Work Environment Fund (FWEF; 104073 and 108203). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors thank Sirkku Hopeakangas for help with collection of blood samples, Marja-Leena Haavisto for the recruitment of participants, and Sirpa Hyttinen for help with cortisol analysis.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 819414, 6 pages
doi:10.1155/2010/819414

Research Article

Chronic Sleep Disturbance Impairs Glucose Homeostasis in Rats

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Received 16 October 2009; Revised 22 December 2009; Accepted 2 January 2010

Academic Editor: Jessica A. Mong

Epidemiological studies have shown an association between short or disrupted sleep and an increased risk for metabolic disorders. To assess a possible causal relationship, we examined the effects of experimental sleep disturbance on glucose regulation in Wistar rats under controlled laboratory conditions. Three groups of animals were used: a sleep restriction group (RS), a group subjected to moderate sleep disturbance without restriction of sleep time (DS), and a home cage control group. To establish changes in glucose regulation, animals were subjected to intravenous glucose tolerance tests (IVGTTs) before and after 1 or 8 days of sleep restriction or disturbance. Data show that both RS and DS reduce body weight without affecting food intake and also lead to hyperglycemia and decreased insulin levels during an IVGTT. Acute sleep disturbance also caused hyperglycemia during an IVGTT, yet, without affecting the insulin response. In conclusion, both moderate and severe disturbances of sleep markedly affect glucose homeostasis and body weight control.

1. Introduction

Sleep and metabolism seem to be related. Epidemiological studies have established a link between disturbed sleep and increased risk for the development of obesity and type 2 diabetes [1–4]. These studies revealed that habitual short sleep is a risk factor, independent of classical risk factors such as BMI, food intake, and reduced exercise. (For reviews; see [5–7]). Whether or not these relationships are causal is still a matter of debate [8].

Experimental studies in both humans and animals have shown clear effects of sleep deprivation on body temperature, food intake, body weight gain, and energy expenditure [9–12]. Sleep deprivation also leads to changes in the activation of the sympathetic nervous system, to reduced levels of leptin and to increased levels of ghrelin in the general circulation [13]. Finally, a number of recent experimental studies suggest that even mild sleep disturbance leads to glucose intolerance, the first step in the development of type 2 Diabetes [14, 15].

While epidemiological studies mainly focused on mild but chronic sleep disturbances, laboratory studies mostly focus on the consequences of acute and short-lasting sleep deprivation. Frequent or chronic sleep disruption may gradually lead to changes in brain and body that are not noticeable after acute sleep deprivation [16–18]. Yet, studies on metabolism and glucose regulation under conditions of mild but chronic sleep disturbance in a controlled experimental setting are scarce [14, 19]. Therefore, in the current study we applied an animal model to investigate the effect of chronically disturbed sleep on glucose homeostasis. To this end, rats were subjected to a series of intravenous glucose tolerance tests (IVGTTs) before and after a period of either moderate sleep disturbance or severe sleep restriction. To compare the effects of acute and chronic sleep disturbance, the experiment was performed after a period of 1 or 8 days of sleep disturbance.

2. Methods

2.1. Animals and Housing. Male Wistar rats (weight ±320 g; Harlan Netherlands BV, Horst, The Netherlands) were individually housed in Plexiglas cages in a climate-controlled room (21°C ± 1) under a 12 h : 12 h light-dark cycle (lights on at 10:00 AM). Animals were maintained *ad lib* on medium

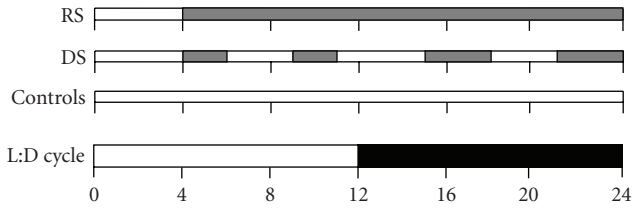

Figure 1: Schematic overview of the sleep disturbance protocols for the restricted sleep group (RS), disturbed sleep group (DS), and control group. For each treatment group, periods of wakefulness induced by forced locomotion are shown in light grey. The RS group was subjected daily to one consolidated block of 20-hour forced activity while the DS group was subjected to blocks of 2-3-hour forced activity interspersed by 3-4-hour blocks of rest. Control animals were left undisturbed.

fat food (45% fat; Arie Blok Diervoeding B.V., Woerden, The Netherlands). Water was available *ad lib* throughout the study. Food intake and body weights were measured daily. Experiments were approved by the Ethical Committee of Animal Experiments of the University of Groningen.

2.2. Surgery. All animals were instrumented with chronic heart catheters bilaterally in the jugular vein [20] allowing stress free blood sampling during an intravenous glucose tolerance test (IVGTT). Surgeries were carried out under general isoflurane (2%) anesthesia. Animals had at least 10 days to recover before the start of the experiments. Cannulas were checked every week for patency.

2.3. Sleep Restriction and Sleep Disturbance. The animals were divided over three groups (see Figure 1): a sleep restricted group (restricted sleep: RS), a moderately sleep disturbed group (disturbed sleep, DS), and a home cage control group (controls). The sleep restricted animals (RS) were allowed to sleep in their home cage for only 4 hours per day at the beginning of the light phase. During the remaining 20 hours, the rats were kept awake by placing them in slowly rotating drums (diameter 40 cm), rotating at a constant speed of 0.4 m/min [17, 18]. The animals of the sleep disturbed group (DS) were forced to walk in the rotating drums for a total of 10 hours/day with the aim to disturb their normal sleep-wake cycle without restricting their sleep time. The 10 hours of forced activity in this group was divided in 4 blocks of 2 or 3 hours with 3 or 4 hours of rest in between (Figure 1). The animals of the DS group walked at double speed (0.8 m/min) and therefore covered the same distance as the RS animals (0.48 km/day). For comparison, rats run approximately 2-3 km/day when allowed to run voluntarily [21]. Both RS and DS animals spent the first 4 h of the light phase in their regular home cages for IVGTTs and blood sampling. All animals were habituated to the experimental conditions by placing them in the drums for 1-2 hours for 3 consecutive days before the onset of the experiments. Control animals were left undisturbed in their home cage.

2.4. Intravenous Glucose Tolerance Test and Chemical Analyses. To assess the effects of sleep restriction and/or sleep disturbance on glucose regulation, rats were subjected to a series of intravenous glucose tolerance tests (IVGTTs). The IVGTTs were performed during the third and fourth hour of the light phase. Food was removed at lights on and rats were connected to the blood sampling and infusion tubes at least one hour before the IVGTT. During the IVGTT, a 15% glucose solution was infused for 30 minutes at a rate of 0.1 ml/min. The start of the infusion was designated time point $t = 0$ min. Blood samples (0.2 ml) for determination of blood glucose and plasma insulin levels were taken before, during, and after the infusion of glucose at time points $t = -10, -1, 5, 10, 15, 20, 25, 30, 35, 40$, and 50 minutes. Note that the glucose infusion prevented any hypovolemic effect of the blood sampling. Blood samples were collected in EDTA (20 μL/ml blood) containing tubes on ice. Blood was centrifuged at 2600 g for 10 minutes and plasma was stored at -20°C until analysis. Blood glucose levels were measured by Hoffman's ferrocyanide method and plasma levels of insulin were measured by Millepore Rat Insulin Radioimmunoassay (Linco Research, St Charles, MO, USA).

2.5. Experimental Design. Two experiments were performed. Experiment 1 was designed to study glucose homeostasis under conditions where sleep was disrupted or restricted chronically. In this experiment, the animals were subjected to an IVGTT before (pre-experimental baseline) and after an 8-day period of sleep disturbance (RS or DS). Rats that remained in their home cage without any sleep disturbance served as controls. Experiment 2 served as a control experiment for the chronic sleep disturbance study and assessed the effects of acute sleep disturbance. In this second experiment a single IVGTT was performed after 1 day of sleep disturbance. In both experiments, blood samples were collected for measurement of glucose and insulin levels. In the second experiment an additional 0.1 ml blood sample was taken at $t = -10$ minutes for determination of plasma corticosterone levels (ImmuChem 125I Corticosterone Radioimmunoassay, MP Biomedicals, Orangeburg, NY, USA).

2.6. Statistical Analysis. Data are expressed as averages ± SEM. Body weight is expressed as the change in weight relative to day 0 (the onset of sleep disturbance). The effects of RS and DS on food intake and body weight as well as glucose and insulin responses to IVGTT were tested by comparing the experimental and control groups with each other and, in Experiment 1, with the pre-experimental baseline using repeated measures analysis of variance (ANOVA). When appropriate, a post hoc Tukey test was applied to establish differences between the three groups (controls, RS, and DS). $P < .05$ was considered statistically significant.

3. Results

The average 24-hour food intake before, during, and after the treatment for the different groups is shown in Figure 2(a). There were neither differences in food intake between the

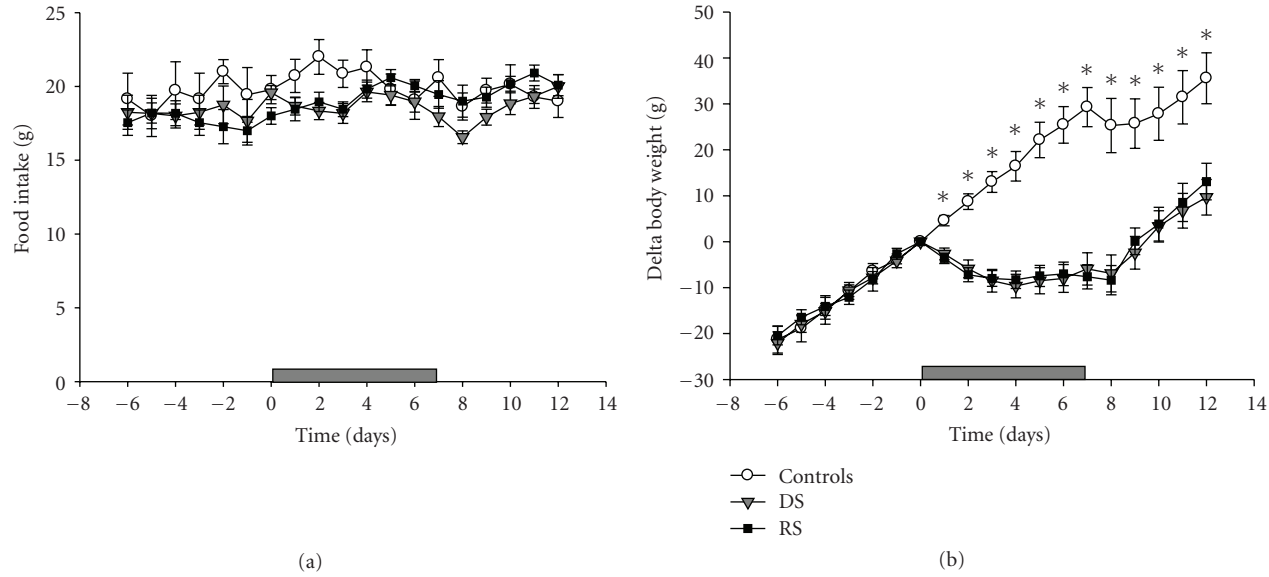

Figure 2: Average daily food intake (a) and body weight (b) in the baseline, experimental, and recovery phase of the experiment for RS ($n = 11$), DS ($n = 12$), and control ($n = 7$) animals. The horizontal grey bars at the bottom of the graphs represent the 8-day period of RS or DS. Data are average values ± SEM. Asterisks indicate a significant difference between sleep disturbed (DS and RS) and control animals ($^*P < .01$).

3 groups nor changes over time within the groups. Body weights are shown in Figure 2(b). The RS and DS animals were significantly lower in body weight than the home cage controls already after 2 days of sleep disturbance (Repeated Measures ANOVA: F(36,486) = 11.02, $P < .001$; post hoc Tukey Test: controls versus RS $P < .01$ and controls versus DS $P < .01$). There were no body weight differences between the RS and the DS animals.

Figure 3 depicts the glucose and insulin levels before, during, and after the 30-minutes intravenous infusion of glucose, both under baseline (pre-experimental) conditions and after 8 days of sleep disturbance (RS and DS versus controls). In all groups, intravenous infusion of glucose led to an increase in both blood glucose and plasma insulin levels. After termination of the infusion, both glucose and insulin returned to pre-infusion levels. Eight days of sleep disturbance markedly changed the glucose and insulin responses to an IVGTT. Blood glucose levels were higher and plasma insulin levels were lower in the RS and DS animals compared to the pre-experimental IVGTT levels (Glucose RS: F(10,140) = 10.05, $P < .0001$; Glucose DS: F(10,160) = 9.64, $P < .0001$; Insulin RS: F(10,150) = 10.53, $P < .0001$; Insulin DS: F(10,160) = 8.97, $P < .0001$). Also in comparison to the home cage controls, glucose levels were higher and insulin levels were lower in both experimental groups (Glucose: F(20,200) = 3.37, $P < .0001$; post hoc Tukey Test: RS versus controls $P < .05$ and DS versus controls $P < .05$; Insulin: F(20,190) = 3.70, $P < .0001$; post hoc Tukey Test: RS versus controls $P < .01$ and DS versus controls $P < .05$). No differences were found between the RS and DS rats.

Figure 4 shows the glucose and insulin levels before, during, and after the glucose infusion after a single day of sleep disturbance. In both the RS and DS animals, glucose levels were significantly higher than the levels in undisturbed home cage controls (F(21,210) = 12.49, $P < .0001$; post hoc Tukey Test: RS versus controls $P < .001$ and DS versus controls $P < .001$). There were no differences between the groups with regard to the plasma insulin response to an IVGTT after one day of sleep disturbance.

In Experiment 2, after 1 day of RS or DS, at time point t = −10 min immediately preceding the IVGTT, plasma levels of corticosterone were low and not different between the groups (RS: 1.4 ± 0.2 μg/dl, DS: 1.3 ± 0.1 μg/dl, controls: 2.4 ± 0.2 μg/dl).

4. Discussion

This study shows that eight days of sleep disturbance markedly interferes with body weight maintenance and glucose metabolism in rats. The main findings are that (1) chronic sleep disturbance reduces body weight without changes in food intake; (2) chronic sleep disturbance leads to hyperglycemia and a concomitant reduction in the insulin response to an IVGTT; (3) acute sleep disturbance also leads to hyperglycemia without changes in the insulin response to an IVGTT; (4) the metabolic effects of moderate sleep disturbance and more severe sleep restriction are remarkably similar.

The elevated glucose levels that occurred after both short- and long-term sleep disturbance confirm the data from previous studies in humans in which was found that moderate sleep restriction or even suppression of sleep intensity without affecting sleep time may lead to glucose intolerance [14, 15]. In our study, the increase in blood glucose during the IVGTT already occurred after one day of sleep disturbance. The data from the chronic sleep

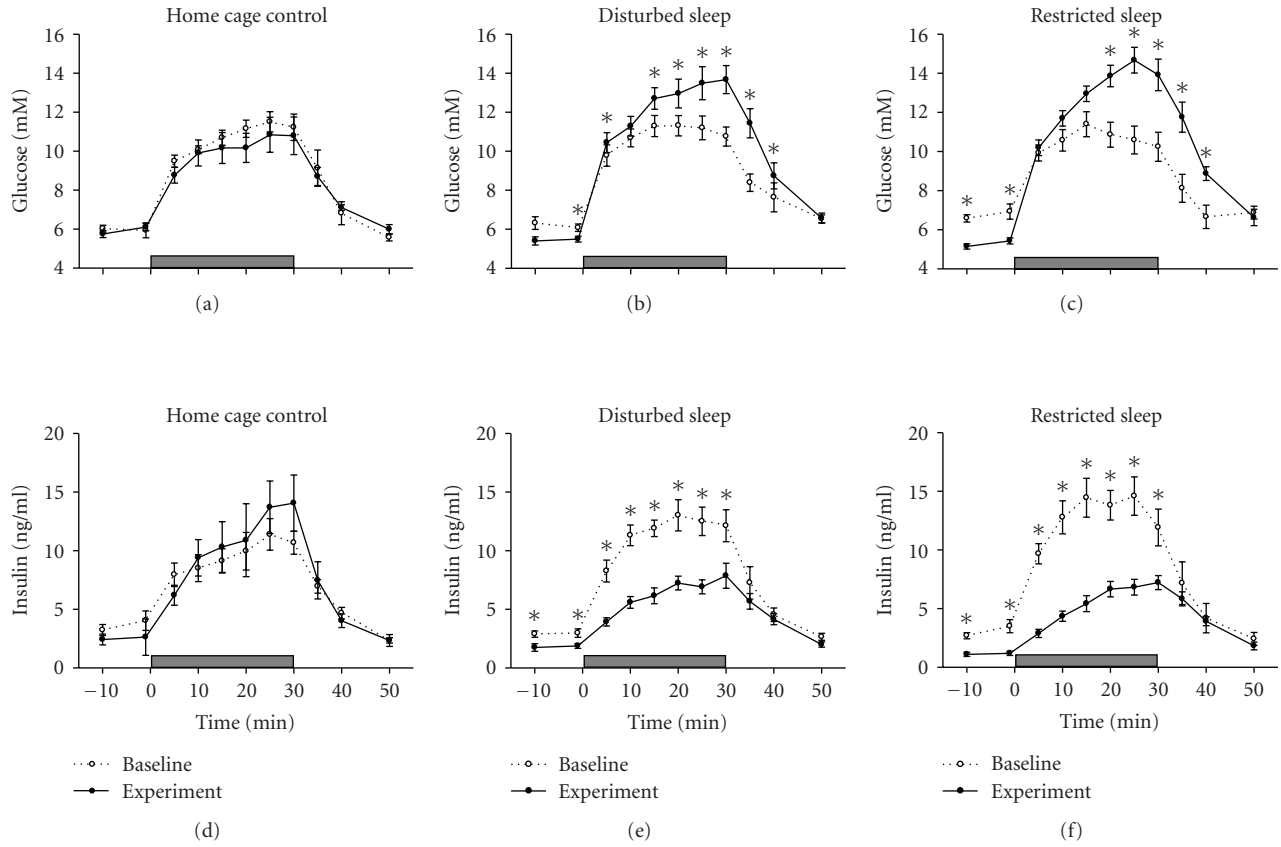

Figure 3: Blood glucose and plasma insulin levels in response to a 30-minutes intravenous glucose infusion after 8 days of sleep restriction (graphs (c) and (f), $n = 11$), sleep disturbance (graphs (b) and (e), $n = 12$), or control (graphs (a) and (d), $n = 7$). Each graph presents the glucose or insulin profiles under pre-experimental baseline conditions (Baseline: open circles) and after 8 days of sleep disturbance (Experiment: closed circles). The horizontal grey bars at the bottom of each graph represent the 30 minutes of 15% glucose infusion. Data are average values ± SEM. Asterisks indicate a significant difference between baseline and experimental conditions ($^*P < .05$).

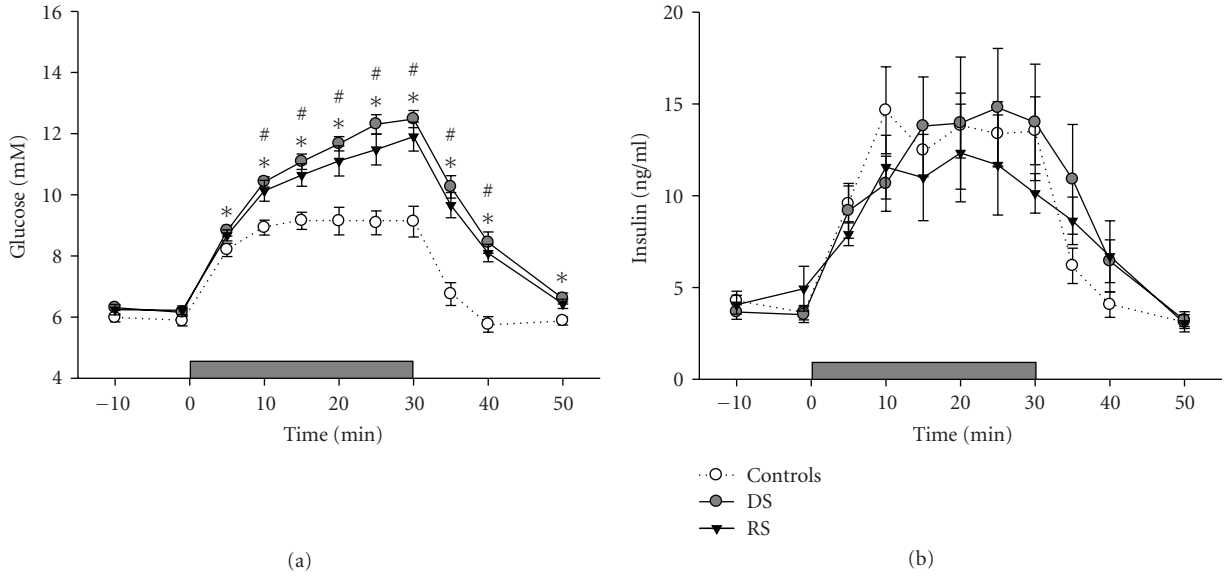

Figure 4: Blood glucose (a) and plasma insulin levels (b) in response to a 30-minutes intravenous glucose infusion after 1 day of sleep restriction (closed triangles, $n = 8$), sleep disturbance (closed circles, $n = 8$), or control (open circles, $n = 8$). The horizontal grey bars at the bottom of the graphs represent the 30 minutes of 15% glucose infusion. Data are average values ± SEM. Asterisks indicate a significant difference between sleep restricted rats and controls ($^*P < .05$) and # indicates a significant difference between sleep disturbed rats and controls ($^\#P < .05$).

disturbance experiment might suggest that the elevated glucose levels are caused by a reduced insulin response. However, the finding of hyperglycemia without changes in plasma insulin response after acute sleep disturbance makes this explanation less likely. An alternative explanation might be that the hyperglycemia is caused by increased HPA-axis activity reflecting the stress of sleep disturbance. To test this possibility we measured plasma corticosterone levels in the sleep disturbed animals just prior to the infusion of glucose. Since corticosterone levels were not different between the groups, elevated HPA-axis activity can also not explain the hyperglycemia after sleep disturbance. Therefore, the reason for the hyperglycemia following both short- and long-term sleep disturbance remains unclear. Our current studies focus on the hypothesis that this hyperglycemia may be secondary to changes in hypothalamic orexin, a neuropeptide known to be involved in both the sleep/wake cycle and glucose metabolism [22–24]. A number of recent studies suggest that REM sleep deprivation increases orexin immunoreactivity in the lateral hypothalamic area and orexin levels in the CSF, which may underlie some of the metabolic changes described after restricted or disrupted sleep [25, 26].

Eight days of sleep disturbance caused a reduction in body weight together with a decrease in basal levels of glucose and insulin and a decrease in IVGTT levels of insulin. The literature suggests that the lower levels of glucose and insulin and the attenuated insulin response to the glucose tolerance test are most likely a direct consequence of the drop in body weight [27].

Surprisingly, the weight loss in our rats was not accompanied by a change in food intake, which may suggest that sleep disturbance leads to increased daily energy expenditure. The latter indeed is supported by data in the literature [11, 28]. One cause of an increased energy expenditure in our protocol of sleep disturbance might be the forced locomotion in the rotating drums. However, one should note that in both the RS and DS conditions the rats walked only 480 m/day, which is less than 20% of the distance they would voluntarily run in a running wheel [21]. Furthermore, although long-term exercise may lead to improved insulin sensitivity and therefore reduced plasma insulin levels [29], in rats, it does not lead to extensive weight loss and/or hyperglycemia [30]. Therefore, the decrease in body weight and hyperglycemia in our study are not likely a result of the mild increase in activity involved in our sleep disturbance protocols.

The metabolic changes after sleep disturbance were similar in the RS and DS animals. This was unexpected because the degree of sleep restriction was markedly different between the two groups. The DS rats were subjected to a disruption of the normal sleep-wake cycle without restriction of their sleep time, whereas the RS rats were genuinely sleep restricted. Based on this observation, we speculate that the metabolic consequences of sleep curtailment are mainly related to the occurrence of frequent sleep interruptions and a disturbed sleep-wake cycle rather than sleep loss per se. In other words, it is the quality rather than the quantity of sleep that is important. Indeed, a recent study in humans found that suppression of sleep intensity without changes in total sleep time was sufficient to cause glucose intolerance and a decreased acute insulin response [15]. Patients suffering from obstructive sleep apnea (OSA) provide comparable evidence [31, 32]. Total sleep time in OSA patients is not dramatically altered; still there are direct correlations between OSA and obesity, type 2 diabetes, and cardiovascular diseases [33]. The opposite is true as well: modest weight gain or weight loss leads to a significant worsening or improvement, respectively, of sleep apnea in middle-aged individuals [34, 35]. Thus, several lines of evidence together suggest that disturbed sleep by itself is sufficient to affect glucose homeostasis.

In conclusion, our data reveal that disturbance of the regular sleep-wake rhythm has a marked effect on glucose homeostasis and body weight control. Sleep disturbance directly leads to glucose intolerance and hyperglycemia and, on the long term, to weight loss accompanied with reduced insulin responses. The data further suggest that a disturbance of the normal sleep pattern, even without restriction of total sleep time, is sufficient to affect glucose metabolism and body weight maintenance.

Acknowledgments

The authors thank Jan Bruggink for technical assistance and radioimmunoassays. They also thank Maurien Pruis and Daan Middendorp for their assistance with the experiments.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 759234, 16 pages
doi:10.1155/2010/759234

Review Article

Impact of Sleep and Its Disturbances on Hypothalamo-Pituitary-Adrenal Axis Activity

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Received 11 December 2009; Accepted 27 March 2010

Academic Editor: Deborah Suchecki

The daily rhythm of cortisol secretion is relatively stable and primarily under the influence of the circadian clock. Nevertheless, several other factors affect hypothalamo-pituitary-adrenal (HPA) axis activity. Sleep has modest but clearly detectable modulatory effects on HPA axis activity. Sleep onset exerts an inhibitory effect on cortisol secretion while awakenings and sleep offset are accompanied by cortisol stimulation. During waking, an association between cortisol secretory bursts and indices of central arousal has also been detected. Abrupt shifts of the sleep period induce a profound disruption in the daily cortisol rhythm, while sleep deprivation and/or reduced sleep quality seem to result in a modest but functionally important activation of the axis. HPA hyperactivity is clearly associated with metabolic, cognitive and psychiatric disorders and could be involved in the well-documented associations between sleep disturbances and the risk of obesity, diabetes and cognitive dysfunction. Several clinical syndromes, such as insomnia, depression, Cushing's syndrome, sleep disordered breathing (SDB) display HPA hyperactivity, disturbed sleep, psychiatric and metabolic impairments. Further research to delineate the functional links between sleep and HPA axis activity is needed to fully understand the pathophysiology of these syndromes and to develop adequate strategies of prevention and treatment.

1. Introduction

The release of nearly every hormone in humans is characterized by daily oscillations that result mainly from the interaction between circadian rhythmicity and the sleep-wake cycle. Circadian rhythms are generated by the endogenous master pacemaker located in the paired suprachiasmatic nucleus (SCN) of the hypothalamus and are kept entrained to the local conditions by environmental timing cues; the most important of these cues is light, that signaled to the SCN by direct input from the retina via the retinohypothalamic tract [1]. In addition to the master clock in the SCN, circadian oscillators have been found in a number of peripheral tissues, such as liver, heart, lung, skeletal muscle, and adrenal glands [2, 3].

Apart from circadian rhythmicity and sleep-wake cycle, plenty of other factors which tend to recur at regular 24-hour intervals, such as postural changes, food intake, exposure to light and dark, have an influence on daily hormonal changes.

Given the close interaction of these periodic factors, the study of the impact of each single component, and in particular of sleep, on the hormonal profiles has faced several methodological problems: sleep is, indeed, a period of fasting, associated with changes in posture and light exposure. Furthermore, the tight concordance of habitual sleep and wake times with certain circadian phases has made it difficult to distinguish sleep and circadian effects.

Hence, specific protocols have been designed to dissociate the contribution of the alternation of sleep and wake states from that of circadian process on 24-hour rhythms of hormonal release. The most common study protocols involve shifts of the sleep period (with volunteers kept awake at night and allowed to sleep at different times of the day), sleep deprivation, including constant routine conditions (in which human volunteers remain awake for 30–60 hours, in a semirecumbent position, in dim light and receive frequent small identical meals) [4] and ultradian protocols (in which subjects live on a very short "day" such as a 20 or 90 or 180

minutes "day," with 2/3 of the time awake and 1/3 of the time asleep) [5–7].

2. Physiology of Hypothalamo-Pituitary-Adrenal (HPA) Axis

The hypothalamo-pituitary-adrenal (HPA) axis is the major neuroendocrine mediator of the stress response. A stressful stimulus perceived by the senses ultimately induces the release of CRH from the paraventricular nucleus (PVN) of the hypothalamus. CRH stimulates the release of ACTH from the anterior pituitary and ACTH subsequently initiates the liberation of glucocorticoids from the adrenal cortex. Cortisol has numerous actions, including feedback inhibition at the level of the PVN and the anterior pituitary to control CRH or ACTH synthesis and release. In addition, the HPA axis receives relevant feedback from other areas of the brain, such as the hippocampus and amygdala [8]. An important interplay is also the excitatory reciprocal interaction between the HPA axis and the brainstem sympathetic locus coeruleus (LC)-norepinephrine (NE) system: CRH activates the LC; in turn, NE, a known wake-promoting neurotransmitter, activates hypothalamic CRH [9, 10].

The basal activity of the HPA axis displays a clear daily rhythm: the 24-hour profiles of peripheral levels of ACTH and cortisol occur in close parallelism and are characterized by high levels in the early morning (acrophase), a decline throughout the day, with a prolonged period of low levels (quiescent period), centered around midnight (nadir), and a rapid rise during the second half of the night. The amplitude of the circadian oscillation is generally defined as 50% of the difference between the value of the acrophase and the value of the nadir [11–13] (Figure 1). The nocturnal onset of the cortisol rise and the morning peak may be seen as the response to an endogenous stimulus driven by the circadian clock, as it is suggested by the fact that the onset of the cortisol rise takes many days to adapt to an abrupt shift of the sleep-wake and light-dark cycle [14]. The daylong cortisol decline may represent the rate of recovery of the axis from this endogenous challenge.

The results of constant routine, shifted sleep, and ultradian schedule experiments have revealed prominent endogenous circadian components in this well-characterized and highly reproducible daily rhythm. As a confirmation, lesions of the SCN in rats result in the loss of corticosteroid periodicity [15, 16]. The SCN shows, indeed, direct and indirect projections (mainly via the subparaventricular zone and the dorsomedial nucleus of the hypothalamus) to the PVN [17, 18]. In addition, significant evidence now points to a neural SCN-adrenal gland connection, via the autonomic nervous system and independent from the HPA axis activation [19, 20]: this multisynaptic pathway from the SCN to the adrenal gland is able to transmit light information to the adrenal glands, modulating corticosterone release without changes in ACTH secretion [21]. Moreover, a role in the circadian regulation of glucocorticoid secretion is probably played by an intrinsic circadian oscillator in the adrenal glands: indeed, a study by Valenzuela and colleagues

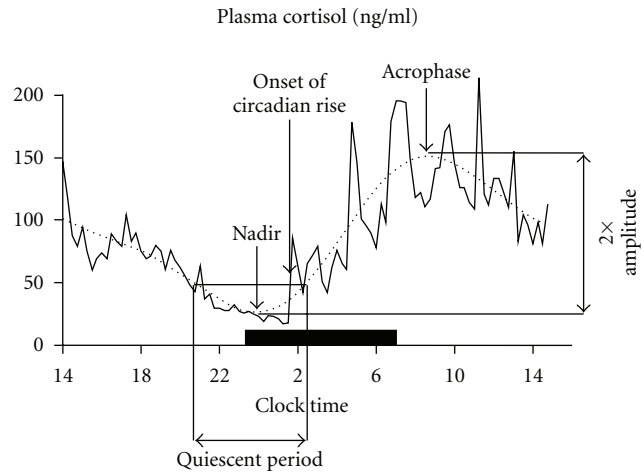

Figure 1: 24-hour individual cortisol profile (solid line).The smoothing curve (dotted line) is calculated to determine the minimum (nadir), the maximum (acrophase), the onset of the circadian rise, and the amplitude (50% of the difference between the acrophase and the nadir) of the cortisol profile. The black bar represents the sleep period.

has recently demonstrated the rhythmic expression of clock genes in the adrenal cortex of a diurnal primate [22]. Notably, the oscillation of the transcriptional expression of the adrenal clock genes, accompanied by rhythmic expression of the steroidogenic enzyme 3-beta-hydroxysteroid dehydrogenase, was directly modulated by melatonin, shown to be a potent time signal for the entrainment of peripheral circadian oscillators, but was also maintained for 36 hours in cultured adrenal explants, independently from the SCN oscillations.

The distinct circadian pattern of cortisol secretion may be driven not only by circadian oscillators, but also by metabolic factors. The HPA axis plays a key role in mobilizing energy resources in conditions of reduced energy supply, such as during hypoglycemia [23]. In response to HPA axis activation, both liver and kidney increase endogenous glucose production, ensuring sufficient glucose supply to glucose-dependent organs, in particular the brain [24]. Correspondingly, mild transient hyperglycemia has been shown to suppress HPA secretory activity in rats [25]. In a recent study, nocturnal glucose administration in young healthy males significantly reduced the early morning rise in ACTH and cortisol concentrations, regardless of whether the subjects were asleep or awake, supporting the view that increasing energy demands of the brain toward the end of the night essentially contribute to the early morning peak in the HPA axis activity [26].

The impact of age and sex on HPA function has been an object of great interest and a matter of debate. Most early studies investigating this topic, limited by small sample sizes and heterogeneous composition, seemed to indicate that there are no major sex and age differences in basal functioning of the HPA axis [27–29]. However, aging has been more often associated with an hyperactivation of the axis in response to a stimulus: interestingly, what appears to be more affected is the ability of the axis to recover from

a challenge (resiliency), rather than the rate of the initial response or the magnitude of the response [29, 30].

A study that analyzed almost 200 temporal profiles of plasma cortisol from men and women, with ages from young adulthood to late senescence, found, indeed, subtle but substantial sex and age-related differences [31] (Figure 2). In young adulthood, women appeared to have, compared to men, lower 24-hour mean cortisol levels, a longer quiescent period (that started earlier and ended later), a lower acrophase, and a lower absolute amplitude of the circadian variation. Therefore, the female response to the circadian signal appeared to be slower and of lesser magnitude than in men and the recovery from the morning peak more rapid with a longer quiescent period; a modulatory role of estrogens in the greater resiliency of the HPA axis observed in premenopausal women cannot be ruled out and might be involved in their lower rate of cardiovascular risk compared to men. In the same study, aging was associated, in both sexes, with a progressive increase of 24-hour mean levels from the 2nd to the 8th decade, associated with a shorter quiescent period and higher nadir values. These findings are consistent with the reported association of aging with an impairment in the inhibitory feedback mechanisms and in the ability of the system to turn off the signal after the morning stimulation [29]. A sex difference in the effects of aging on HPA function was apparent as in women, but not in men, an increase in the level of the acrophase was detected, as expression of increased responsiveness of the axis; moreover, the reduction in the duration of the quiescent period appeared to be even sharper in women than in men. Sleep complains in older adults are more common in women than in men and this could play a role in the greater female reduction of the quiescent period. Of note, the most common sleep disorder, obstructive sleep apnea, is as prevalent in older women as in older men. In addition, the timing of the nadir and of the onset of the nocturnal cortisol rise are advanced in older adults of both sexes and the circadian amplitude, when expressed as a percentage of the 24-hour mean level, is decreased: hence, during senescence a progressive advance of circadian phase seems to occur, associated with a loss of strength of the circadian signal.

Another recent protocol investigated the effect of age, gender and BMI on the pulsatile pattern of secretion of ACTH and cortisol [32]. In this study, mean ACTH concentrations, basal and pulsatile ACTH secretion directly correlated with BMI and were higher in men than in women, after controlling of BMI. The secretory regularity of ACTH and cortisol was also evaluated with approximate entropy (ApEn) statistic; the univariate ApEn quantifies the orderliness of a single hormone release, while the bivariate cross-ApEn quantitates the relative pattern synchrony of coupled time series: increased randomness of coupled hormonal secretion patterns is interpreted as reflecting weaker feedback and feedforward control mechanisms [33]. ApEn analysis revealed that greater age is associated with more irregular patterns of cortisol, but not ACTH secretion, suggesting that aging might alter intra-adrenal paracrine or neurogenic mechanisms that modulate glucocorticoid secretion. In addition, in men, ACTH-cortisol feedforward synchrony and cortisol-ACTH feedback synchrony both decline with age, as quantified by cross-ApEn, denoting a deterioration of coordinate control of ACTH and cortisol secretion patterns.

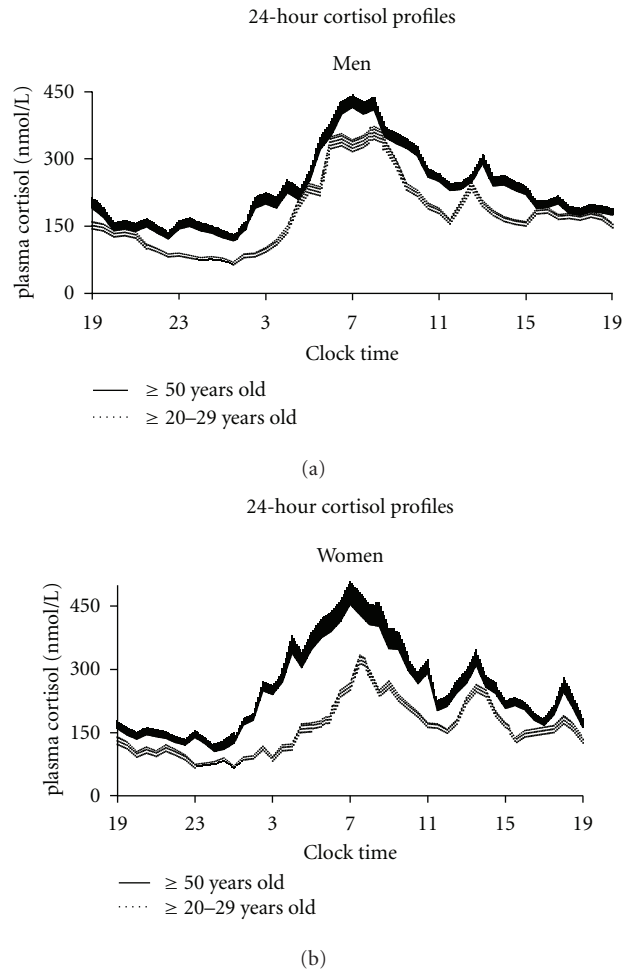

Figure 2: Effects of age and sex on cortisol profile: Mean 24-hour (+ or − SEM) cortisol profiles in men (left profiles) and women (right profiles) for 2 age groups that is, 50 years of age and older (solid lines) and 20 to 29 years old (hatched lines). (adapted from Van Cauter [30])

3. Effects of Normal Sleep on HPA Axis

Although modest, effects of sleep on cortisol profile are clearly present and have been well documented.

Sleep is a dynamic process characterized by the alternation between two different states: REM and non-REM sleep (NREM). NREM sleep is further classified into 3 different stages of increasing intensity (stage 1, 2, and slow wave sleep, or SWS). Each sleep stage has characteristic EEG frequencies and waveforms. During REM sleep the EEG resembles that of stage 1, with relatively low amplitude, mixed frequency waveforms; muscle tone is inhibited and eye movement are present. NREM sleep includes a variably synchronous cortical EEG: in particular SWS exhibits high-amplitude delta frequency (0.5–4.5 Hz) oscillations as a defining feature

and are considered to have a fundamental role in the restoration of cognitive, emotional, and metabolic functions.

Some changes in cortisol profile seem to be sleep-state dependent, others may be related to specific sleep stages.

3.1. Impact of Sleep Onset and Offset. Sleep onset exerts a modest inhibitory effect on cortisol profile that persists for 1-2 hours. This was evident in subjects undergoing a 3-hour sleep-wake cycle [34], in subjects reversing the phase of sleep-wake cycle by 180° [35] and during temporal isolation (free running condition) [36]. Under free-running conditions, sleep is generally initiated at a much later phase of the endogenous circadian cortisol rhythm, that is, after the rising phase of cortisol has begun; in this case sleep onset interrupts the rise of cortisol and inhibits its secretion for 1–3 hours. In a similar way, sleep onset during habitual wake time lowers cortisol levels [37]. In a study that compared the effect of nighttime sleep (sleep period 2300–0700) with daytime sleep (sleep period 0700–1500, that is, sleep onset at the peak of corticotropic activity), a transient decrease in cortisol levels at the time of sleep onset was observed [13].

An influence of sleep-wake transitions on cortisol secretion is also detectable during nocturnal awakenings which are consistently associated with a transient elevation of cortisol levels, followed by temporary inhibition of cortisol secretion [38].

Similarly, the final morning awakening elicits a rapid and marked rise in cortisol levels, augmenting the circadian acrophase of cortisol concentrations, but in contrast to nocturnal awakenings, the elevation of cortisol levels associated with final morning awakening persists for about one hour. In addition, it is detectable independently of the time and the mode of awakening (naturally or induced) [39], both in long and short sleepers [40]. In the previously mentioned work from Weibel et al. the acrophase of cortisol occurred at the same time in the morning both in nighttime sleepers and in daytime sleepers, demonstrating the strength of circadian rhythmicity, but the amplitude of the morning pulse was smaller if the subjects were asleep [13].

3.2. Modulatory Effects of Sleep Stages. A consistent temporal association between low cortisol levels and high SWS has been demonstrated [41]. The inhibitory effect that sleep onset seems to exert on HPA axis has been mostly attributed to SWS. Indeed the quiescent period of HPA activity, although starting before sleep onset, occurs during the first half of the night when SWS is present to its greatest degree [34, 35] and some authors have even hypothesized the existence of an unknown factor, possibly GHRH secreted during SWS, exerting inhibitory properties on corticotropic activity [42]. Cortisol levels have been shown to decrease in the first 20 minutes after the onset of SWS [41]; in addition, a study that compared morning sleep after a regular night of sleep, with morning recovery sleep after a night of sleep deprivation, found increased SWS and decreased cortisol levels in the latter condition [43], in agreement with the hypothesis of an inhibitory role of SWS on cortisol secretion. Furthermore, the response of ACTH and cortisol to a stimulus (CRH administration, alone or in association with vasopressin) has been shown to be blunted if the test was performed during nighttime sleep, and in particular during SWS, compared with nighttime wakefulness [44, 45].

Nevertheless, some authors have questioned the direction of the inverse link found between cortisol and SWS, suggesting that a decreased HPA tone may promote sleep deepening and, conversely, that increasing cortisol levels may prevent the occurrence of SWS [13, 46]. Gronfier et al, investigated the relationship between cortisol secretion and slow-wave activity (SWA), the spectral power in the low frequency range of the EEG (0.5–4.5 Hz), that is considered a stable trait dependent marker of the intensity of SWS. These authors showed that, during the period of pulsatile release, the cortisol secretory variations were concomitant with or anticipated opposite variations in SWA, by 10–20 minutes [47], suggesting the existence of a common central control.

An association between REM sleep and periods of low adrenal cortex secretory activity has been reported [48] and it has been shown that a significant proportion of REM sleep phases starts at a time of stable or decreasing cortisol levels, but may persist after cortisol increases again [41]. In a study investigating simultaneous chronological changes in sleep duration and quality and in the 24-hour cortisol profiles from young adulthood to old age, it was observed that a decrease in the amount of REM sleep (stable and unchanged until 50 years of age, decreased by approximately 50% in late life compared with young adulthood) occurred in synchrony with an elevation of evening cortisol levels. A trend for an association between lower amounts of REM sleep and higher evening cortisol concentrations, independently of age, was also detected [49].

The association between cortisol secretion and specific sleep stages has also been investigated in relation to memory consolidation. It is well known that a central cognitive function of sleep is to consolidate newly acquired memories for long-term storage [50] and, moreover, different sleep stages seem to be implicated in the consolidation of different types of memory [51]. Retention of declarative memory critically depends on the integrity of the hippocampus and has been shown to benefit specifically from early nocturnal sleep, in which SWS predominates and cortisol concentrations are minimal [52, 53]. Consistent with a role for quiescent cortisol release in this process, hippocampus-dependent declarative memory has been impaired by the infusion of a low dose of cortisol during a period of early SWS-rich sleep [54]. A similar result has been achieved with the administration of the glucocorticoid receptor (GR) agonist dexamethasone [55]. Thus, inhibition of cortisol secretion and in particular inactivation of GRs appear to be critical for hippocampus-mediated formation of declarative memories.

When declarative memory for highly emotional rather than neutral material is assessed, the data point to a more beneficial influence of REM sleep which prevails during the late night, when cortisol concentrations rise [56]. Declarative memory for emotional events, although still hippocampus-dependent, is under critical modulation by the amygdala [57]. A recent randomized, double-blind, placebo-controlled study examined the effect of the cortisol synthesis inhibitor

metyrapone on sleep-associated consolidation of memory for texts of either neutral and emotional valence [58]. Metyrapone suppressed cortisol concentrations, especially the rise in cortisol during late sleep, and decreased time spent in SWS, which was replaced by shallow NREM sleep. REM sleep was preserved. While memory for the neutral texts was reduced, interestingly metyrapone even amplified emotional enhancement in text recall, which has been shown in many clinical and neuroimaging studies to depend on the amygdala [59–61]. Thus, the late night rise in cortisol appears to dampen amygdala-dependent emotional processing and could exert a protective function by preventing excessive emotionality in memory.

Cortisol secretory pattern, in association with specific EEG frequencies, has been studied not only during sleep, but also during wake: during daytime wakefulness cortisol release follows the increase in EEG absolute power of the beta frequency band (13–35 Hz) with a 10-minute delay [62]; this finding has been subsequently confirmed in a more recent study [63] in which a significant temporal association has been found between cortisol secretory rate and waking EEG absolute power in the gamma frequency range (20–45 Hz), in a group of young males not sleep deprived. Given that high-frequency EEG over 20 Hz is considered a marker of daytime arousal [64], a functional link between the regulatory mechanisms controlling the HPA activity and the level of central arousal has been hypothesized.

4. Effects of Shifted Sleep on Hpa Axis

As mentioned before, one of the strategies to differentiate between effects of circadian rhythmicity and effects of sleep-wake homeostasis on physiological variables has been to design studies of shifted sleep, in which volunteers are submitted to a large sudden advance or delay in their dark-light, rest-activity, sleep-wake cycle, similar to what occurs in jet lag or shift work rotations. Hence, these protocols allow for the effects of circadian modulation to be observed in the absence of sleep and for the effects of sleep to be observed at an abnormal circadian time. The most important external time cue, that aligns the circadian system with the environment, is the light-dark cycle, and these experiments take advantage of the fact that the circadian pacemaker takes several days to adjust to an abrupt shift in the dark-light cycle. The rate of re-entrainment of the biological rhythms to the new environmental time has been recognized to be different among physiologic variables, being slower for those mainly controlled by the circadian process, and faster for those mainly under the sleep-wake homeostasis control [65]. In the cortisol profile, the end of the quiescent period and the onset of the daily rise are mostly under the control of circadian rhythmicity, while the timing of the acrophase and the amplitude of the diurnal variation are more influenced by sleep-wake transitions. Indeed, in studies of real and simulated jet-lag, the synchronization of the acrophase to the new clocktime occurred faster than the adaptation of the quiescent period [14, 66].

4.1. Delay of the Sleep-Wake Cycle. The effect of an abrupt 8-hour delay of the sleep-wake cycle on plasma cortisol profiles was investigated in a study designed to mimic westward travel across eight time zones [67]. The protocol involved a three-day period of habituation in which the subjects followed a standardized schedule with fixed meal times and sleep time (23:00–7:00). On day 4, baseline 24 hours hormonal profiles starting at 18:00 and sleep recordings were obtained. At the end of the baseline sampling period, the subjects were kept awake until 7:00 the next day, and then allowed to sleep between 7:00 and 15:00, that is, 8 hours later than under baseline conditions. Nocturnal wakefulness was enforced in light intensity averaging 1.500 lux, that is, very bright indoor light. For the next four 24-hour spans the same sleep schedule was maintained. Blood samples for 24-hour hormonal profiles, starting at 2:00, and sleep recordings were collected on the first, third, and fifth days of the shifted sleep period. Cortisol profiles are shown in Figure 3.

On the first day after the shift, profound disruptions in the 24-hour cortisol rhythm were found: a reduction of more than 3 hours in the duration of the quiescent period resulted in an increase of the 24-hour mean levels and in the advance of the circadian onset. Both a higher nadir value, due to the lack of the inhibitory effect of sleep onset, and a lower acrophase value, due to the lack of the stimulatory effect of awakening, were observed. As a consequence the relative amplitude of the rhythm was reduced by approximately 40%. The timing of the acrophase was delayed by about 3 hours and 30 minutes. On the third day, as a sign of partial adaptation to the new schedule, the circadian onset of cortisol was delayed by more than 5 hours, while the timing of the acrophase was delayed by more than 6 hours. Relative amplitude remained lower than at baseline. On day 5, the cortisol profile had essentially been adapted to the new schedule.

4.2. Advance of the Sleep-Wake Cycle. The impact on HPA axis activity of an acute 8-hour advance of the rest-activity cycle has also been examined [68]. In this study, eight healthy young subjects were studied for four consecutive days. The first day was a baseline condition and sleep was allowed between 23:00 and 7:00; on day 2 the sleep period was advanced, and subjects were allowed to sleep between 15:00 and 23:00. The same shifted cycle was maintained on day 3. Blood samples for plasma cortisol were collected for 68 consecutive hours, starting at 11:00, before the baseline night (Figure 4). In the first postshift period, compared with the baseline profile, the timing of the nadir was advanced by about 3 hours and 20 minutes; the quiescent period was markedly reduced mainly due to an advance of the offset by more than 3 hours. No shift in the timing of the acrophase occurred, thus the duration of the rising phase of cortisol secretion was increased by nearly 3 hours and presented a biphasic pattern. No significant changes were found in the acrophase value. These changes, together with the slight increase in the nadir values, resulted in a trend toward higher 24-hour mean levels. During the second postshift period (day 3), minor signs of further adaptation of the cortisol profiles were detected: there was no further advance of the

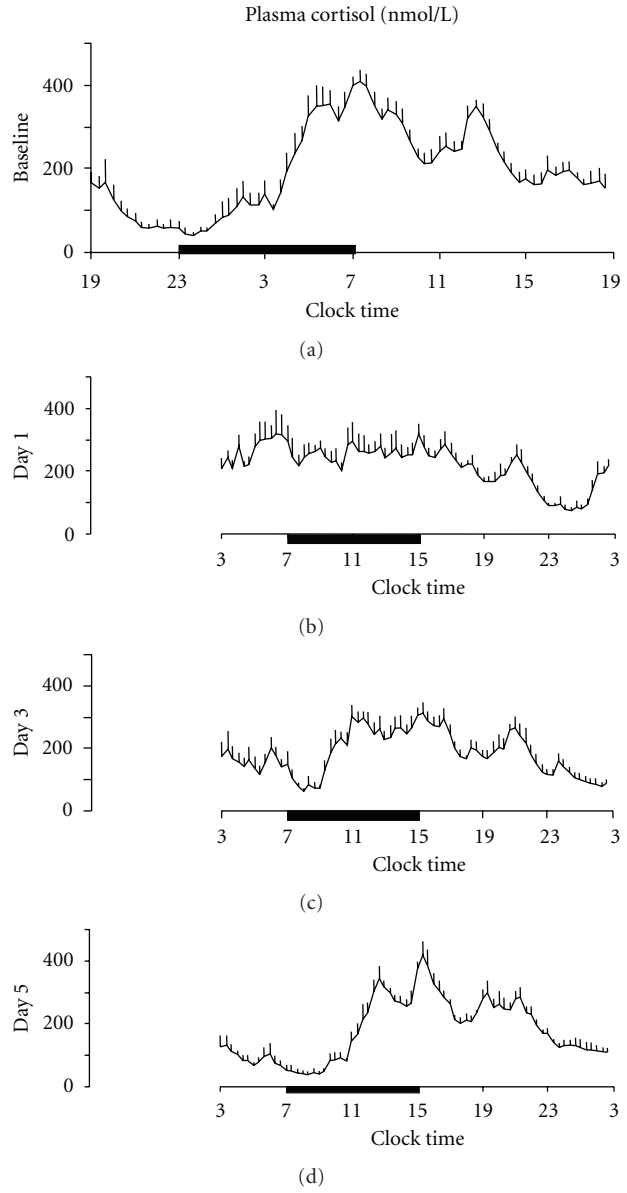

Figure 3: Effect of an 8-hour sleep delay on cortisol profiles. Mean 24-hour (+ SEM) cortisol profiles under baseline conditions (bedtimes from 23:00 to 7:00), and one, three, five days after an 8-hour delay of the sleep-wake and dark-light cycles (bedtimes from 7:00 to 15:00). Black bars represent the sleep periods. (Adapted from Buxton et al. [67].)

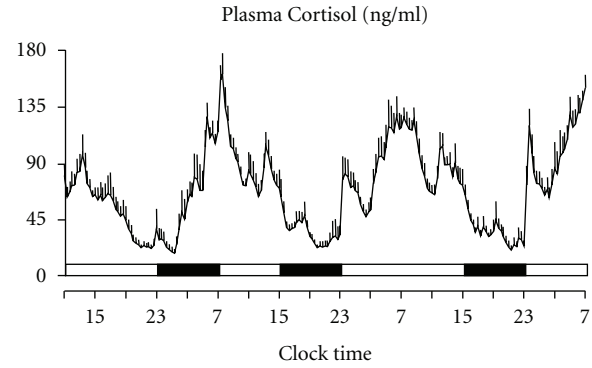

Figure 4: Effect of an 8-hour sleep advance on cortisol profiles. Mean (+ SEM) cortisol profiles obtained during 68 consecutive hours including baseline conditions and 2 postshift periods, that is, after an 8-hour advance of the sleep-wake and dark-light cycles. Black bars represent the sleep periods whereas wake time was spent in dim light conditions. (Adapted from Caufriez et al. [68].)

timing of the nadir and only a minor additional advance of the onset of the quiescent period. However a further shift of almost 1 hour was observed for the offset of the quiescent period. Hence, the findings of this study showed that an abrupt 8-hour advance of the sleep-wake, rest-activity and dark-light cycle results in a 3- to 4-hour advance of the timing of the nadir and of the end of the quiescent period, which are both reliable markers of central circadian rhythmicity. In this protocol, however, there was a temporal coincidence between the phase markers and the sleep-wake and dark-light transition (at 23:00), which elicited robust cortisol pulses. Thus, the advance of the timing of the nadir and of the end of the quiescent period may only partly reflect an advance of the circadian phase, because it could also be partly due to the effect of the awakening from the shifted sleep. The lack of adaptation of the timing of the acrophase to the new schedule has been interpreted as a consequence of the biphasic pattern of the cortisol rise after the shift: the first peak induced by the sleep-awakening transition may have delayed the subsequent circadian rise and prevented the advance of the timing of acrophase. Therefore, despite a relatively fast adaptation of some circadian markers, the lack of adaptation of acrophase, the longer duration of the rising phase, and the shorter duration of the quiescent period resulted in elevated cortisol levels at the time of the usual trough of the profile. Circadian misalignment may lead to central and peripheral deleterious consequences, such as memory deficit and insulin resistance [69–71].

5. Effects of Sleep Loss and Sleep Disrupion on HPA Axis

Given the modest but clearly detectable inhibitory effect exerted by sleep onset on the activity of the HPA axis, it has been hypothesized that sleep loss might increase cortisol levels. Protocols examining both acute total sleep deprivation (prolonged wakefulness for 24 hours, 48 hours, or even 72 hours) and semichronic partial sleep restriction (reduction of the nocturnal time in bed for a variable number of days) have been designed to test this hypothesis.

5.1. Acute Total Sleep Loss. Several studies have reported an elevation of cortisol levels both during the night of total sleep deprivation [13, 35, 72] and, if wakefulness was further prolonged, during the following day, particularly in the afternoon and evening [63, 73]. The findings of high glucocorticoid levels in a condition of acute sleep loss have been interpreted as reflecting the stress of the effort to maintain wakefulness and is consistent with the positive

correlation found between high frequency EEG activity in wake, indices of arousal, and cortisol release [63].

However, divergent findings have also been reported. Indeed, some authors have reported no change [41, 43, 74, 75] or even a slight decrease in cortisol levels [76, 77] after one or several nights of total sleep deprivation. These discrepancies could be due to a lack of control of experimental conditions, such as physical activity and posture, and/or to an insufficient frequency of blood sampling; indeed, short naps may have gone undetected and estimation of cortisol levels with infrequent blood sampling are often inaccurate. Findings of decreased cortisol levels after sleep deprivation have been interpreted as related to an increase in fatigue and sleepiness. Notably, the decrease in plasma or urinary cortisol found by Kant et al. [77] and Åkerstedt et al. [76] occurred after 48 hours or more of prolonged wakefulness. Hence, a biphasic HPA response to sleep deprivation has been suggested [63] where activation of the HPA axis, as part of the stress response, may be one of the arousal mechanisms recruited early on to adapt to sleep loss; however, when wakefulness is prolonged, the increased sleep pressure may eventually cause a blunting of the HPA axis activity.

Some protocols have examined cortisol profiles during the recovery night after a night of total sleep deprivation. Again contradictory results have been reported: while in some studies cortisol secretion seemed to be almost unaffected by recovery sleep following prolonged wakefulness [78–80], Vgontzas et al. [81] found a significant decrease in plasma cortisol levels, that appeared to be negatively correlated with the rebound increase of SWS. The timing of the period of recovery sleep is likely to have played a role in these conflicting findings.

5.2. Semichronic Partial Sleep Restriction. Recurrent partial sleep restriction has become a widespread habit in modern society [82] and its hormonal and metabolic consequences have only begun to be appreciated.

The first systematic study of HPA axis activity in a state of sleep debt assessed the effect of 6 consecutive nights of 4 hours in bed in eleven young men [83]. The sleep debt condition was compared with a fully rested condition, obtained after 6 nights of 12 hours in bed. Plasma and salivary cortisol were measured under both conditions. The state of sleep debt, as compared to the fully rested state, was associated with elevated cortisol concentrations in the afternoon and in the early evening and with a shorter quiescent period, due to a delay in its onset by nearly 1.5 hour. In addition, the rate of decrease of free cortisol concentrations in saliva between 16.00 hours and 21.00 hours was about six times slower in the sleep-debt than in the fully rested condition. Nine of the eleven subjects of the previous study participated, one year later, in a separate protocol with 8-hour bedtime, using the same experimental procedures. Interestingly, cortisol evening levels observed under 8-hour bedtime condition were intermediate between those measured under 4-hour and 12-hour bedtime conditions [84] (Figure 5).

Consistent findings indicative of an elevation of evening cortisol levels following partial sleep loss had been previously reported after only 1 night of sleep restricted to 4 hours in

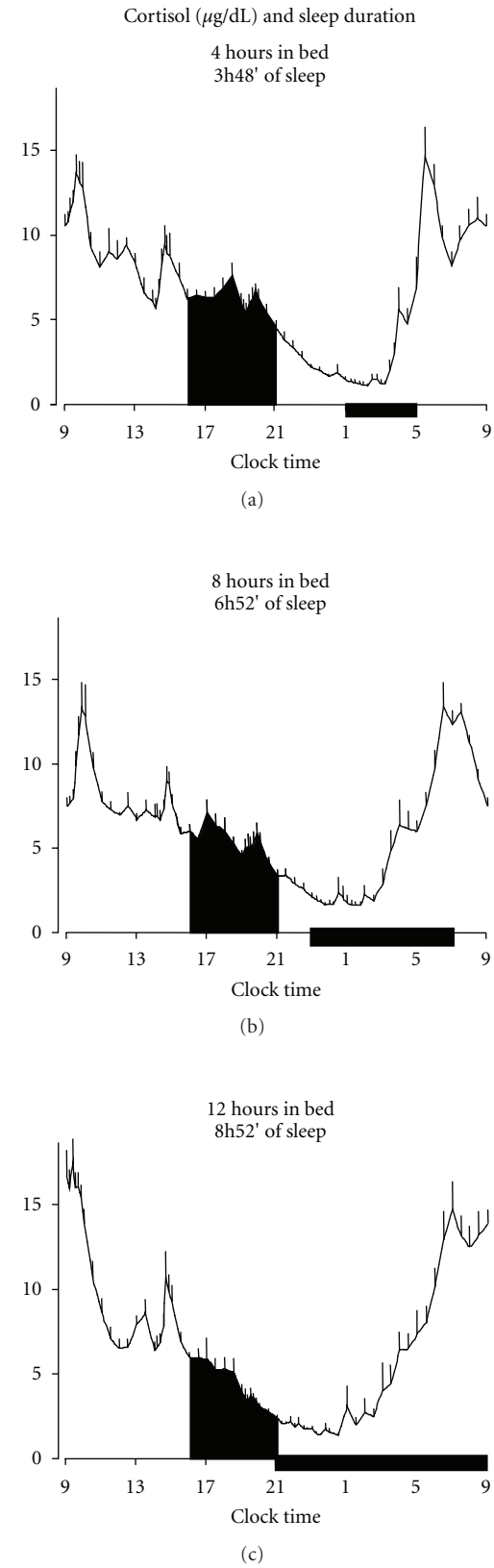

Figure 5: Inverse "dose-response" relationship between evening cortisol levels and sleep duration. Mean 24-hour (+ SEM) cortisol profiles and AUC (black areas) under 4 hours, 8 hours, and 12 hours bedtimes. Black bars represent the sleep periods. (Adapted from Spiegel et al. [84].)

bed [73]. In this study, plasma cortisol levels over the 1800–2300 hour period were 37% higher on the day following the night of restricted sleep than on the previous day, and the onset of the quiescent period occurred 1 hour later.

Thus, sleep deprivation appears to be associated with an elevation in evening cortisol levels that may reflect decreased efficacy of the negative feedback regulation of the HPA axis. Even if modest, this elevation may result, under conditions of chronic sleep loss, in a significant glucocorticoid overload and consequently expose the body to the central and peripheral deleterious effects associated with glucocorticoid excess.

In this regard, it is notable that chronic short sleepers have been found to have higher nocturnal cortisol levels compared with chronic long sleepers [40], suggesting that, even in the long term, mechanisms of adaptation and down-regulation of the HPA axis fail to occur. In a cross-sectional analysis of data collected from the Whitehall II study, the relationship between self-reported sleep duration, sleep disturbances, and salivary cortisol levels has been assessed in a cohort of more than 2700 middle-aged men and women [85]. Short sleep duration was associated with an acute increased cortisol awakening response and both short sleep duration and disturbances were independently associated with a slower rate of decline of cortisol levels across the day and thus with increased evening levels.

An increasing number of epidemiological studies have reported an association between short sleep duration and higher risk of developing obesity and type II diabetes [86–89]. The evidence summarized above suggests that HPA axis hyperactivity could be one of the mechanisms involved in the pathogenesis of these metabolic impairments.

5.3. Impact of Disrupted Sleep Quality. Only a few experimental studies have examined the effect of changes in sleep quality on activity of the HPA axis. Some of them were designed to suppress specific stages of sleep, others involved sleep fragmentation across all stages of sleep.

The two studies that examined the impact of SWS suppression on the temporal profiles of cortisol secretion had negative findings: the earlier study [90] conducted in young men, compared the nocturnal cortisol profile during a baseline night with that observed during partial SWS sleep suppression (between 2300 and 0200). The more recent study [91] investigated 24 hours cortisol profiles in a group of young men and women after 2 nights of normal sleep and after 3 nights of selective suppression of SWS throughout the night. In both studies, suppression of SWS was achieved by sending acoustic stimuli to the bedside whenever delta waves occurred and both studies attempted to avoid complete awakenings. Therefore stages of deep sleep were replaced with more shallow sleep, without increase in wake after sleep onset. No significant changes in cortisol profiles were found.

Decreased cortisol levels have been reported in a study of REM suppression [92]. However, REM sleep suppression was achieved through brief awakenings, resulting in a significant increase in wake time.

A recent experiment of sleep fragmentation led to different findings [93]. Following 2 nights of experimental sleep fragmentation across all stages, an increase in morning cortisol levels was observed, in association with a shift in the sympatho-vagal balance, estimated from the analysis of the heart rate variability towards an increase of sympathetic nervous system activity, and a decrease in insulin sensitivity.

6. HPA Axis and Sleep Disturbances in Clinical Syndromes

While sleep loss and sleep disruption are generally thought of as activating the HPA axis, there is in turn strong evidence that elevated CRH tone increases sleep EEG frequency, thereby decreasing SWS, and increasing light sleep and wakefulness [94]. In addition, CRH reciprocally activates the locus coeruleus/norepinephrine (LC/NE) system, one of the most important components of the arousal systems [95]. Consistently, CRH1 receptors, mediators of the CRH action, have been extensively studied as potential drug targets and a large number of CRH1 receptors antagonists have been developed for the treatment of stress-related diseases as well as sleep disorders [96]. Glucocorticoids, on the contrary, may exert a dual effect on sleep, depending on the prevailing concentrations: low levels of cortisol are associated with mineralocorticoid receptor (MRs) binding in the hippocampus, that mediate a negative feedback on hypothalamic CRH secretion. In contrast, at higher cortisol levels, glucocorticoid receptors (GRs) are activated, which may exert either inhibitory or excitatory feedback on CRH, depending on the location of the receptors. In times of stress, amygdala GRs may be preferentially activated, increasing CRH secretion, therefore promoting sleep disruption [8]. Moreover, it is well known that activation of HPA axis plays an essential causative role in the pathogenesis of metabolic and mood disorders that are often also associated with sleep disturbances [97, 98].

Given these functional links, it is not surprising that HPA hyperactivity, disturbed sleep, psychiatric disorders, and metabolic impairment are characteristic features of several clinical syndromes. We therefore describe below the interactions between sleep and HPA activity in insomnia, depression, Cushing's syndrome, and sleep disordered breathing (SDB).

6.1. Insomnia. Insomnia is a sleep disorder characterized by difficulties falling or staying asleep or having restorative sleep, associated with daytime impairment or distress [99]. Even though it is one of the most commonly encountered sleep disorders in medical practice, the understanding of its neurobiological basis and etiology is still limited and therefore even the treatment of this condition is challenging and often unsatisfactory [100].

Despite the evidence linking sleep and HPA axis, and the clear association between insomnia and perceived stress [101, 102], of which the HPA axis is a major mediator, there is a paucity of studies assessing HPA axis activity in this disorder.

An early study failed to show any difference in urinary cortisol excretion between control and self-reported poor sleepers [103]. However, the EEG recorded difference

between the two groups was only half an hour in total sleep time: such a small difference may have prevented the detection of alteration in cortisol secretion. On the contrary, in a more recent experiment, 24-hour urinary free cortisol excretion was positively correlated with polysomnographic indices of sleep disturbance in a group of adult insomniacs [104]. Moreover, a study that collected 24-hour plasma ACTH and cortisol profiles in young insomniacs and in matched healthy controls found mean ACTH and cortisol levels higher in insomniacs than in controls, with the stronger elevations observed in the afternoon, in the late evening and in the early part of the night [105] (Figure 6). In addition, within the insomniacs, those with a high degree of sleep disturbance, compared with those with a low degree of sleep disturbance, secreted a higher amount of cortisol, particularly in the evening and in the nighttime periods.

It is still matter of debate if the activation of the HPA system observed in insomnia is secondary to sleep loss or is, on the contrary, a marker of increased central CRH activity. In the latter case, the elevation of CRH tone, possibly following the repeated exposure to a stress, such as in the post traumatic stress disorder (PTSD), may be primarily responsible for the sleep disturbance. Even though some authors lean towards this second hypothesis, suggesting an HPA axis dysfunction as causative factor in the pathogenesis of insomnia [8, 105], a contribution of sleep loss to the evening cortisol elevation seen in insomniacs, cannot be ruled out. An intriguing and plausible model has been proposed to explain the perpetuation of chronic insomnia. In fact, evening cortisol levels while awake correlate with the number of awakenings during the subsequent night in subjects with and without insomnia [106, 107]. If elevated HPA activity before sleep promotes sleep fragmentation, sleep fragmentation and sleep loss have in turn been shown to increase evening cortisol levels, as discussed before. Taken together, these data suggest the occurrence of a vicious circle that could be responsible for the chronicity of insomnia. Of note, multiple studies have shown that insomnia precedes and is a risk factor for the development of psychiatric conditions, including depression and anxiety [101]. The activation of HPA axis in chronic persistent insomnia might play a role in the pathogenesis of these disorders.

6.2. Major Depression. Alterations of sleep architecture and HPA axis are commonly observed in patients with major depression.

Characteristic sleep-EEG findings in depressed patients include disturbed sleep continuity, increased wakefulness, shorter REM latency, and increased REM density [108–110]. Spectral analysis further reveals lower slow-wave activity during the first non-REM period [111].

Well-documented neuroendocrine changes in depressed patients include increased cortisol levels, in particular at the time of the cortisol nadir [112, 113], increased ACTH levels [113], lack of inhibition of cortisol to the suppression test with dexamethasone [114, 115] or exaggerated response of ACTH and cortisol to the combined dexametasone+CRH test [116]. An alteration of circadian rhythmicity, namely, a phase advance of the ACTH and cortisol nadir has been found in some studies [117, 118], but not in others [119, 120].

It is still unclear if these neuroendocrine and EEG alterations are a trait marker of depression, detectable independent from the phase (relapse or remission) of the syndrome or a state marker, able, therefore, to normalize during periods of remission.

One report documented a normalization of both ACTH-cortisol profiles and REM sleep in adult patients after recovery [117], but in other studies, cortisol levels or the response to Dex-CRH test were improved after recovery, but pathological sleep-EEG persisted [121–123].

Interestingly, it has been hypothesized that the nature and the extent of the alterations in HPA axis activity and in sleep architecture may help to identify distinct subtypes within major depression [124]. Indeed, an HPA overdrive seems to be most consistently observed in patients with melancholic features, associated with major sleep EEG alterations (low amount of SWS, short REM latency, high REM density). In contrast patients with atypical features may be characterized by reduced HPA activity, hypersomnia and less consistent alterations of SWS and REM sleep [124, 125].

6.3. Cushing's Syndrome. Endogenous Cushing's syndrome results from chronic exposure to excess glucocorticoids produced by the adrenal cortex. It may be caused by an excess of ACTH production (usually by pituitary adenomas, less frequently by extrapituitary ACTH- or CRH-secreting tumors) or it can result from the excess secretion of cortisol by unilateral adrenocortical tumors (benign or malignant) or by bilateral adrenal hyperplasia or dysplasia [126].

Hallmarks of the Cushing's syndrome are the loss of the typical circadian rhythm of cortisol secretion [127] associated with the peripheral and central consequences of the glucocorticoid excess: metabolic impairments (hyperinsulinism and insulin resistance decreased glucose tolerance, visceral adiposity, hyperlipidemia, and hypertension), coagulopathy, osteoporosis, and increased risk of psychiatric disorders (major depression, anxiety, mania, and cognitive dysfunctions).

Only a few studies have assessed sleep by polysomnography (PSG) in Cushing's syndrome.

In a recent experiment that analyzed nocturnal cortisol secretion in a group of patients with pituitary Cushing's syndrome compared with a group of matched healthy subjects, adrenal secretory activity was shown to start predominantly during periods of NREM sleep in both groups. Thus, even though the normal nocturnal circadian oscillation of pituitary-adrenal activity is absent or markedly blunted in Cushing patients, a link between pituitary-adrenal activity and the ultradian rhythmicity of REM-non REM sleep appears to be preserved [127].

Alterations of PSG recordings have been consistently found in Cushing's syndrome, confirming the deleterious effects of glucocorticoids at high concentrations on sleep architecture. A reduction of SWS has been reported [46, 128]. In one study disturbances of sleep continuity (increased sleep latency, enhanced waketime) and of REM sleep (shortened REM latency, elevated REM density) have been found

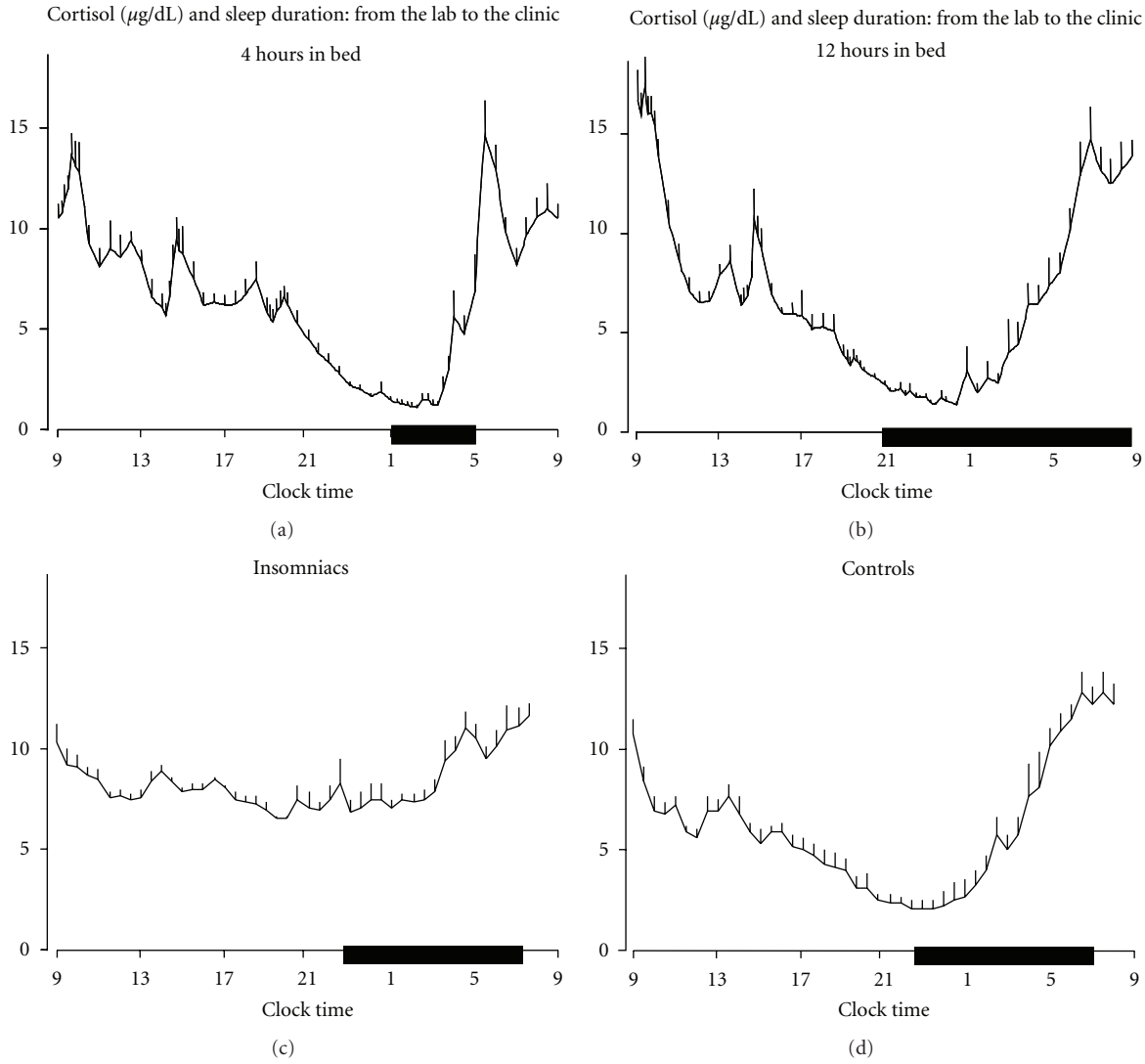

Figure 6: Cortisol rhythm under different sleep conditions. (a) and (b): 24-hour (+ SEM) cortisol profiles under 4 hours (a) and 12 hours (b) bedtimes (Adapted from Spiegel et al. [84]). (c) and (d): 24-hour (+ SEM) cortisol profiles in young insomniacs (c) and age, and BMI-matched controls (d) (Adapted from Vgontzas et al. [105]). Black bars represent the sleep periods.

[128]. Interestingly, these sleep alterations are similar to those occurring in major depression.

6.4. Sleep Disordered Breathing. Sleep disordered breathing (SDB) and, in particular, obstructive sleep apnea (OSA) are increasingly common conditions characterized by repetitive episodes of hypopnea or apnea, due to the loss of muscle tone in the upper airways; subsequent progressive hypoxemia and hypercapnia occur, followed by autonomic and EEG arousal aimed to open the airway and resume normal breathing. However, as sleep occurs again, the cycle repeats itself, throughout the night.

Major sleep disturbances result from this condition when untreated: total sleep time and sleep efficiency are reduced and sleep is more fragmented; wake, stage 1 and stage 2 are increased, SWS and REM sleep are markedly reduced [129, 130]. Treatment with continuous positive airway pressure (CPAP), that represents at the moment the most efficacious therapy for sleep apnea, has been shown to improve sleep architecture in SDB patients [131].

Moreover, important metabolic impairments are part of the clinical features that characterize this syndrome: indeed, SDB is associated with elevated body mass index (BMI), hypertension, increased risk of diabetes, insulin resistance and dyslipidemia [132]. Even though, until recently, it was unclear if alterations in glucose metabolism and hypertension were the results of obesity or of SDB per se, there is a growing evidence to indicate that SDB may represent an independent risk factor in the pathogenesis of these metabolic alterations [133–136].

The mechanisms that underlie this increased metabolic risk are not fully understood yet. It is likely that an increase in the sympathetic activity, secondary to the respiratory distress [137] or to the sleep loss/fragmentation per se [91] plays

a role in the development of metabolic morbidities associated with SDB.

The role of HPA axis has also been investigated, with the hypothesis of a hyperactivation of the axis, due to sleep fragmentation and sleep loss. An additional activating factor could be hypoxia, able to stimulate ACTH and cortisol secretion both in animals and in humans [138–140].

Contradictory findings have been reported regarding the effects of SDB on the HPA system and the results are limited by small sample sizes and methodological differences among the studies, such as variable hours of sleep recording and variable severity of SDB.

Elevated cortisol levels have been found in patients with OSA present in some studies [141, 142] but not in others [143, 144]. Responsiveness of ACTH to CRH administration has been shown to be higher in obese patients without OSA compared with lean subjects and to be even higher in obese patients with OSA [145], probably as the result of an alteration in the central control of ACTH secretion, as well as of an impaired sensitivity to the negative feedback action of glucocorticoids. In a recent study the existence of a mild hypercortisolism in OSA patients has been suggested by the finding of a blunted response of cortisol to the dexamethasone suppression test [146].

The effects of CPAP therapy on cortisol levels have also been investigated. Some authors have reported that CPAP does not reduce cortisol levels [147] or that acute withdrawal of CPAP treatment does not result in an increase in cortisol levels [148]. On the contrary, CPAP does reverse hypercortisolemia according to other authors [149, 150], particularly with prolonged use [142]. Noteworthy, several of these studies were limited in that cortisol was measured at a single time point, and consequently do not measure potential clinically important HPA axis and rhythm changes. Variable compliance levels may also explain discrepant findings. In a recent study that measured nocturnal cortisol profiles, sleep apnea in obese men compared with nonapneic obese controls was associated with an elevation of cortisol levels, which was corrected after 3 months of CPAP use [151].

HPA hyperactivation, as result of sleep disturbance, hypoxemia,s and autonomic activation, may play a significant role in the development of the metabolic alterations that characterize OSA. Given the impact of OSA on sleep architecture, it may contribute to the perpetuation of the sleep disorder. Moreover, it may be a risk factor for insomnia and depression, as both are associated with hypercortisolemia.

7. Conclusions

The interaction between sleep and the HPA axis is complex and bidirectional. HPA hyperactivity and decreased sleep duration/quality seem to be tightly linked in a vicious circle and could play an essential causative role in the pathogenesis of metabolic and mood disorders. Hypercortisolism, sleep disturbances, metabolic and psychiatric impairments are common features of several clinical syndromes, such as insomnia, depression, Cushing's syndrome, and SDB. The exact understanding of the interaction between sleep physiology and HPA activity appears to be a crucial prerequisite to better elucidate the physiopathology of these syndromes and may lead to new forms of prevention and treatment.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 326151, 12 pages
doi:10.1155/2010/326151

Research Article

Modulation of Sleep Homeostasis by Corticotropin Releasing Hormone in REM Sleep-Deprived Rats

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Received 17 December 2009; Accepted 5 April 2010

Academic Editor: Jessica A. Mong

Studies have shown that sleep recovery following different protocols of forced waking varies according to the level of stress inherent to each method. Sleep deprivation activates the hypothalamic-pituitary-adrenal axis and increased corticotropin-releasing hormone (CRH) impairs sleep. The purpose of the present study was to evaluate how manipulations of the CRH system during the sleep deprivation period interferes with subsequent sleep rebound. Throughout 96 hours of sleep deprivation, separate groups of rats were treated i.c.v. with vehicle, CRH or with alphahelical CRH_{9-41}, a CRH receptor blocker, twice/day, at 07:00 h and 19:00 h. Both treatments impaired sleep homeostasis, especially in regards to length of rapid eye movement sleep (REM) and theta/delta ratio and induced a later decrease in NREM and REM sleep and increased waking bouts. These changes suggest that activation of the CRH system impact negatively on the homeostatic sleep response to prolonged forced waking. These results indicate that indeed, activation of the HPA axis—at least at the hypothalamic level—is capable to reduce the sleep rebound induced by sleep deprivation.

1. Introduction

One of the most interesting sleep phenomena is its homeostatic regulation, which can be manifest by the rebound in sleep that ensues after total or partial sleep deprivation, for example, increased time spent in sleep during the recovery period [1]. This phenomenon, known as sleep rebound, is also observed after deprivation of selected sleep stages, when recovery of the suppressed stage is observed [2]. However, sleep deprivation is considered a form of stress both in humans [3] and rats (for review, see [4]), although there is not complete agreement on the matter [5]. Animal models of sleep deprivation indicate that not only the loss of sleep per se, but also the method employed to induce sleep deprivation generates stress, resulting in increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, with elevated corticosterone (CORT) and adrenocorticotropic (ACTH) plasma levels and adrenal hypertrophy [6–9]. Additional data demonstrate that sleep deprivation induces increased immunoreactivity [10] and expression of hypothalamic CRH [11].

Interestingly stressors can induce specific changes in sleep patterns, including increased REM sleep after immobilization stress [12], increased slow wave sleep after social defeat stress [13], and decreased REM sleep after footshock [14–16]. When associated with sleep deprivation, however, immobilization stress inhibits the homeostatic REM sleep rebound [17], whereas intermittent chronic foostshock exacerbates the expression of REM sleep during recovery, in an apparently prolactin- and CORT-dependent effect [18]. Curiously, both exogenous corticosterone administration and dexamethasone treatment inhibit sleep in unstressed rats [19, 20] or after immobilization stress [21], indicating that other mediators participate in this phenomenon. Corticotropin-releasing hormone (CRH), the primary orchestrator of the endocrine stress response, is synthesized in the paraventricular nucleus of the hypothalamus [22] and is a major regulator of waking in rats [23–25]. It increases neuronal excitability and convulsions [26], and stimulates the locus coeruleus noradrenergic neurons [27]. CRH receptors are densely distributed in basal prosencephalic areas, thalamus, hypothalamus, mesencephalus,

brainstem, and pons [28], areas which are involved in cerebral activation and waking maintenance [29].

The pioneering study by Ehlers and coworkers [25] on the effects of CRH on sleep in rats demonstrates that low doses of this peptide reduce slow wave sleep (NREM) and low frequency activity. However, in high doses, CRH exhibits an opposite effect and reduces fast frequency activity (32–64 Hz). In human beings, however, peripheral administration of CRH does not significantly alter REM sleep [30]. Moreover, CRH modulates the homeostatic rebound induced by sleep deprivation, by increasing REM sleep rebound when administered immediately after the sleep deprivation procedure [31]. In contrast, α-helical-CRH$_{9-41}$ (αhCRH), a CRH receptor blocker, prevents immobilization stress-induced sleep rebound and does not influence sleep in stress-free conditions [32].

In an attempt to determine the role of hormones of the HPA axis, we recently demonstrated that 96 hours of REM sleep deprivation together with repeated administrations of metyrapone, a corticosterone synthesis inhibitor, impaired sleep deprivation-induced NREM compensation [33]. We then hypothesized that increased production of CRH elicited by removal of the CORT negative feedback signal at the hypothalamic level [34] could be, at least in part, responsible for this effect. If this hypothesis were correct, then i.c.v. administration of CRH in sleep-deprived rats should produce similar results to those obtained with metyrapone, and α-helical-CRH$_{9-41}$ and should increase sleep rebound in these animals.

2. Methods

2.1. Subjects. Male adult Wistar rats (350–450 g) from the animal facility of the Department of Psychobiology—UNIFESP—were used (eight to ten animals per group) and prior approval from the Ethics Research Committee of Universidade Federal de São Paulo was obtained in accordance with international guidelines for care in animal research (CEP 0125/04). Constant 12 hours light-dark cycle (fluorescent white lamps-lights on at 7:00 h) and 20–22°C temperature were maintained in all experimental rooms throughout the experimental protocol. Rats were allowed free access to food and water.

2.2. Electrophysiological Procedures. Under ketamine-xylazine anaesthesia (9.0–10.5 mg/kg, i.p.), rats were fitted with electrodes to monitor the sleep-wake cycle: two bipolar electrodes placed ipsilaterally with stainless-steel micro-screws (0.9 mm in diameter) were used for EEG monitoring: one pair on the right lateral parietoparietal (for minimum theta activity EEG) and the other on the left medial frontoparietal (for maximum theta activity EEG) areas [35, 36]. One pair of insulated nickel-chromium flexible fine wire electrodes was implanted in the dorsal neck muscle for EMG recording. For intracerebroventricular—i.c.v. injections, a 22-gauge stainless steel guide cannula (constructed from hypodermic needle, Becton Dickinson, Brazil, cut at 10 mm in length) was inserted 1.0 mm posterior to bregma, 1.4 mm lateral to midline, and 3.4 mm ventral to dura membrane, within the EEG electrodes. The guide cannula was covered with an easily removable lid adopted from a fine stainless steel wire, which was inserted tightly onto the guide cannula hole. After the surgical procedure, antibiotics (Pentabiótico Fort-Dodge, Brazil) and sodium diclofenac were administered and the animal was allowed to recover from surgery for 15 days. Three days before the beginning of experiments, lateral ventricular cannula placement was verified by assessing the drinking response elicited to up to 5 nmol angiotensin II administration. After the multiple injections schedules, the ventricular cannula placement was confirmed postmortem by injection 3 μL of methylene blue followed by microscope visualization. Animals were habituated to the cables and to the recording environment for 3 days before baseline recording. Baseline sleep was recorded on two consecutive days (2×24 hours) and the parameters are represented by the average of these two days. After the baseline recording, in the period that preceded REM sleep deprivation (REMSD), animals were adapted to the sleep deprivation chambers for 30 minutes per day for three consecutive days.

Electrophysiological signals were recorded on a digital polygraph (Neurofax QP 223 A Nihon Kohden Co., Tokyo, Japan). After conventional amplification, the EEG signals were conditioned through analog filters, using cut off frequencies of 1.0 Hz and 35.0 Hz and were then sampled at 200 Hz using a 16 bit A/D converter. Recordings were displayed on 10 s epochs and submitted off-line to visual scoring routine, as described previously [37]. In summary the stages of wake-sleep were defined as follows: (a) waking (low voltage and high frequency EEG, whereas EMG displays high voltage during active waking or low during voltage quiet waking); (b) NREM sleep (EEG high voltage within slow waves and spindles, also classified, separately, in low—between 2.0 and 3.0 μV, and high amplitudes—from 3.0 μV on, and low EMG amplitude); and (3) REM sleep (low EEG voltage with prominent theta rhythm on medial EEG deviation accompanied of the very low EMG activity). Each 10 s epoch was characterized by the predominant wave pattern present in more than half of the epoch. In some periods, interference or noise made it impossible to characterize the behavioral state and a critical evaluation of the previous and subsequent periods was made. The percentage of 10 s periods excluded from sleep scoring was below 9%.

The parameters used for sleep analysis were the following: total sleep time, total NREM time (considering low and high amplitude fractions) REM time and bouts, and total wake time—active and quiet periods—and episodes of waking (2.0 minutes). Fast Fourier Transform (Hanning window) was computed on 256 points for each 10 s epochs (corresponding to each vigilance state) with a resolution of 0.78 Hz (null value was attributed to the remaining time). Nonoverlapping bands were set giving 0.5 Hz bins from 1.0 to 5.0 Hz, and 1.0 Hz bins from 5.1 Hz to 25.0 Hz; those above 25.0 Hz were discarded from the analysis. EEG epochs containing noise or artifacts (those that did not allow doubtful behavioral state classification) were excluded from the analysis by visual inspection and/or spectral tools (e.g., if average power exceeded 2000 μV^2 over a 1.0–25.0 Hz

frequency range). Slow wave activity was calculated as mean power density on 1.0–4.0 Hz band (delta) and the theta-delta ratio, dividing the power density of the fast theta (6.0–9.0 Hz) band by the mean power density on the delta band. Although two ipsilateral bipolar electrodes were used for sleep scoring, only the lateral parietoparietal deviation was used for spectral data analysis, except for the theta-delta ratio, when the two deviations were employed (the lateral to delta and the medial frontoparietal to theta activity measures).

2.3. REM Sleep Deprivation (REMSD) Procedure and Drug Administration. Sleep deprivation was accomplished by the single platform method, in which each animal was placed onto a narrow cylindrical platform, 6.5 cm in diameter, surrounded by water to about 1 cm below the platform surface. This method is well known to selectively suppress REM sleep; however, it also produces partial NREM deprivation, with 37–50% reduction from baseline levels [38, 39].

CRH (Sigma, USA): 3 μg/animal [22, 40, 41] or αhCRH (Sigma, USA): 20 μg/animal [42–44] were diluted in artificial cerebrospinal fluid—ACSF (NaCl 127 mM, KCl 2.5 mM, $MgCl_2$ 0.9 mM, Na_2HPO_4 1.2 mM, $CaCl_2$ 1.3 mM, $NaHCO_3$ 21 mM, $C_6H_{12}O_6$ 3.4 mM, and pH 7.3, sterile- and pyrogen-free) and administered twice/day, at 7:00 h and 19:00 h, in addition to a single injection at the end of the REM deprivation period, making a total of nine administrations. Control animals were treated with ACSF under the same scheme. Final volume of each i.c.v. injection was 3-4 μL, delivered at a flow rate of 1.5 μL/minute with an injection cannula, made from another 30-gauge dentist needle (Becton Dickinson, Brazil, cut at 25 mm in length, but inserted into guide cannula up to 10.5 mm limit) connected to a polypropylene tubing (PE 10, Becton Dickinson, USA) which, in turn, was linked on another terminal end to a 10 μL microsyringe (Hamilton, USA), placed onto a automatic microinfusion pump (Insight, Brazil). Prophylactic aseptic techniques were strictly employed during all administrations and less than 20% of animals were not used during the chronic experiments because of signs of infection (e.g., fever, weight loss, apathy, wet fur, and poor physical appearance). After four days under this protocol, rats were returned to sleep freely in their individual home cages (recovery period). Over the subsequent three days, the rats were continuously monitored.

2.4. Plasma Hormone Determination. Trunk blood was obtained by decapitation, approximately 2 hours after the last administration from matched groups, run simultaneously with the sleep study. During this period, the REMSD animals were not allowed to sleep (they were put back into the deprivation chambers). Blood was collected in chilled K_2EDTA (0.46 mM, e.g., 7.5% solution at a volume of 0.1 mL diluted in 5 mL of blood)-containing vials, centrifuged at 2300 rpm at 4°C for 20 minutes, and plasma was collected and frozen at −20°C for further analysis. Plasma ACTH was determined by sequential immunometric assay (DPC Immulite, Los Angeles, CA) and the sensitivity of the method is 9 pg/mL, and intra- and interassay variations are 9.4% and 9.6%, respectively. Corticosterone levels were assayed by specific radioimmunoassay (INC Biomedicals, Costa Mesa, CA). The sensitivity of the assay is 1.25 ng/mL and the intra- and inter-assay variations are, respectively 6.5% and 7.1%, as informed by the manufacturer. All samples were assayed in duplicate.

2.5. Statistics. Hormonal data were analyzed by a two-way ANOVA, with main factor Group (CTL—control home cage and REM sleep deprivation—REMSD) and Treatment (ACSF, CRH, and αhCRH). Sleep parameters were analyzed by a two-way ANOVA for repeated measures, with main factors Treatment (ACSF, CRH, and αhCRH) and Day (repeated measure: Baseline and Recovery days 1 [R1], 2 [R2], and 3 [R3]). The spectra power density was analyzed by Student's t tests for independent samples, every 12 hours period, for each behavioral state separately. The theta-delta ratio was analyzed by covariance analyses (ANCOVA) where the baseline index was the predictive factor and treatments, the independent variable. All EEG data were analyzed during the light and dark phases, separately. Posthoc analysis was performed by the Newman-Keuls test. The level of significance was set at $P \leq .05$.

3. Results

3.1. HPA Axis Hormones (Figure 1)

ACTH. There was a significant interaction between Group and Treatment ($F_{2,54} = 0.67$, $P \leq .0005$), in which REMSD + ACSF animals showed higher ACTH levels than their CTL counterparts ($P \leq .05$), whereas REMSD+ αhCRH animals exhibited lower levels than CTL+ αhCRH ones ($P \leq .05$). In addition, in CTL animals, both CRH and αhCRH resulted in higher ACTH levels than ACSF administration ($P \leq .0005$).

Corticosterone. Again, a significant interaction between Group and Treatment ($F_{2,53} = 19.52$, $P \leq .00005$) was found. Newman-Keuls analysis of this interaction showed that all groups exhibited higher corticosterone plasma levels than CTL + ACSF animals (CTL+CRH: 853.3%, $P \leq .0005$; CTL + αhCRH: 230.5%, $P \leq .05$; REMSD + ACSF: 115.4%, $P \leq .05$; REMSD + CRH: 575.6%, $P \leq .0005$ and REMSD + αhCRH: 747.6%, $P \leq .0005$). However, CRH treatment in REMSD rats resulted in lower CORT levels than in CTL rats (−29.1%, $P \leq .01$), although they were still higher than REMSD+ACSF animals (213.6%, $P \leq .0005$). On the other hand, αhCRH treatment led to higher CORT levels in REMSD than in CTL (156.4%, $P \leq .0005$) and REMSD + ACSF rats (293.5%, $P \leq .0005$). Finally, CORT concentrations were lower in CTL + αhCRH than in CTL+CRH (−65.33%, $P \leq .0005$).

3.2. Sleep Parameters

3.2.1. Total Sleep Time (Figure 2)

Light Phase. A main effect of Day ($F_{3,63} = 2.52$, $P \leq .00001$) was found. Reduced sleep time was observed on the 2nd

(10.2%, $P \leq .05$) and 3rd recovery days when compared to baseline (22.9%, $P \leq .0005$).

Dark Phase. Again main effect of Day was observed ($F_{3,63} = 13.89$, $P \leq .00001$). Animals showed 24.4% increased sleep time on the first recovery day ($P \leq .001$).

3.2.2. Total NREM Time (Figure 2)

Light Phase. A main effect of Day was detected ($F_{3,63} = 6.84$, $P \leq .0005$). Total NREM was reduced (20.3%) on the 3rd recovery day, relative to baseline.

Dark Phase. An effect of Day emerged ($F_{3,63} = 9.05$, $P \leq .00005$) and the rats showed more NREM (16.8%, $P \leq .01$) than baseline.

3.2.3. REM Sleep Time (Figure 3)

Light Phase. A main effect of Day was found ($F_{3,63} = 22.70$, $P \leq .00001$). Animals showed an increase on this phase (53.3%, $P \leq .0005$) during the first recovery day, whereas a reduction of REM was also observed during the last recovery day (32.8%, $P \leq .02$).

Dark Phase. Again, a main effect of Day was found ($F_{3,63} = 15.32$, $P \leq .00001$) and the animals showed an increase of 71.2% ($P \leq .0005$) during first recovery day, when compared to baseline amounts.

3.2.4. REM Bouts (Figure 3)

Light Phase. A main effect of Day was found ($F_{3,63} = 11.29$, $P \leq .00001$) and a decrease of REM bouts was detected on the 3rd recovery day (39.3%, $P \leq .0005$).

Dark Phase. Again, a main effect of Day was detected ($F_{3,63} = 7.83$, $P \leq .0005$). During the first recovery day, animals displayed more bouts than baseline sleep ($P \leq .01$).

3.2.5. Mean Length of REM Episodes (Figure 3)

Light Phase. A two-way interaction between Day and Treatment was found ($F_{6,63} = 3.59$, $P \leq .005$). Posthoc analysis showed that REM episodes were longer after ACSF administration than at baseline (124.2%, $P \leq .0005$). Administration of CRH (45.5%, $P \leq .005$) and αhCRH (40.0%, $P \leq .005$) shortened the length of REM episodes during the first recovery day compared to ACSF-treated rats.

Dark Phase. There was a Day effect ($F_{3,57} = 4.10$, $P \leq .02$), in which the animals showed longer REM episodes on the first recovery night (28.7%, $P \leq .05$).

3.2.6. Total Wake Time (Figure 4)

Light Phase. A two-way interaction between Day and Treatment was detected ($F_{6,63} = 3.53$, $P \leq .005$) and post-hoc tests revealed that CRH-treated animals spent more time awake during the last recovery day than in baseline (41.8%, $P \leq .01$).

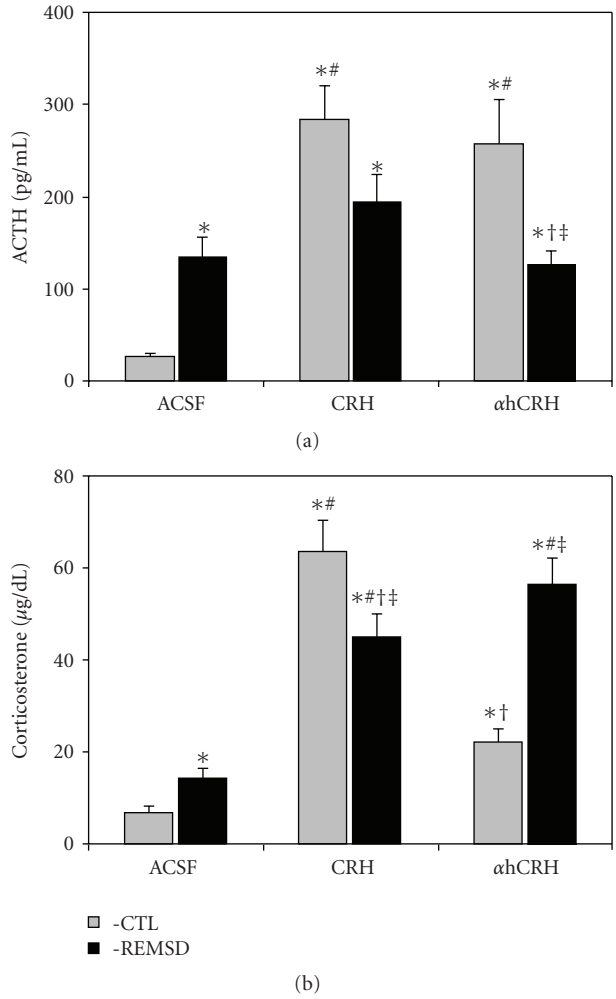

Figure 1: *ACTH and CORT Plasma Levels*. CTL, Control; ACSF, artificial cerebrospinal fluid; CRH, corticotrophin-releasing hormone; αhCRH, alpha-helical CRH_{9-41} *- different from CTL+ACSF, $^{\#}$- different from PSD+ACSF, and †- different from CTL+CRH, ‡- different from CTL+αhCRH; ANOVA, followed by Newman-Keuls test, $P \leq .05$.

Dark Phase. A two-way interaction was found between Day and Treatment ($F_{6,63} = 2.94$, $P \leq .02$) and both CRH- and αhCRH-treated rats showed less total wake during the first recovery day than on baseline (19.1%, $P \leq .05$ and 21.4%, $P \leq .05$, resp.).

3.2.7. Number of Awakenings (Figure 4)

Light Phase. A two-way interaction was found ($F_{6,63} = 2.61$, $P \leq .05$). Post-hoc tests showed that CRH-treated rats displayed more events of awakenings during the last recovery day relative to baseline (62.6%, $P \leq .05$).

Dark Phase. No changes were found.

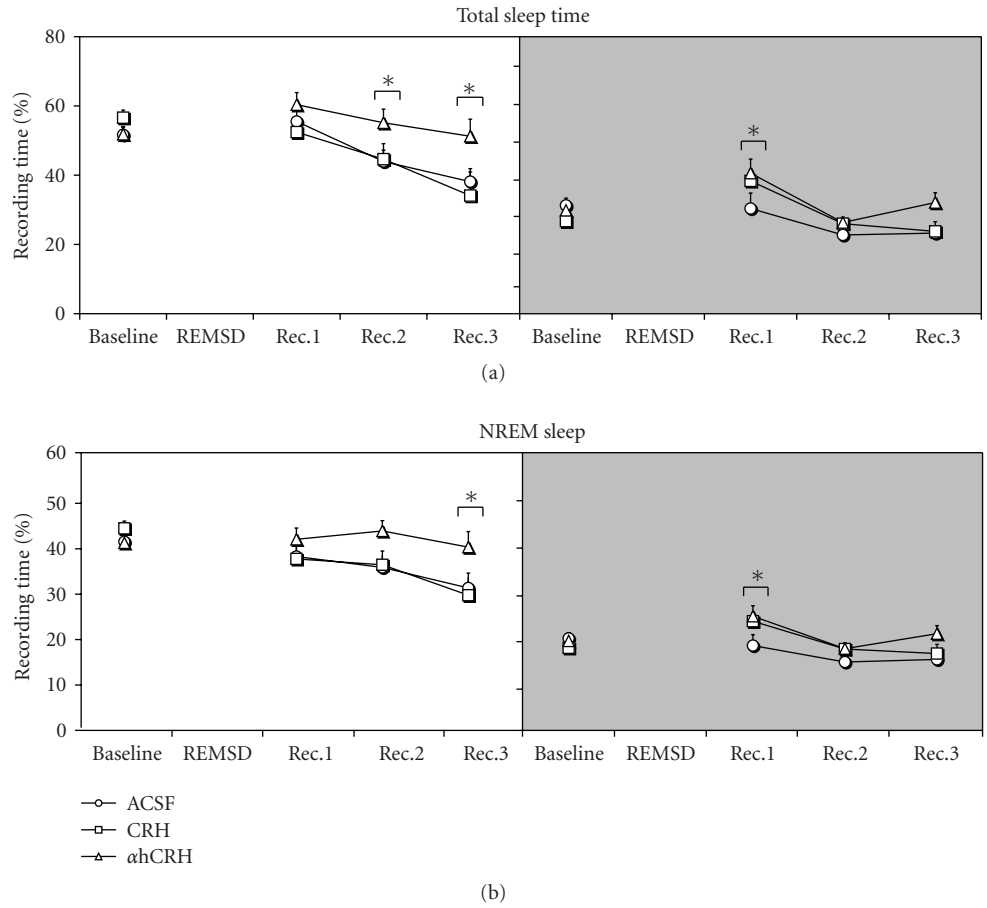

Figure 2: *NREM Sleep*. Data were obtained in recording periods of approximately 11 hours during the light and dark phases. ACSF, artificial cerebrospinal fluid; CRH, corticotrophin-releasing hormone; αhCRH, alpha helical CRH_{9-41}; REMSD, 96 hours REM sleep deprivation period; Rec. Recovery period. The white back panels indicate the light phase and the shaded ones, the dark phase. * - different from baseline, effects of day are indicated by connecting lines above the symbols. ANOVA, followed by Newman-Keuls, $P \leq .05$.

3.3. Spectral Data

3.3.1. Spectral Power during NREM (Figure 5)

Light Phase. During the third recovery day, CRH-treated animals showed reductions in the 19.01–20.0 Hz (19.2%, $P \leq .05$) and 20.1–21.0 Hz bands (18.4%, $P \leq .05$) when compared to ACSF-treated rats. Moreover, increased power above ACSF animals was observed in the 1.6–2.0 Hz band (53.3%, $P \leq .02$) in CRH- and in the 1.0–1.5 Hz band (34.8%, $P \leq .05$) in αhCRH-treated groups.

Dark Phase. On the second recovery day, αhCRH led to increased power in the 1.0–3.0 Hz bands (average of 4 bins of 0.5 Hz each = 53.7%, $P \leq .05$), when compared to ACSF group and increased all bands above 6.0 Hz when compared to CRH-treated rats (average of 19 bins of 1.0 Hz each = 28.5%, $P \leq .05$). Finally, during the last recovery day, αhCRH produced an increase in all bands above 7.0 Hz when compared to CRH-treated animals (average of 18 bins of 1.0 Hz each = 27.1%, $P \leq .05$).

3.3.2. Theta-Delta Ratio (Figure 6)

Light Phase. A main effect of Treatment was detected for active wake (AW) ($F_{2,20} = 4.45$, $P \leq .05$) and post-hoc analysis showed that CRH animals showed reductions of θ/δ relative to ACSF (12.3%, $P \leq .05$) and αhCHR rats (17.6%, $P \leq .01$). During Quiet Wake (QW), effect of Treatment was again revealed ($F_{2,19} = 3.94$, $P \leq .05$), and CRH-displayed smaller θ/δ ratio than αhCHR-treated animals (16.8%, $P \leq .01$). No effects were found in Low-Amplitude NREM (L-NREM) or in High-Amplitude NREM (H-NREM) during the recovery period. During REM sleep, a significant effect of Treatment ($F_{2,20} = 7.14$, $P \leq .005$) and an interaction between Day and Treatment ($F_{4,40} = 2.90$, $P \leq .05$) were found. In regards to the Treatment factor, CRH-treated animals showed a smaller θ/δ ratio than ACSF- (15.6%, $P \leq .01$) and αhCHR-treated animals (22.1%, $P \leq .005$). No post-hoc differences were detected for the interaction.

Dark Phase. During AW a main effect of Day was observed ($F_{2,40} = 12.61$, $P \leq .00005$); however, the post-hoc analysis

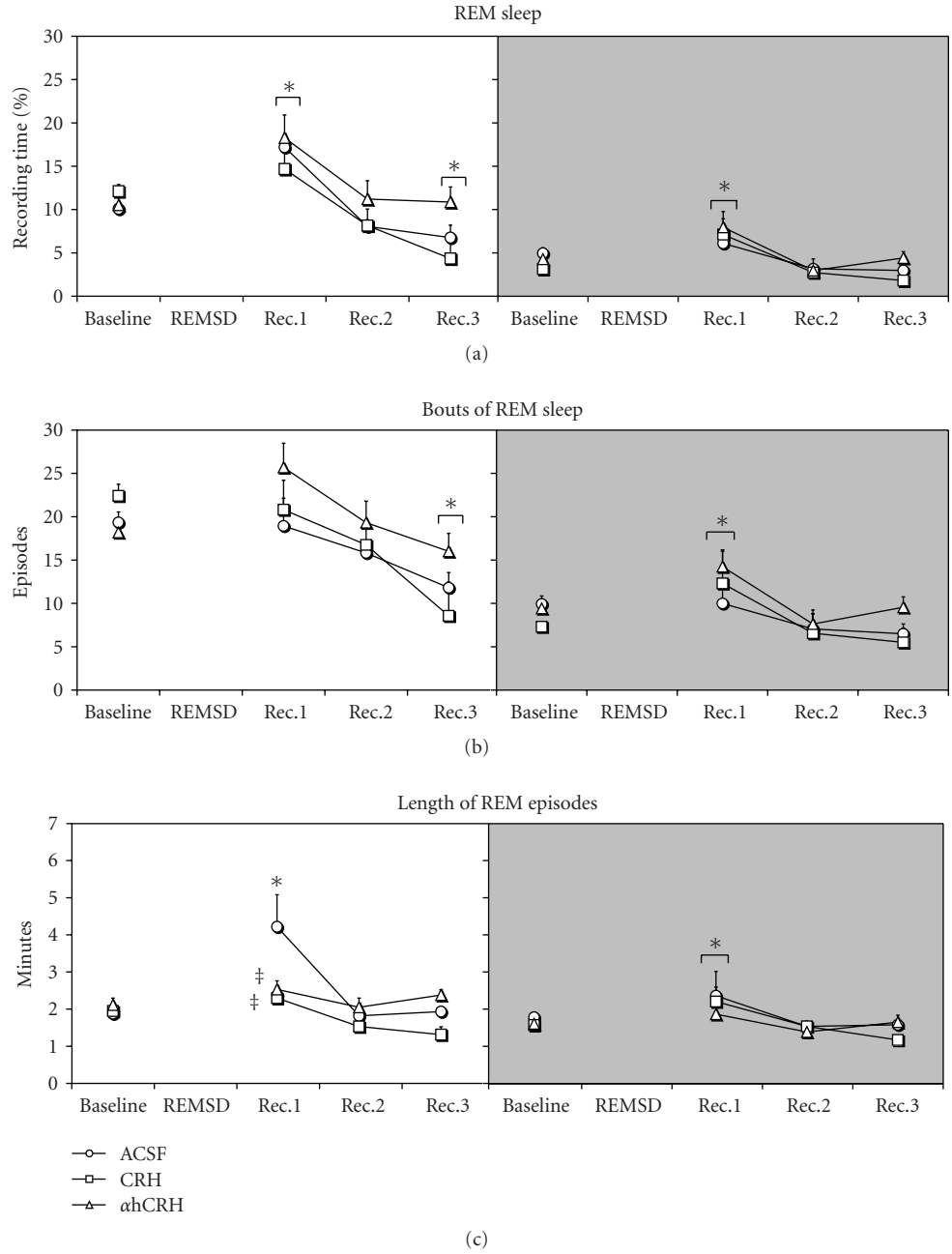

Figure 3: *REM Sleep*. Data were obtained in recording periods of approximately 11 hours during the light and dark phases. ACSF, artificial cerebrospinal fluid; CRH, corticotrophin-releasing hormone; αhCRH, alpha helical CRH_{9-41}; REMSD, 96 hours REM sleep deprivation period; Rec. Recovery period. The white back panels indicate the light phase and the shaded ones, the dark phase. *- different from baseline, ‡- different from ACSF group. Main effects of day are indicated by connecting lines above the symbols. ANOVA, followed by Newman-Keuls, $P \leq .05$.

did not revealed any differences among the days. For QW, main effects of Treatment ($F_{2,20} = 3.59$, $P \leq .05$) and Day ($F_{2,40} = 10.27$, $P \leq .0005$) were found. The Newman-Keuls test showed that CRH treatment reduced θ/δ ratio when compared to ACSF (9.7%, $P \leq .05$) and αhCHR (15.0%, $P \leq .005$) treatments. In regards to the effect of Day, there was a reduction of θ/δ on the 3rd compared to the 1st recovery day (6.1%, $P \leq .05$). No effects were detected in L-NREM, whereas a main effect of Day was detected in H-NREM ($F_{2.40} = 3.35$, $P \leq .05$) and the post-hoc analysis showed that the θ/δ ratio was reduced on the 2nd and 3rd recovery days (9.7%, $P \leq .0001$ and 13.7%, $P \leq .0001$, resp.). During REM sleep, a main effect of Treatment was detected ($F_{2,18} = 4.00$, $P \leq .05$) and CRH treatment reduced the θ/δ ratio compared to ACSF (12.4%, $P \leq .05$) and to αhCHR (17.1%, $P \leq .01$).

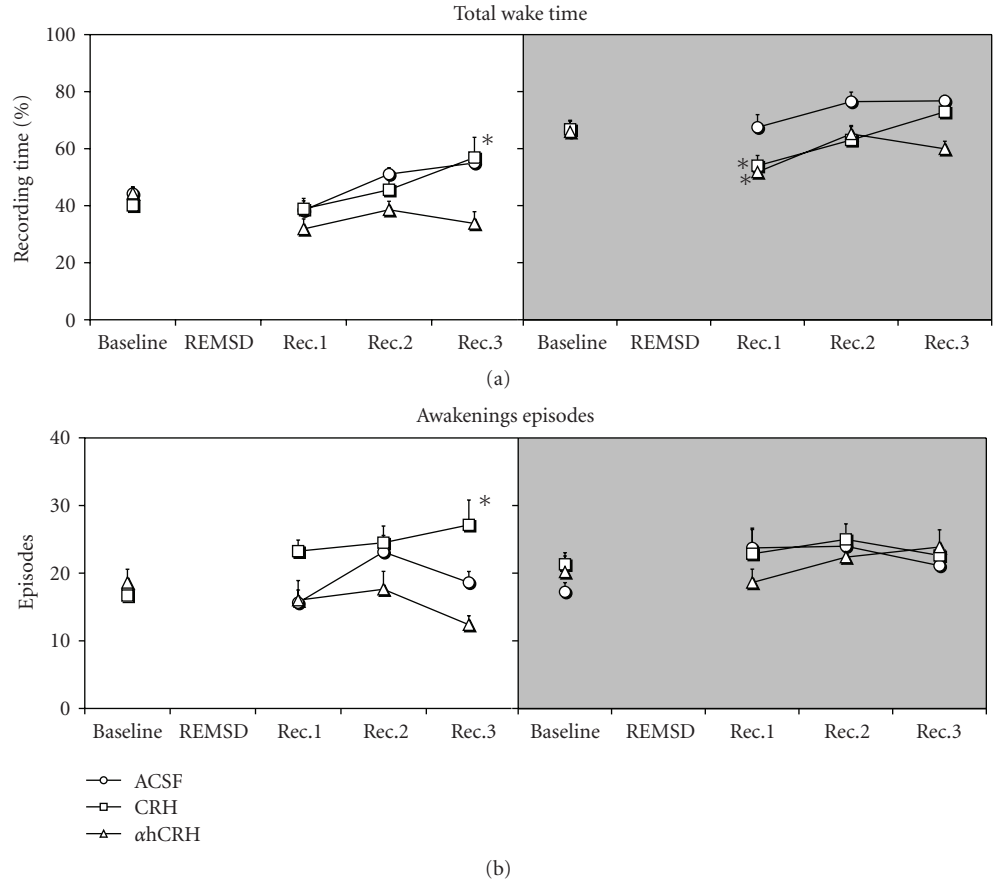

Figure 4: Awake. Data were obtained in recording periods of approximately 11 hours during the light and dark phases. ACSF, artificial cerebrospinal fluid; CRH, corticotrophin-releasing hormone; αhCRH, alpha helical CRH_{9-41}; REMSD, 96 hours REM sleep deprivation period; Rec, Recovery period. The white back panels indicate the light phase and the shaded ones, the dark phase. * - different from baseline. Main effects of day are indicating by connecting lines above the symbols. ANOVA/Newman-Keuls, $P \leq .05$.

4. Discussion

The main results of the present study can be summarized as follows: (1) both CRH and αhCRH increased ACTH and CORT secretions, although these were lower in REMSD than in control rats; (2) both peptides impaired sleep in later periods of the recovery sleep, but did not interfere with the immediate sleep rebound, except for a reduction in the length of REM sleep episodes; (3) rats treated with αhCRH exhibited more high frequency bands in NREM than rats treated with CRH during the last dark phase of the recovery period; and (4) CRH-treated rats exhibited lower theta/delta ratio, indicating an impairment of the homeostatic sleep rebound.

As expected, REMSD resulted in increased secretion of ACTH and CORT levels, relative to control, nondeprived rats. Repeated administration of CRH, during REMSD, however, led to opposite effects, for example, levels in REMSD were lower than those of control rats. This result can be explained by the well-known stimulating effect that REMSD exerts on the CRH-producing neurons, with increased mRNA [11] and immunoreactivity of CRH [10] in the PVN, which could lead to lower density of CRH receptors. In fact, a previous study showed that REMSD results in lower CRH receptor density in the pituitary and striatum [45]. Despite that, no major effects in the sleep macrostructure were observed during rebound, except for a reduction of the length of REMS episodes.

We found that αhCRH reduced ACTH, but increased CORT release by almost 3-fold in REMSD rats compared to CSF-treated animals. Alpha-helical CRH-induced attenuation of the ACTH response to REMSD resembled those of a previous study with restraint stress [46]. Some studies indicate that in order to achieve an effective blockade of the behavioral stress response, αhCRH dose must be higher than 25 μg (in the present study the dose was 20 μg/animal) [42, 47, 48], even though ACTH and CORT secretions may still not be completely suppressed [42]. Some studies even indicate that αhCRH, in doses higher than 25 μg, acts as an agonist of the type 1 CRH receptor (CRH-R1), leading to behavioral and hormonal responses similar to those elicited by CRH [49–52]. αhCRH antagonist action is evident in stressful, but not under basal conditions [53–55], possibly due to the fact that it binds more efficiently to CRH-R2 receptors [56], whereas CRH-R1 is the predominant type in the pituitary

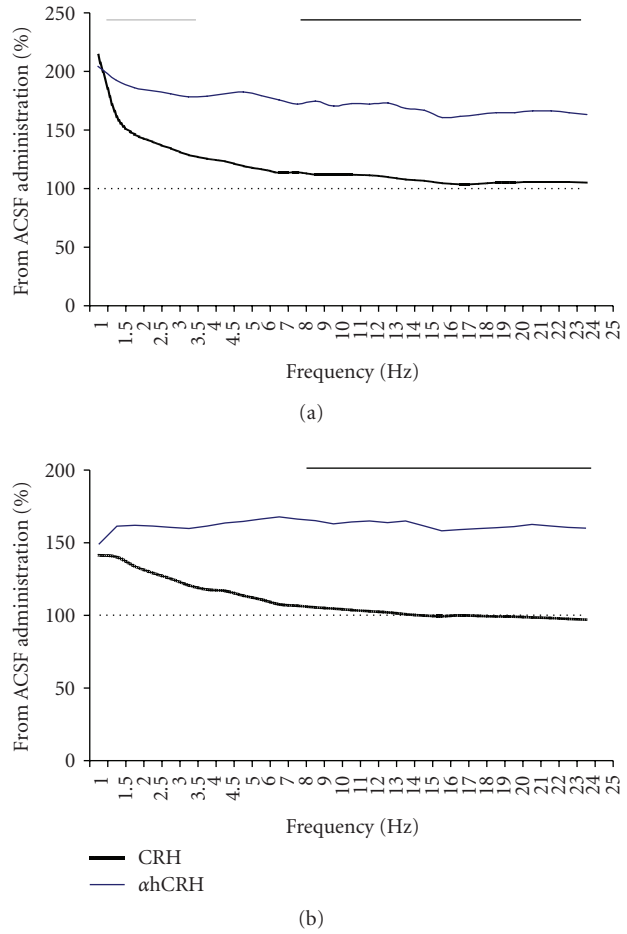

Figure 5: *Spectral Power During Total NREM on the 2nd (a) and 3rd (b) Recovery Dark Phases*. Results are expressed as percentage of ACSF-treated group, obtained from the mean power of each spectra band. ACSF, artificial cerebrospinal fluid; CRH, corticotrophin-releasing hormone; αhCRH, alpha helical CRH_{9-41}. Grey line above graphics indicates differences of αhCRH from ACSF and black ones, the difference between the CRH and αhCRH treatments. Student's *t* tests, $P \leq .05$.

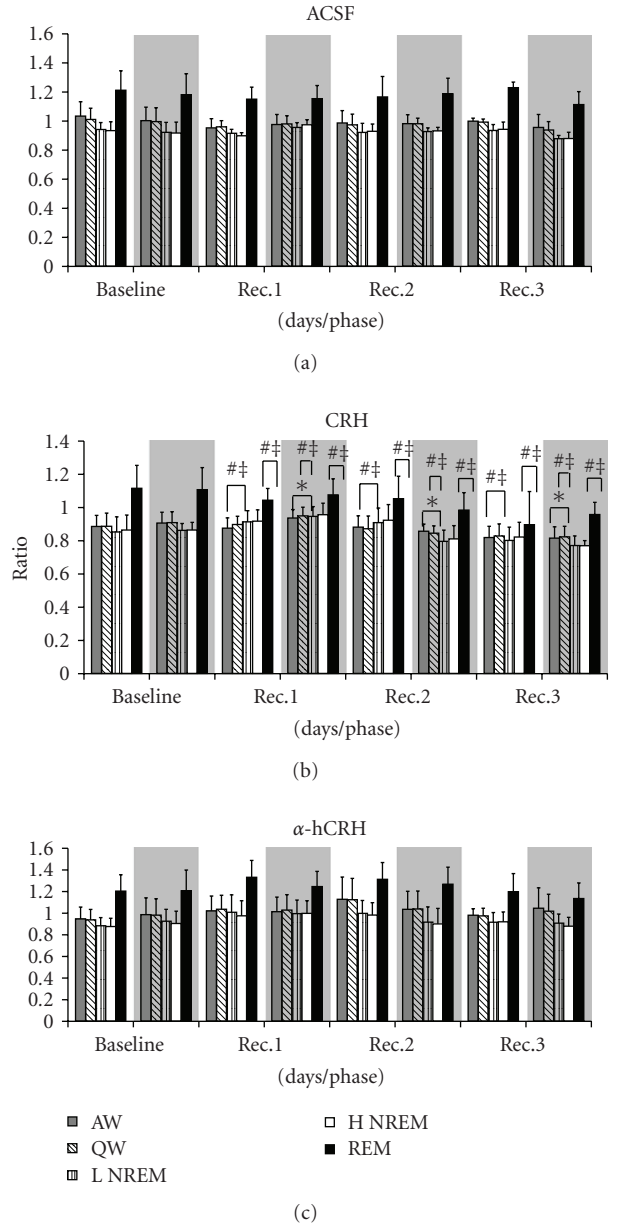

Figure 6: *Theta/Delta*. Theta/delta ratio is shown as mean of the total power in fast the θ (6.6–9.0 Hz) band divided by total power in fast δ (2.5–4.0 Hz) band, computed throughout ~11 hours period in the light and dark phases of the recovery period. ACSF, artificial cerebrospinal fluid; CRH, corticotrophin-releasing hormone; αhCRH, alpha helical CRH_{9-41}; AW, active wake; QW, quiet wake; L NREM, low amplitude NREM sleep; H NREM, high amplitude NREM sleep; PS, REM sleep; Rec. Recovery period. The white panels indicate the light phase and the gray ones, the dark phase. *- different from baseline, #- different from ACSF group, and ‡- different from αhCRH group. Main effects of sleep parameter are indicated by connecting lines above the bars. ANCOVA, followed by the Newman-Keuls test, $P \leq .05$.

[57–59]. Interestingly, the distribution of CRH receptors in sleep-related areas indicates that CRH-R1 is densely located in the laterodorsal tegmental nucleus and CRH-R2, in the dorsal raphe, without any overlapping [59], suggesting that both receptors types may be involved in sleep regulation.

Increased NREMS is seen with higher doses of αhCRH (i.c.v., 25 μg/rat) within two hours of drug administration [43], whereas a higher dose (i.c.v., 100 μg/rat) prevents immobilization stress- and sleep deprivation-induced sleep rebound [32, 60]. It is possible that the dose of αhCRH used in the present study, also infused i.c.v., was not high enough to produce the same sleep changes as reported by Gonzalez and Valatx's [60] paper, however, in their study, the compound was administered every two hours throughout the deprivation period, mounting to a much larger dose in a much shorter period of sleep deprivation. Moreover, this schedule of administration is likely to maintain receptors blocked throughout the entire sleep deprivation period.

The most remarkable effect of CRH and αhCRH treatments in sleep macrostructurewas a shortening of the length

of REMS episodes, compared with vehicle-infused rats, during the first light period of recovery sleep, indicating and impairment of REM sleep regulation. The influence of CRH on REM sleep appears to be bimodal. On the one hand, intra-hippocampal CRH infusion reduces theta rhythm by acting on both CRH receptors, present in hippocampal CA1 field and dentate gyrus [61]. On the other hand, overexpression of CRH leads to more spontaneous and sleep deprivation-induced REM sleep [62]. At present, it is not possible to determine how both drugs, acting predominantly through different CRH receptors, could lead to similar results in REM sleep regulation. One possibility may involve changes in serotonergic transmission, since it has been shown that the raphe nucleus projects heavily to the hippocampus and medial septum [63, 64] and that stimulation of this region suppresses theta rhythm in the EEG, regardless of the activity in the septal area [65, 66]. Lesions of the raphe may result in permanent hippocampal theta rhythm [67] and infusion of 5-HT_{1A} agonist in the dorsomedial raphe impairs hippocampal and cortical theta rhythm [68]. Considering that the predominant CRH receptor in the raphe is the low affinity CRH-R2 [61] and that activation of these receptors with high or repeated αhCRH administrations lead to serotonin release in this area [69], there is a possibility that the treatment used in the present study might have caused an increase in serotonergic activity, which impaired theta rhythm and, consequently, REM sleep.

Regarding sleep microstructure, during NREM sleep, αhCRH produced an increase in the high frequency bands during the last two dark phases, compared to CRH, suggesting opposite homeostatic and late circadian responses exerted by these peptides. Thus, αhCRH-treated rats appeared to exhibit shallower NREM sleep than CRH-treated rats, considering that high frequency bands are predominant during waking. However, shallower NREM sleep during the active period of rats indicates normal circadian rhythm and, therefore, a return to homeostasis. CRH also reduces low frequency (1.0–6.0 Hz) spectral potency in rats [25] and in humans, there is an increase in waking and delta sleep EEG sigma band (11.0–15.0 Hz) [70]. CRH receptors are present in several thalamic nuclei [71, 72], although they inhibits spontaneous activity of these neurons [73]. Activation of these receptors might result in inactivity of reticular cells, responsible for the generation of synchronization of low frequency waves in the cortical EEG [74] and reduction of the low frequency power spectrum [25]. CRH deleterious effects on sleep appear to be mediated by CRH-R1, since R129919, a specific CRH-R1 antagonist increases slow wave sleep in depressed patients [75]. This may explain why αhCRH did not affect low frequency power spectrum, since this substance blocks preferentially the type 2 CRH receptor. Moreover, CRH mRNA expression on the posterior nucleus of the thalamus is augmented during the rat resting period [76, 77]. Activation of this nucleus is related to the generation of high frequency β waves and suppression of δ and spindle activity during slow wave sleep [78, 79]. Collectively, these data could explain the increased potency of EEG high frequency bands.

A relatively recent index is the theta/delta (θ/δ) ratio, which represents a marker of homeostatic sleep compensation and is known to be increased after sleep deprivation [80, 81], being characteristic of each sleep phase [82]. In humans, for instance, this increase takes place during the dark period, which corresponds to the resting period [83]. The reduction of θ/δ ratio in CRH-treated rats during waking and REM sleep suggests that the homeostatic compensation is flawed, because during REM sleep decreased delta and/or increased theta activity is supposed to occur.

Theta rhythm is one of the most prominent features of REM sleep in the rat [35, 84], which is generated by cell populations that flow to CA1 stratum oriens and dentage gyrus stratum molecular [85, 86]. The reduction of theta/delta rhythm in CRH-treated rats might have occurred due to a reduction of theta potency, rather than an increase in delta power. The reason for this conclusion is threefold: (1) the reduction of the index took place during waking and REM sleep, when theta predominates; (2) there were no changes during low and high NREM sleep, when delta predominates; and (3) as a general rule, low frequencies (1.0–5.0 Hz) were unchanged during NREM sleep.

In conclusion, chronic CRH administration during REM sleep deprivation impaired the homeostatic compensation phenomenon, likely due to its excitatory action on neuronal tissue. This impairment occurred in the sleep macrostructure, with shortening of REM sleep episodes, as well as in the microstructure, in later phases of the recovery period. Because αhCRH acts at the CRH-R2 and may have agonistic properties when repeatedly administered in high doses, it produced paradoxical changes on hormone secretion and sleep homeostasis, being, sometimes, similar to CRH.

Acknowledgments

The authors would like to thank Dr. Teunis van Beelen for EDF converter software. This work was supported by Associação Fundo de Incentivo à Psicofarmacologia (AFIP) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP/CEPID# 98/14303-3). Ricardo Borges Machado is the recipient of PhD fellowship from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP# 04/02213-2). Deborah Suchecki is the recipient of a scholarship from the National Research Council (CNPq).

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2010, Article ID 519607, 7 pages
doi:10.1155/2010/519607

Clinical Study

Increased Daytime Sleepiness in Patients with Childhood Craniopharyngioma and Hypothalamic Tumor Involvement: Review of the Literature and Perspectives

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Received 29 April 2010; Revised 16 August 2010; Accepted 5 October 2010

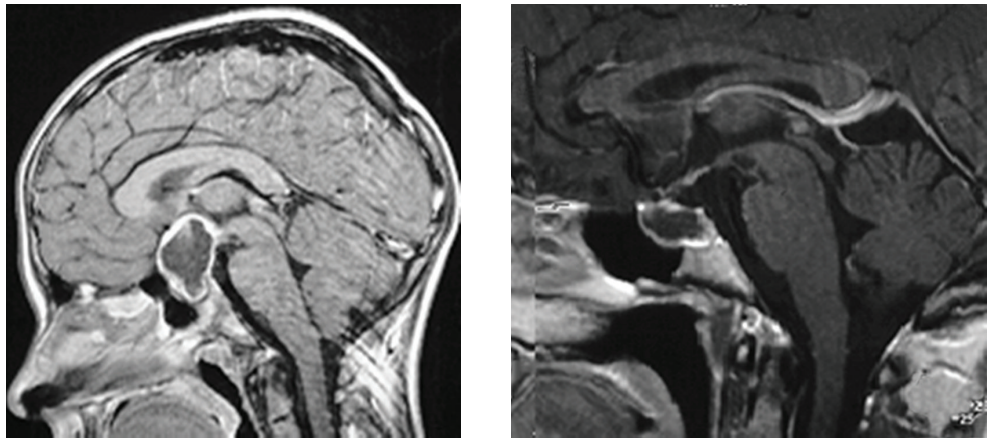
Academic Editor: Jessica A. Mong

Childhood craniopharyngiomas are rare embryogenic malformations of the sellar region, presumably derived from Rathke cleft epithelium. The overall survival rates after neurosurgical intervention and/or irradiation are high (92%). However, the quality of survival is frequently impaired due to endocrine deficiencies, sleep disturbances, daytime sleepiness, and severe obesity caused by hypothalamic lesions. Based on self-assessment using nutritional diaries, caloric intake was similar in patients and BMI-matched controls. Analyses of physical activity by accelerometric measurements showed a markedly lower level of physical activity. Significant daytime sleepiness and disturbances of circadian rhythms have been demonstrated in obese childhood craniopharyngioma patients. Daytime sleepiness and obesity in these patients were both correlated with low nocturnal and early morning melatonin levels. Polysomnographic studies in patients with severe daytime sleepiness revealed sleeping patterns typical for secondary narcolepsy. Reports on a beneficial effect of treatment with central stimulating agents supported the hypothesis that secondary narcolepsy should be considered as a rare cause for severe daytime sleepiness in patients with childhood craniopharyngioma.

Craniopharyngiomas are embryogenic malformations of low histological malignancy (WHO I°), which arise from ectoblastic remnants of Rathke's pouch and can be found anywhere along the path of development of Rathke's pouch in hypothalamic and pituitary regions, both of importance in endocrine regulation and satiety modulation [1]. Craniopharyngiomas are the most common intracranial tumors of nonglial origin in the pediatric population, constituting between 1.2 to 4% of all brain tumors and 6 to 9% of pediatric brain tumors. Overall there are 0.5 to 2 new cases per million population occurring each year, 30 to 50% of which are children and adolescents [2]. The peak incidence is at age 5 to 10 years, but they can occur at any age including infancy and pre- and neonatal period [3].

Whereas the childhood form of craniopharyngioma mainly presents with an adamantinous histology, the adult type of craniopharyngioma occurs at a peak age of 50–75 years and presents mainly with papillary histology. Other tumors with similar localization but different characteristics on magnetic resonance imaging (MRI) are germinoma, germ cell tumours, langerhans cell histiocytosis, and pilocytic astrocytoma [6].

Headaches, visual disturbances, polyuria, reduced growth rates, and weight gain are frequently the first symptoms in the history of patients with childhood craniopharyngioma [7, 8]. The clinical features at the time of diagnosis of craniopharyngioma during childhood are usually unspecific signs of increased intracranial pressure. Major symptoms are headaches, impaired vision (62–84%, primarily in adults), and endocrine failures (52–87%, primarily in children). Chiasmatic involvement may be attended by defects of vision and visual fields. Endocrine deficiencies affect the hypothalamic-pituitary axes for growth hormone (75%), gonadotrophins (40%), ACTH



(a) (b)

Figure 1: Obesity and daytime sleepiness in relation to the localization of craniopharyngioma. The patient whose preoperative MRI (a) showed a large tumor extending to the suprasellar region and infiltrating the hypothalamus developed severe daytime sleepiness and, consequently, obesity (BMI: +14 SD [4]). The patient with a childhood craniopharyngioma of intrasellar localization seen in Figure 1(b) maintained normal weight (BMI: +1 SD [4]) and developed no daytime sleepiness.

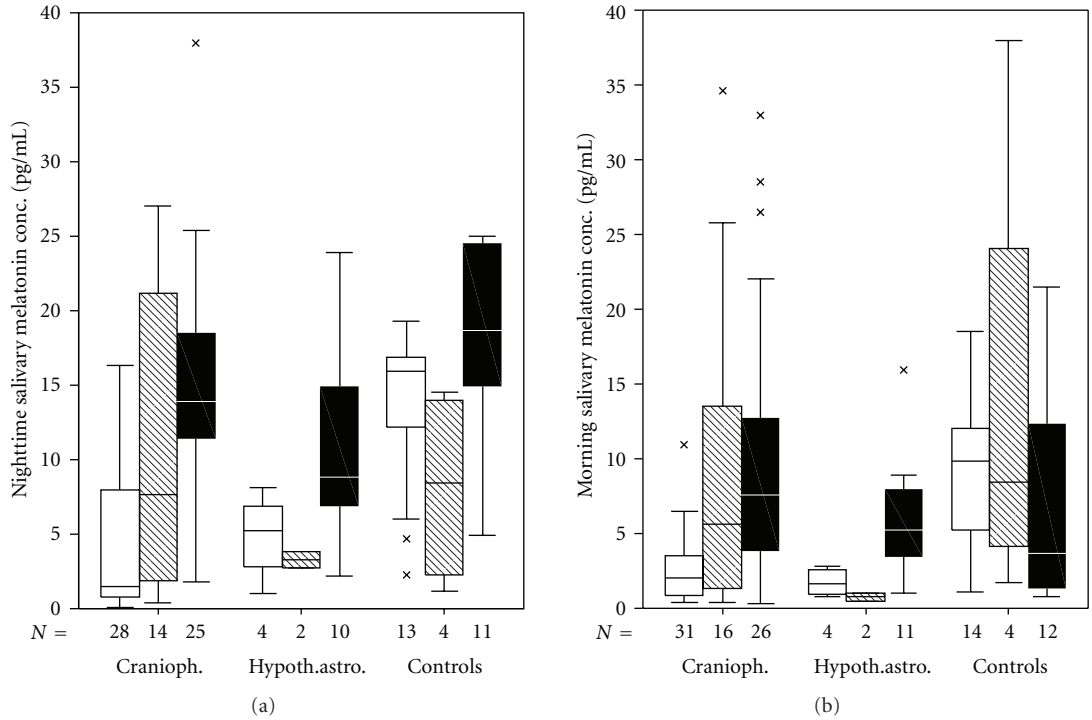


Figure 2: Salivary melatonin concentrations at nighttime (a) and in the morning (b) in patients with childhood craniopharyngioma, hypothalamic pilocytic astrocytoma, and controls in relation to the degree of obesity (body mass index [BMI] <2 SD [filled black boxes], BMI 2–4 SD [hatched gray boxes], or BMI ≥ 4 SD [open boxes]). The horizontal line in the middle of the box depicts the median. Edges of the box mark the 25th and 75th percentile. Whiskers indicate the range of values that fall within 1.5 boxlengths. Values more than 1.5 box-length from the 25th and 75th percentiles are marked by an asterix. (Modified from [5], with the kind permission of Endocrine Press.)

(25%), and thyroid-stimulating hormone (TSH) (25%). 17% of the children with craniopharyngioma present with diabetes insipidus prior to surgery [9].

The therapeutic goal is first to relieve symptoms by urgent surgical decompression and second to achieve an early long-term cure by complete resection but without causing further damage to the hypothalamus or optic tract. Postoperative sequelae are deemed unacceptable in patients with preoperatively intact function. However, the optimal primary therapeutic strategy to achieve the correct balance between late sequelae and successful cure remains unknown. Even after complete surgical resection, craniopharyngioma

relapses occur in up to 17% of patients [10]. With radical resection, the risk of hypothalamic damage is considerable, especially in craniopharyngioma with suprasellar extension to the hypothalamic area. The appropriate time point of irradiation in patients with residual tumor after incomplete resection is controversial as well [10–13].

Although the tumor itself is low-grade histological malignancy and the overall survival rate (92%) of patients is high [9], there is considerable morbidity even when the tumor can be completely resected [5, 7, 9, 10, 14–24]. Childhood craniopharyngioma patients often suffer sequelae of severe obesity. Increased body weight in patients at risk for the development of severe obesity during followup is already detectable at the time of diagnosis of craniopharyngioma [15]. Patients who developed severe obesity presented with a higher body mass index SDS [4] already at the time of diagnosis when compared with patients who kept their normal weight. The evaluation of the patients' history [7] and anthropometric data collected before diagnosis [15] confirmed the observation, that pathogenic mechanisms for the development of later obesity have significant impact on weight already at the time of diagnosis before initiation of therapy. Hypothalamic involvement of craniopharyngioma is the most important risk factor for the development of obesity before and after tumor diagnosis (Figure 1) [9, 10, 15–17, 19, 25].

In spite of hormonal substitution, the management of hypothalamic injury-induced hyperphagia is difficult and severe obesity occurs postoperatively in up to 52% of patients with at least one half of these patients having extreme difficulty controlling their desire to eat [9, 24]. Severe obesity has major negative impact on quality of life in survivors of childhood craniopharyngioma [8, 10, 14, 16, 17, 19, 24]. Conventional strategies for weight control are less efficient because of impaired physical activity due to attendant neurological and visual deficits and the complaint of increased daytime sleepiness.

A German multicenter study on childhood craniopharyngioma patients suggested a secondary hypothalamic disorder as pathogenic factor in patients at risk for severe obesity and increased daytime sleepiness [9]. Müller et al. surveyed a large group of patients with childhood craniopharyngioma and hypothalamic astrocytoma for daytime sleepiness using the German version of the Epworth Sleepiness Scale (ESS) [26]. About 1/3 of the patients reported increased daytime sleepiness, characterized by an ESS score above 10. The severity of their daytime sleepiness was unexpectedly high, especially in obese patients with a BMI > 4 SD [4].

Sleep regulation and circadian rhythms are at least partially mediated by hypothalamic structures, for example, the suprachiasmatic nucleus, regulating melatonin secretion [27]. The secretion of melatonin, a pineal indoleamine, occurs during hours of darkness and as it affects sleep patterns it has been tried in treating jet lag and other disorders from delay of sleep because of its possible role in influencing circadian rhythm. Because a destruction or dysfunction of the suprachiasmatic nucleus seems likely in many craniopharyngioma patients with suprasellar tumor extension [28], Müller et al. compared melatonin secretion in severely obese, obese, and in nonobese craniopharyngioma patients [5]. To analyze the influence of obesity and hypothalamic lesions on melatonin secretion, patients with hypothalamic tumors (pilocytic astrocytomas) and obese and normal weight control subjects were also analyzed. The authors compared salivary melatonin concentrations at morning, midday, evening, and nighttime among severely obese, obese, and nonobese patients and normal controls. Salivary melatonin concentrations correlate with melatonin concentrations in plasma [29, 30].

Whereas several studies [31–33] on different patient cohorts have found no significant relation between melatonin secretion and obesity, Birketvedt et al. [34] reported on a rare night eating syndrome characterized by frequent awakening at night, higher nocturnal energy intake, and attenuation of nocturnal rise in plasma melatonin. As hypothesized based on hypothalamic disorders in the severely obese craniopharyngioma patients, decreased melatonin concentrations at nighttime were detected in patients analyzed by Müller et al. [5] (Figures 2(a), 2(b)). The authors speculated that the diurnal rhythm of melatonin was suppressed in obese patients with hypothalamic tumors as craniopharyngioma or pilocytic astrocytoma. As cortisol may also influence wakefulness, salivary cortisol concentrations were compared in all groups to exclude confounding effects. No differences for cortisol serum concentrations were found among the groups. The significant negative correlations between salivary melatonin concentrations in the morning and at nighttime and the ESS scores indicate that reduced nocturnal melatonin secretion may lead to increased daytime sleepiness in patients with childhood craniopharyngioma. The findings suggested that increased daytime sleepiness in patients with childhood craniopharyngioma was associated with decreased nocturnal melatonin levels, which were related to the degree of obesity and the tumor diagnosis. First promising experiences on experimental substitution of melatonin in obese patients with craniopharyngioma supported the hypothesis that increased daytime sleepiness is associated with reduced nocturnal melatonin secretion [20].

The observations confirmed previous reports on agedependency of melatonin secretion [35]. However, in spite of the fact that age-dependent effects were found similarly in all analyzed subgroups and the agedependency had no statistical impact on reported differences in terms of craniopharyngioma-associated melatonin depression, it has to be stated that the preliminary results have to be confirmed by prospective analysis of larger cohorts with more homogeneous agedistribution. Further studies on the hypothesis are part of the German prospective multicenter study KRANIOPHARYNGEOM 2007 on patients with childhood craniopharyngioma [10, 36]. As it has been reported [9] that hypothalamic damage is a risk factor for severe obesity in craniopharyngioma patients, it can be speculated that hypothalamic damage could have been responsible for disturbances in melatonin secretion. This speculation is supported by similar findings for patients with hypothalamic tumors of other histology such as pilocytic astrocytoma [5].

Studies on physical activity using accelerometric analysis of movement counts revealed that physical activity was reduced in the group of craniopharyngioma patients with obesity and hypothalamic involvement when compared with age and BMI-matched controls [25]. Caloric intake was similar in normal controls (1027 healthy nonobese subjects, representative sample of the 7 to 16 year-old German population with an age distribution: 11.3 ± 2.7 years) and craniopharyngioma patients (27 patients, age distribution: 11.7 ± 2.6 years) and had no significant impact on the degree of obesity and the physical activity in analyzed cohorts [25]. Hypothalamic involvement of craniopharyngioma had major negative impact on functional capacity and quality of life and was a major risk factor for the development of severe obesity in survivors of childhood craniopharyngioma [5, 7–10, 14–21].

Reports [5, 22, 25] on increased daytime sleepiness and reduced physical activity in patients with craniopharyngioma support the hypothesis that physical activity might be decreased in these patients due to yet unknown neuroendocrine disorders. On the other hand, sleep at night was severely disturbed in many patients with increased daytime sleepiness [5]. Accordingly, Müller et al. analyzed daytime sleepiness and polysomnographic patterns in patients with childhood craniopharyngioma in order to define further risk factors for severe obesity.

Since sleep regulation and circadian rhythms are at least partially mediated by hypothalamic structures, for example, the suprachiasmatic nucleus, Müller et al. conducted a two-night polysomnography (PSG) and a multiple sleep latency test (MSLT) consisting of four or five 20-minute naps with nine obese craniopharyngioma patients and one patient with an astrocytoma of the pituitary stalk displaying acute daytime sleepiness [20]. The MSLT was developed to render a better diagnostic sensitivity and specificity in the diagnosis, and usually two or more SOREMP in the MSLT are regarded as necessary for the diagnosis. Usually a mean sleep latency of <5 minutes should be observed for the diagnosis of narcolepsy. The diagnostic validity of MSLT in early infancy is controversial. However, the youngest patient included in our MSLT analyses was 10 years of age [20]. Only two patients showed an obstructive sleep apnea syndrome (OSAS), the usual sleep-related disorder in acutely obese patients. However, seven patients fulfilled the classic PSG criteria for secondary narcolepsy or hypersomnia. These results were unexpected since none of the patients complained of cataplexy, hypnagogic hallucinations, or sleep paralysis on inquiry. What is particularly noteworthy is that recent research has suggested a hypothalamic disorder in narcolepsy. A defect in the orexin II receptor is responsible for canine narcolepsy [37] and orexin knockout mice show characteristic features of narcolepsy [38]. Orexin is expressed exclusively in the lateral hypothalamus, and the orexin receptors seem to be wider spread [39]. In human narcoleptics, 8 of 10 had orexin A below the detection limit of the assay used [40]. Despite excessive research in this field, only one patient could be identified with a genetic defect in the orexin system [41]. In autopsy of narcoleptic patients, the lack of orexin neurons in the lateral hypothalamus was observed in 10 cases [41, 42].

It has also been reported that systemic administration of orexin relieves narcoleptic symptoms in dogs [43, 44]. The peculiar finding that sleep and sleep attacks in narcoleptic patients are initiated by a sleep onset REM period (SOREMP) was recognized in the early 1960s [45]. Since then, this PSG finding is regarded as a phenomenon occurring almost exclusive in narcolepsy, although there are some descriptions of SOREM in subjects without narcolepsy. García-Borreguero et al. [46] reported that glucocorticoid replacement therapy in Addison's patients was permissive for decreased REM latency when hydrocortisone was taken at bedtime. MSLT was not performed in this study. All patients with SOREM were under treatment with hydrocortisone replacement therapy in the study of Müller et al. [20]. However, hydrocortisone replacement treatment alone cannot explain the excessive daytime sleepiness in analyzed patients as this is standard treatment for craniopharyngioma patients, including those not suffering severe daytime sleepiness.

Secondary narcolepsy is a rare disorder. However, several case reports were published on secondary narcolepsy, mainly reporting on patients with tumorous conditions in the hypothalamic area [47, 48]. Diagnostic criteria vary, but all patients presented with hypersomnia as a leading pathology. Interestingly, the majority of reported patients show hypersomnia, but not cataplexy, hallucinations, or sleep paralysis. In fact, a medline search yielded over 30 cases of secondary narcolepsy without cataplexy during the last 50 years, but yielded only 13 cases with secondary cataplexy. These cases are surprisingly very heterogenic and only two cases had tumors in the area of the hypothalamus [49], two cases had tumors in the brain stem pontomedullary astrocytoma [50], glioblastoma of rostral brain stem [51], one patient had a frontal lobe tumor [52], five patients had meningioma [53], and five patients had meningeal carcinomatosis [54].

Not all patients with a tumorous condition in the hypothalamic area suffer from hypersomnia, and even less from cataplexy. This is surprising, since deficiency of orexin is regarded as the cause of hypersomnia and cataplexy in idiopathic narcolepsy. Cases with secondary cataplexy in the literature seem to have more widespread tumor disease than cases with secondary hypersomnia. This leads to speculation that there must be some other pathology operating in addition to orexin deficiency to produce cataplexy in idiopathic narcolepsy. This hypothesis is supported by the fact that some patients with clear idiopathic narcolepsy and cataplexy have normal orexin levels in cerebrospinal fluid [40].

In concert with findings [5, 20] suggesting that increased daytime sleepiness is a common complaint in patients with childhood craniopharyngioma and that the incidence seems to be equal in obese and normal weight patients, reported results [22] together with current research on narcolepsy lead to the conclusion that secondary hypersomnia and secondary narcolepsy may be contributing causes for increased daytime sleepiness and weight control difficulties in obese craniopharyngioma patients. Preliminary positive experiences with central stimulating agent treatment (Modafinil or Methylphenidate) in patients with childhood craniopharyngioma and secondary narcolepsy support this speculation [22, 55].

Based on the literature [56, 57], radical surgery with potential damage to hypothalamic structures and consecutive increased daytime sleepiness is no appropriate treatment strategy in patients with hypothalamic involvement of childhood craniopharyngioma. For such patients innovative treatment strategies are warranted after incomplete resection. Accordingly, in KRANIOPHARYNGEOM 2007 quality of life, event-free survival and overall survival rates in patients (age $\geq$5 years at diagnosis and at incomplete resection) are currently analyzed after randomization of the time point of irradiation after incomplete resection (immediate irradiation *versus* irradiation at progression of residual tumor). The schedule of prospective data collection and the set and definition of parameters is based on a European consensus [13]. Standardized European data sets on a rare disease such as childhood craniopharyngioma should help to increase cohort sizes and facilitate common data evaluation [10]. Hopefully, this international study will lead to treatment recommendations that prevent severe sequelae such as increased daytime sleepiness and secondary narcolepsy in patients with childhood craniopharyngioma.

Acknowledgments

The studies were supported by a grant of Deutsche Kinderkrebsstiftung, Bonn, Germany. The author is very grateful to Mrs. Ursel Gebhardt for her help in preparing the paper.

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