Symposium 11: Stress, glucocorticoids and memory
Organized by M. Oitzl and C. Sandi

Symp 11/1

TEMPORAL DYNAMIC EFFECTS OF STRESS ON COGNITIVE FUNCTIONS

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The hippocampal formation is of crucial importance for cognitive processes and alterations in this brain area are associated with a selective impairment of memory performance. Increasing evidence suggests a connection between structural alterations and volumetric reduction of the hippocampal formation, cognitive impairments and disturbances of the activity of the hypothalamo-pituitary-adrenal (HPA) axis. Several cross sectional studies in humans demonstrated that both a hyperactivity of the HPA-axis with elevated levels of circulating adrenal glucocorticoid (GC) hormones such as cortisol, as well as a hypoactivity of the axis with low GC plasma levels are accompanied by hippocampal atrophy and cognitive impairments. Since the underlying mechanisms are not well understood, there is a great interest to establish animal models which mimic these neuropsychopathological processes. One of the models is the psychosocial stress paradigm in male tree shrews. In subordinate animals, chronic stress experience is characterized by constantly elevated cortisol levels, pronounced structural changes in the hippocampal formation, and impaired hippocampus-dependent memory functions. Using this well characterized system, we investigated the temporal dynamic effects of chronic stress exposure on the volume of the hippocampal formation and hippocampus-mediated memory performance. To assess the specific impact of chronically elevated GC levels a second group of animals received cortisol via the drinking water. By combining various non-invasive methods, animals were submitted to cognitive tests and MRI-sessions before, during and after the stress exposure and cortisol treatment, respectively. Results from a schedule of alternating stress and non-stress phases provided evidence that memory impairments resulting from repeated social encounters must not directly be modulated by glucocorticoids since impairments were found even 10 weeks after termination of the stress exposure when GC levels had returned to baseline levels. Moreover, stress and cortisol treatment differentially affected hippocampus-mediated memory. In cortisol treated animals, hippocampus-mediated memory performance was correlated with cortisol levels. This clearly differs to the finding in chronically stressed animals where circulating cortisol levels were not directly correlated with hippocampus-mediated memory performance. Previous investigations in tree shrews demonstrated that the duration of stress exposure as well as the balance between different transmitter systems might be a critical factor when investigating central nervous mechanisms. These are important issues that require systematic analysis to understand how stressful life events may affect brain structures such as the hippocampal formation which is an especially plastic region of the brain and critical for information processing.

Symp 11/2**EARLY LIFE EVENTS, VULNERABILITY TO STRESS AND COGNITIVE DECLINE***M.S. Oitzl *, J.O. Workel, and R.E. de Kloet**LACDR, Division of Medical Pharmacology, University of Leiden, P.O.Box 9503, 2300 RA Leiden, The Netherlands*

Cognitive functions and the neuroendocrine stress system are programmed by genotype, but increasing evidence suggests that the genetic program can be modified by early life experiences. A traumatic early life event, realised by the deprivation of the rat-pup from maternal care for one single day resulted in augmented stress responses until weaning (van Oers et al. *Stress* 1,249-261,1997). Our studies were designed to test the hypothesis that maternal deprivation has life-long negative consequences for stress-responsiveness and cognition, in line with the current glucocorticoid cascade hypothesis of brain ageing which predicts that the rise of corticosteroids during the ageing process activates a cascade of degenerating responsible for cognitive decline. We used male Brown Norway rats. Half of the litter was deprived from the mother at postnatal day 3 for 24 hours, the other pups served as non-deprived controls. Subsequently, from 3 to 32 months of age the responses of circulating hormones and neuronal markers to the stress of a novel environment were assessed. Due to the long and healthy life span, senescent rats of this strain form a representative ageing group (80 % survival rate). The data show that basal resting levels of corticosterone remain comparable from youth to senescence. The magnitude of the corticosterone response to novelty stress slowly declined in the non-deprived control rats. However, animals deprived as pups from maternal care displayed a midlife surge in stress responsiveness, while at young age and at senescence the ACTH and corticosterone responses to stress were relatively attenuated. Ageing markedly reduced the expression of mineralocorticoid receptors in discrete regions of the hippocampus, while glucocorticoid receptors showed more subtle changes. The ability to learn the Morris water maze task slowly declined with age. In the deprived animals, this decline started already at adulthood. At senescence the mean performance of deprived rats did not differ from control rats. Analysis of individual data revealed that the control group contained mostly rats with partially impaired performance, while this is the case for only few of the deprived littermates. Maternal deprivation resulted in a dichotomy: rats were either non-impaired or impaired in spatial navigation. The underlying mechanism is not known yet. As low levels of corticosterone were present in senescent and cognitively impaired rats, the outcome of the present study questions the generalised suggestion of a beneficial effect of low corticosteroid levels for cognition.

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Symp 11/3**INTERACTION BETWEEN GLUCOCORTICOIDS AND DOPAMINE AS A POSSIBLE SUBSTRATE OF VULNERABILITY TO DRUGS***PV. Piazza *, V. Deroche, M. Marinelli, M. Barrot, F. Rouge-Pont, and M. Le Moal**INSERM U.259, Rue Camille Saint Saëns, Domaine de Carreire, 33077 Bordeaux Cedex, France*

An enhanced responsiveness of the dopaminergic projection to the nucleus accumbens seems to be an important substrate of the propensity of an individual rat to self-administer psychostimulant drugs. Animals predisposed to self-administer psychostimulants (HR) compared to less prone rats (LR) have a higher release of dopamine in the nucleus accumbens in basal conditions, in response to stress and to psychostimulants. Furthermore, an experimentally-induced increase in the responsiveness of this dopaminergic projection will increase the likeliness of a subject to self-administer psychostimulants. Among experimental manipulations that can increase vulnerability to drugs stress seems to play a central role. Glucocorticoid hormones seem to be an important factor in determining the higher dopaminergic activity observed in drug prone subjects. Three lines of observations prompt this idea. First, glucocorticoids facilitate dopamine release in the nucleus accumbens. Second, glucocorticoids increase the psychomotor and reinforcing effects of drugs of abuse and spontaneously prone subjects have a longer-stress induced corticosterone secretion and a higher sensitivity to the dopaminergic effects of these hormones. Third, stress-induced increase in vulnerability to drugs depend on glucocorticoids. In conclusion, it is proposed that an enhancement of the functional activity of glucocorticoid hormones through an action on dopaminergic neurons may be one of the pathophysiological mechanisms determining a higher vulnerability to intake drugs.

Symp 11/4**NEUROENDOCRINE AND NEUROCHEMICAL CHANGES FOLLOWING CHRONIC SOCIAL STRESS***R. R. Sakai**University of Pennsylvania, Department of Animal Biology, Philadelphia, Pennsylvania, USA*

Male rats housed in mixed-sex groups in a visible burrow system (VBS) form a dominance hierarchy in which subordinate animals show stress-related changes in behavior, endocrine function and neurochemistry. Dominants also appear to be moderately stressed compared to controls, although these animals do not develop the more pronounced behavioral and physiological deficits seen in the subordinates that include reduced social, sexual and aggressive activity, changes in sleep cycles, weight loss associated with lower food intake, elevated plasma corticosterone and decreased plasma testosterone. Further, we have identified that a subset of the subordinate animals are non-responsive to a novel stressor and we have correlated the inability to further release glucocorticoids with a deficit in hypothalamic CRF mRNA. In examining the brains of the VBS animals we have also found significant

changes in serotonin receptor binding levels in various brain areas examined. A profound downregulation of serotonin 5HT_{1A} receptors is found in the hippocampus. Interestingly, the dominant animals show a similar degree of 5HT_{1A} receptor downregulation as the subordinates. In contrast, the subordinates demonstrate the highest upregulation of 5HT₂ receptors the cerebral cortex as compared to dominant and control males. In the present study, we examined the effects of chronic psychosocial stress on the morphology of Golgi-impregnated CA3 pyramidal neurons. In addition, since serotonin has been implicated in the mechanisms mediating the dendritic remodeling seen with other chronic stress regimens, we used quantitative autoradiography to measure binding to the serotonin transporter (5HTT) in hippocampus and dorsal and medial raphe. Chronic social stress led to a decrease in the number or branch points and total dendritic length in the apical dendritic trees of CA3 pyramidal neurons in dominant animals compared to unstressed controls; subordinates also had a decreased number of dendritic branch points. [³H] paroxetine binding to the 5HTT was decreased in Ammon's horn in both dominants and subordinates compared to controls, while 5HTT binding remained unchanged in dentate gyrus and raphe. The similarity of the changes in 5HTT binding and dendritic arborization between both groups of VBS animals, despite apparent differences in stressor severity, suggests that these changes may be part of the normal adaptive response to chronic social stress. The mechanisms underlying dendritic remodeling in CA3 pyramidal neurons are likely to involve stress-induced changes in glucocorticoids and in 5HT and other transmitters.

Symp 11/5

NEURAL MECHANISMS INVOLVED IN GLUCOCORTICOID ACTIONS ON LEARNING AND MEMORY

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Stress and glucocorticoids can exert different actions on neural function and cognition depending on the exposure time (i.e., acute vs. chronic treatments). Using different animal species (rats, chicks) and learning tasks (water maze, contextual fear conditioning, passive avoidance), our work has suggested that, acutely, glucocorticoids exert a facilitating effect on memory consolidation processes. However, chronic exposure to either stress or glucocorticoids can result in altered cognitive processing and learning and memory abilities in hippocampus-dependent tasks. In our studies, chronic stress or glucocorticoid treatments for 21 consecutive days were shown to induce task-dependent learning alterations; i.e., impairing reversal learning in the water maze and facilitating contextual fear conditioning. We are interested on studying the neural mechanisms underlying the time- and task-dependent biphasic actions of glucocorticoids on cognitive processes. Given the role of cell adhesion molecules (CAMs) – particularly NCAM, its polysialylated form PSA-NCAM, and L1- on synaptic plasticity, as well as the recent proposal that a breakdown in the organization of key CAMs might be a possible mechanism