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Research Article

Increased Mesohippocampal Dopaminergic Activity and Improved Depression-Like Behaviors in Maternally Separated Rats Following Repeated Fasting/Refeeding Cycles

Jeong Won Jahng,[1] Sang Bae Yoo,[1] Jin Young Kim,[1] Bom-Taeck Kim,[2] and Jong-Ho Lee[1]

[1] *Department of Oral and Maxillofacial Surgery, Dental Research Institute, School of Dentistry, Seoul National University, Seoul 110-768, Republic of Korea*
[2] *Department of Family Practice, College of Medicine, Ajou University, Suwon 443-721, Republic of Korea*

Correspondence should be addressed to Jeong Won Jahng, jwjahng@snu.ac.kr

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We have previously reported that rats that experienced 3 h of daily maternal separation during the first 2 weeks of birth (MS) showed binge-like eating behaviors with increased activity of the hypothalamic-pituitary-adrenal axis when they were subjected to fasting/refeeding cycles repeatedly. In this study, we have examined the psychoemotional behaviors of MS rats on the fasting/refeeding cycles, together with their brain dopamine levels. Fasting/refeeding cycles normalized the ambulatory activity of MS rats, which was decreased by MS experience. Depression-like behaviors, but not anxiety, by MS experience were improved after fasting/refeeding cycles. Fasting/refeeding cycles did not significantly affect the behavioral scores of nonhandled (NH) control rats. Fasting/refeeding cycles increased dopamine levels not only in the hippocampus but also in the midbrain dopaminergic neurons in MS rats, but not in NH controls. Results demonstrate that fasting/refeeding cycles increase the mesohippocampal dopaminergic activity and improve depression-like behaviors in rats that experienced MS. Together with our previous paper, it is suggested that increased dopamine neurotransmission in the hippocampus may be implicated in the underlying mechanisms by which the fasting/refeeding cycles induce binge-like eating and improve depression-like behaviors in MS rats.

1. Introduction

Neonatal maternal separation is considered as an animal model of stressful experience early in life. A number of studies have demonstrated that neonatal maternal separation may lead to permanent alterations in the characteristics of the hypothalamic-pituitary-adrenal (HPA) axis responding to stress [1–3] and the development of depression- [4, 5] and anxiety-like behaviors [6, 7] later in life. We have previously demonstrated that rats experienced 3 h of daily maternal separation during the first 2 weeks of birth (MS) exhibit depression- and anxiety-like behaviors [8, 9] with altered response of the HPA axis to stress challenges later in life [10, 11]. Dysfunction of the HPA axis is implicated in the pathogenesis of eating disorders [12–14], and symptoms of anxiety and depression are associated with the pathophysiology of eating disorders [15, see for review], especially with binge-like eating disorders [16, 17]. Our MS rats showed binge-like eating behavior when they were challenged with repeated fasting/refeeding cycles during adolescent period, and their binge-like eating behavior appeared to be related with increased activity of the HPA axis [11].

The dopaminergic system has been of particular interest, as dopamine in the nucleus accumbens (NAc) has been shown to be associated with motivation, reward, and hedonia [18]. Our MS rats showed anhedonia, a symptom of depression, with decreased dopaminergic activity in the NAc responding to acute stress [19, 20]. It has been suggested that serotonergic transmission regulates dopamine release within the NAc [21], and malregulation of dopaminergic activity in the NAc by serotonin may be involved in a depressive phenotype [22]. Although serotonin contents

in the NAc of our MS rats did not significantly differ from nonhandled (NH) control rats, not only serotonin contents in the hippocampus and the raphe but also gene expression of serotonin reuptake transporter in the raphe nucleus were decreased in our MS rats [8, 20]. Serotonergic dysfunction is implicated in a variety of psychiatric disorders, including major depression [23, 24] and anxiety [25], and serotonin neurotransmission in the hippocampus is believed to be involved in the regulation of the HPA axis activity throughout life. Thus, it is likely that decreased serotonin neurotransmission in the hippocampus may be implicated in the pathophysiology of depression- and/or anxiety-like behaviors [8, 9], likely in relation with dysfunctions of the HPA axis activities [10, 11] in our MS rats.

The hippocampus as well as the NAc receives dopaminergic fibers from the ventral mesencephalon [26–28], and dopamine modulates the hippocampal plasticity [29–31]. The hippocampal dysfunction is associated with symptoms of depression [32, 33]. The hippocampus is known to be involved in the feedback regulation of the HPA axis activity, and dysfunction of the HPA axis is implicated in the pathophysiology of anxiety [34], depression [35], and eating disorders [12, 14]. Together with our previous reports demonstrating that our MS rats show anxiety- and depression-like behaviors [8, 9] and binge-like eating behavior with increased HPA axis activity when they are subjected to repeated fasting/refeeding cycles [11], it was hypothesized that the fasting/refeeding cycles may alter dopamine neurotransmission in the hippocampus of our MS rats, perhaps leading to an alteration in anxiety- and/or depression-like behaviors. In this study, we have examined the changes in the brain dopamine contents and the psychoemotional behaviors following repeated fasting/refeeding cycles in MS and NH rats.

2. Materials and Methods

2.1. Animals. Sprague-Dawley rats were purchased (Samtako Bio, Osan, Korea) and cared in a specific-pathogen-free barrier area with constant control of temperature (22 ± 1°C), humidity (55%), and a 12/12 hr light/dark cycle (lights on at 07:00 AM). Standard laboratory food (Purina Rodent Chow, Purina Co., Seoul, Korea) and membrane filtered purified water were available *ad libitum*. Animals were cared according to the Guideline for Animal Experiments, 2000, edited by the Korean Academy of Medical Sciences, which is consistent with the NIH guidelines for the Care and Use of Laboratory Animals, revised 1996. All animal experiments were approved by the Committee for the Care and Use of Laboratory Animals at Seoul National University.

2.2. Experimental Protocol. Nulliparous females and proven breeder males were used for breeding in the laboratory of the animal facility, and the pups were reared in a controlled manner to minimize and standardize unwanted environmental stimulation from *in utero* life. Twelve hours after confirming delivery (PND 1), pups were culled to 5 males and 5 females per litter. Each litter was assigned either for the maternal separation (MS) group or for the nonhandled (NH) group. MS was performed as we previously described [8–11]. In brief, MS pups were removed from their dam and home cage and placed closely together in a new cage bedded with woodchips (Aspen Shaving, Animal JS Bedding, Cheongyang, Korea) for 180 min and then returned to their home cage and dam. MS was performed at room temperature, that is, no additional treatment to keep the pups warm during the separation period, other than placing them closely together, was offered and pup-cooling during MS was expected. MS was performed during 9:00 h–12:00 h daily from PND 1 through 14, and then the pups were left with their dam undisturbed until weaning on PND 22. The NH group remained undisturbed until weaning except for routine cage cleaning. For cage cleaning, all rats were moved to a clean cage twice a week. Female pups were excluded from the study, because our previous studies supporting the rationale to plan the present study had been performed with male offspring [11]. On the weaning day, 4 male pups were randomly selected from each litter and placed 2 pups together in each cage. Two pups in one cage were subjected together to repeated fasting/refeeding cycles, that is, a 24-h fasting followed by a 24-h refeeding repeatedly (RFR) from PND 28, and the rest 2 littermates in another cage remained with free access to chow as the fed control (FC) group. The RFR groups (NH/RFR or MS/RFR) were deprived from food, but not water, for 24 h every other day from 09:00 AM, otherwise had *ad libitum* access to chow and water during refeeding days. The FC groups (NH/FC or MS/FC) received free access to chow and water for the whole experimental period.

NH/RFR and MS/RFR rats ($n = 10$ per each group, total 20 rats from 10 different litters) were subjected to the behavioral sessions from PND 54 at the end of the 13th refeeding session, and they remained on the repeated fasting/refeeding cycles during the whole experimental period. Age-matching free fed control pups in each NH and MS group (NH/FC and MS/FC, $n = 7$-8 per each group, total 15 rats from 8 different litters) were processed in parallel.

2.3. Ambulatory Activity. NH/RFR and MS/RFR rats and their age-matching free fed control rats (NH/FC and MS/FC) were subjected to the ambulatory test on PND 54. On each trial, the rat was placed in the center of the activity chamber (43.2 cm in length, 42.2 cm in width, and 30.5 cm in height, MED Associates, VT, USA), a transparent acryl chamber equipped with two horizontal planes of 16 infrared photocell-detector pairs placed in x, y dimension, spaced 2.5 cm apart, and its ambulatory activity was monitored by the computerized system for 60 min. Light condition of the test room was maintained in the same intensity with animal rooms under day-light condition. Ambulatory activity was measured as the total counts of beam interruptions in the horizontal sensor during each consecutive 5-min session. The activity chamber was cleaned with 70% ethanol after each use to eliminate any olfactory cues of the previously tested rat.

2.4. Elevated Plus Maze. Two days after the ambulatory activity test (at the end of the 14th refeeding session), rats

were subjected to the behavioral assessment in an elevated plus maze, a plus-shaped acryl maze with two opposite open arms (50 cm in length and 10 cm in width) and two opposite closed arms (50 cm in length, 10 cm in width, and 31 cm in height), extending out from a central platform (10 cm × 10 cm). The whole apparatus was elevated 50 cm above the floor. The test procedure was followed as previously described [7]. Each rat was placed in the center of the maze facing one of the open arms and then allowed to explore the open or closed arms of the maze for 5 min. The time spent in the different arms was recorded, respectively. Four paws had to be inside the entrance line to each arm, which signaled the start of the time spent in the specific arm, and then the end time was recorded when all four paws were outside the line again. The maze was cleaned with 70% ethanol after each test to prevent influences of the previously tested rat.

After the end session of maze test, rats were allowed to rest in their home cages for a week to minimize any effects of previous stress and then subjected to the forced swim test.

2.5. Forced Swim Test. Rats were subjected to the forced swim test at the end of the 18th refeeding session, according to the method previously described [36]. Each rat was allowed to swim in a glass cylinder (54 cm in height and 24 cm in diameter) filled with water in 40 cm of depth (23–25°C) for 5 min, and the test sessions were recorded by a video camera from the side of the cylinder. Duration of rat's immobility in the water was scored from videotapes by a trained observer who was blinded to the experimental conditions. Immobility was defined as the state in which rats were judged to be making only the movements necessary to keep their head above the surface.

Rats were placed in the test room at least 2 h prior to each test to minimize unwanted stress effects, and all behavioral assessments were performed between 9:00 AM and 12:00 PM of the day to avoid the influences of circadian variances. Behavioral scoring was done with the observer blind of the treatment of the rats.

2.6. High-Performance Liquid Chromatography. A week after the end session of behavioral tests (PND 70), satiated rats were rapidly decapitated after brief anesthesia in a carbon dioxide chamber. Tissue samples of the dorsal hippocampus, the nucleus accumbens, and the midbrain covering the ventral tegmental area and substantia nigra were rapidly dissected on ice immediately after decapitation, frozen in liquid nitrogen, and stored at −80°C until used. Tissue contents of dopamine and its metabolite dihydroxyphenylacetic acid (DOPAC) were measured by high-performance liquid chromatography (Waters Instrument, Model 700, Milford, MA, USA), which consisted of a 600 E solvent delivery system equipped with a 2487 UV Detector set at 254 nm and a 717 Autosampler. The mobile phase, comprising of 88% distilled water, 2% acetonitrile, and 10% ammonium acetate buffer (0.1 M, pH 5.0), was pumped at a rate of 1 mL/min. The column used is a Atlantis dC18 (150 × 4.6 mm, 5 μm particle size, Waters, Milford, MA, USA).

2.7. Statistical Analysis. Data were analyzed by one- and two-way (maternal separation X feeding condition) analysis of variance (ANOVA) and preplanned comparisons between groups performed by *post hoc* Fisher's Protected Least Significant Difference (PLSD) test, using StatView software (Abacus, Berkeley, CA). Significance was set at $P < 0.05$, and all values were presented as means ± SE.

3. Results

3.1. Behavioral Assessments. Rats were subjected to the ambulatory activity test on PND 54 (Figure 1). Two-way ANOVA of the activity counts revealed main effects of maternal separation ($F(1,18) = 4.875$, $P = 0.0405$, total counts), feeding condition ($F(1,18) = 4.602$, $P = 0.0458$, initial 10 min; $F(1,18) = 13.833$, $P = 0.0016$, total counts), and an interaction between maternal separation and feeding condition ($F(1,18) = 7.451$, $P = 0.0138$, initial 10 min). Main effects of feeding condition ($F(1,18) = 6.109$, $P = 0.0237$, initial 10 min; $F(1,18) = 15.653$, $P = 0.0009$, total counts) and an interaction between maternal separation and feeding condition ($F(1,18) = 9.841$, $P = 0.0057$, initial 10 min) were found in the distance travelled. Not only the ambulatory counts but also the distance travelled in the activity chamber during the initial 10 min was decreased in MS/FC rats compared with NH/FC controls, and the total ambulatory counts and travel distance during 60 min of the test session were also decreased in MS/FC rats compared with NH/FC controls (Figure 1). Repeated fasting/refeeding cycles significantly increased the ambulatory activities of MS rats (MS/FC versus MS/RFR) both in the activity counts and the distance travelled, but not of NH rats. These results reveal that repeated fasting/refeeding cycles do not affect the ambulatory activities in NH rats, but normalize them in MS rats which were decreased by MS experience.

In order to assess anxiety-like behaviors, rats were subjected to the elevated plus maze test after the 14th refeeding session (Figure 2). Analysis of the % arm entry (percent entries into the closed or open arms out of total arm entries) with 2-way ANOVA revealed main effects of MS ($F(1,27) = 4.604$, $P = 0.0410$ for closed arms, $F(1,27) = 4.604$, $P = 0.0411$ for open arms), no effect of feeding condition, and no interaction between MS and feeding condition. MS/FC rats visited the closed arms more, and the open arms less, than NH/FC rats. Repeated fasting/refeeding cycles did not affect the arm entry of MS rats.

In order to assess depression-like behaviors, rats were subjected to forced swim test after the 18th refeeding session (Figure 3). Two-way ANOVA revealed an interaction between MS and feeding condition ($F(1,26) = 4.291$, $P = 0.0484$). Immobility duration of MS/FC rats was longer than NH/FC rats and shortened after repeated fasting/refeeding cycles. Repeated fasting/refeeding cycles did not alter the immobility duration of NH rats.

3.2. Dopamine Contents in the Brain Regions. After the 21st refeeding session (PND 70), tissue contents of dopamine and its metabolite DOPAC in the hippocampus, the midbrain

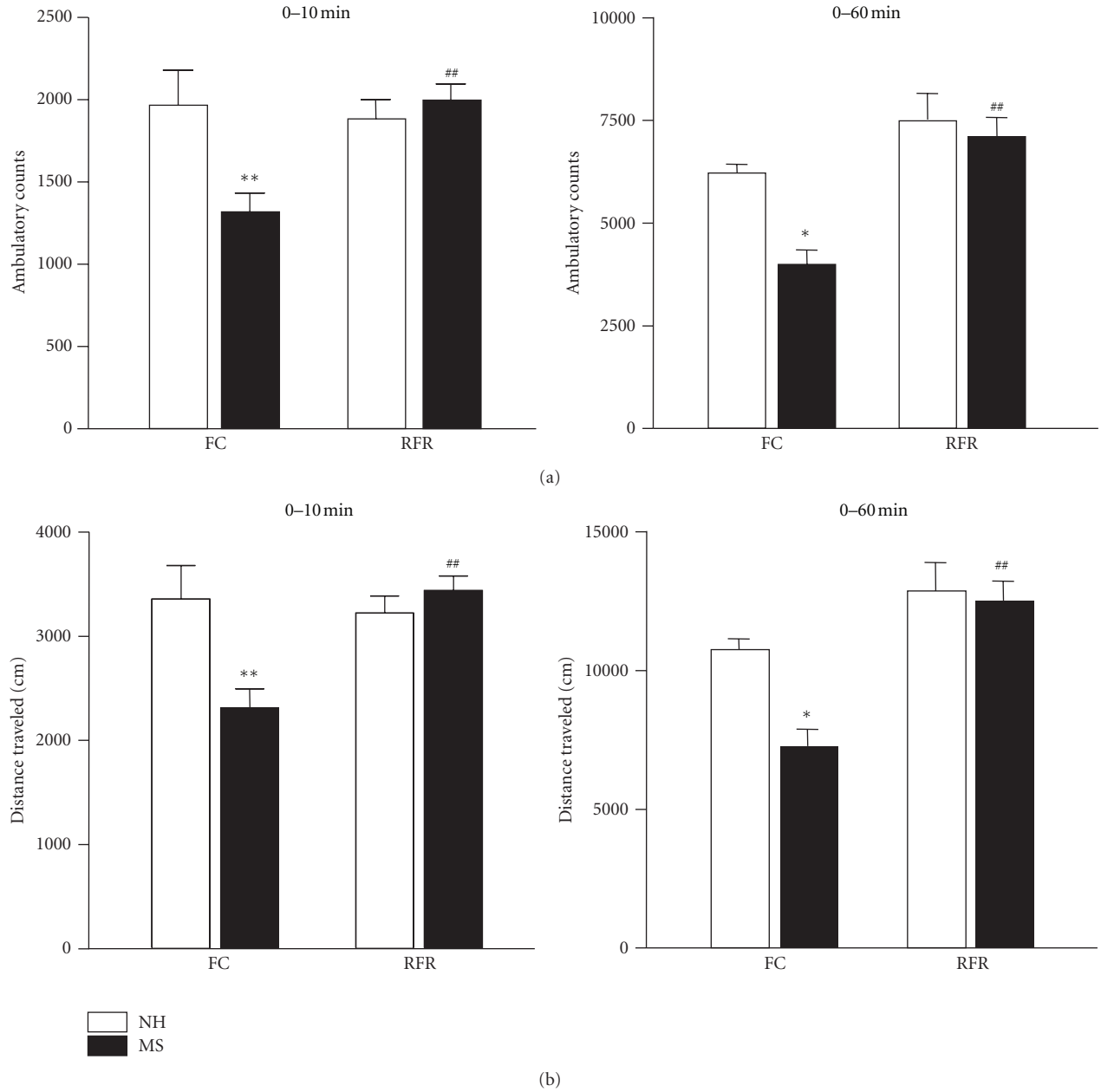

Figure 1: Ambulatory counts (a) and travel distance (b) of NH and MS rats, which were recorded consecutively at every 5 min during 60 min of test period. NH/RFR and MS/RFR rats and their age-matching free fed control rats (NH/FC and MS/FC) were subjected to the ambulatory test on PND 54 at the end of the 13th refeeding session. $^{*}P < 0.05$, $^{**}P < 0.01$ versus NH/FC, $^{\#\#}P < 0.01$ versus MS/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding, min: minutes. Data are presented as means ± S.E.

covering substantia nigra and ventral tegmental area, and the nucleus accumbens were analyzed (Figure 4). Analysis of dopamine contents with 2-way ANOVA revealed interactions between MS and feeding condition in the hippocampus ($F(1,11) = 5.344$, $P = 0.0412$) and the midbrain dopaminergic neurons ($F(1,11) = 6.093$, $P = 0.0312$). Dopamine and DOPAC levels in the brain regions of MS/FC rats did not significantly differ from NH/FC rats. Dopamine and DOPAC levels in the hippocampus of MS rats were markedly increased by repeated fasting/refeeding cycles, but not in NH rats (Figure 4(a)). Repeated fasting/refeeding cycles significantly increased dopamine level in the midbrain of MS rats, where most of dopaminergic neurons in the brain are located (Figure 4(b)). Dopamine and DOPAC levels in the nucleus accumbens of MS rats were not significantly changed by repeated fasting/refeeding cycles (Figure 4(c)). Repeated fasting/refeeding cycles did not affect the tissue contents of dopamine and DOPAC in all three brain regions of NH rats.

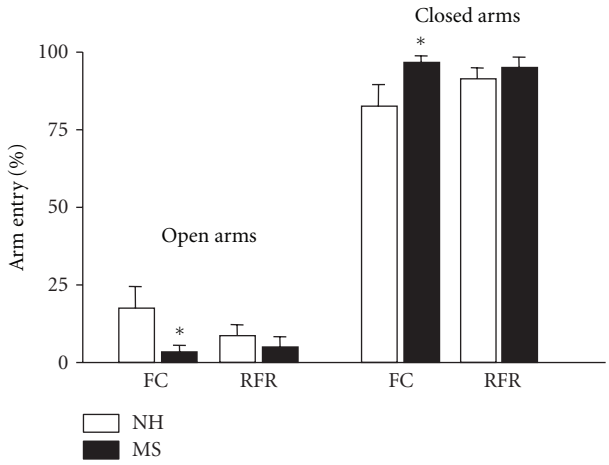

Figure 2: Percent arm entries during elevated plus maze test. The test was performed 2 days after the ambulatory test, at the end of the 14th refeeding session. $^{*}P < 0.05$ versus NH/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding. Data are presented as means ± S.E.

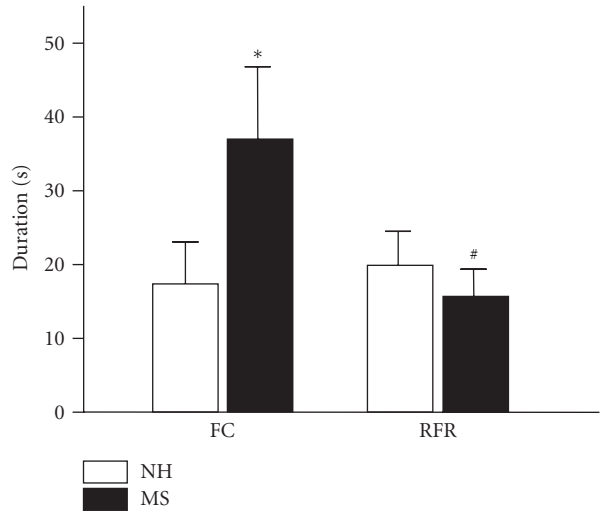

Figure 3: Immobility durations of rats during forced swim test. Rats were subjected to forced swim test at the end of the 18th refeeding session. $^{*}P < 0.05$ versus NH/FC, $^{\#}P < 0.05$ versus MS/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding, sec: seconds. Data are presented as means ± S.E.

4. Discussion

In this study, we have demonstrated that repeated fasting/refeeding cycles increase dopamine levels not only in the midbrain dopaminergic neurons but also in the hippocampus of MS rats and these increases are not observed in NH rats, suggesting an increased activity of the mesohippocampal dopaminergic pathway in MS rats, but not in NH, by repeated fasting/refeeding cycles. The increased DOPAC levels by repeated fasting/refeeding cycles in the hippocampus of MS rats further supported an increased dopaminergic activity in their mesohippocampal pathway, since released dopamine is converted to DOPAC after reuptake by the nerve terminal. We have previously reported that repeated fasting/refeeding cycles promote sustained hyperphagia in our MS rat model, in relation with increased activity of the HPA axis [11]. Hippocampus is known to be involved in the regulation of the HPA axis activity. Thus, it is suggested that increased dopamine neurotransmission in the mesohippocampal pathway may be implicated in the increased HPA axis activity by repeated fasting/refeeding cycles in our MS rat model.

Previous studies have reported that dopamine modulates the hippocampal plasticity with both synapse-specific and activity-dependent mechanisms [29–31]. Human studies have suggested that the hippocampal malfunction is associated with symptoms of depression [32, 37, 38]. Optimal function of the hippocampal formation is critical for the regulation of the HPA axis and stress response, dysregulation of which is observed in almost half of all depressed patients [39, 40]. In this study, MS rats showed depression-like behaviors with increased immobility during swim test, in accordance with our previous report [8]. Interestingly, repeated fasting/refeeding cycles appeared to improve the depression-like behaviors of MS rats, that is, immobility duration was reduced in the MS rats that subjected to repeated fasting/refeeding cycles, compared to their free fed control group. Contrarily, repeated fasting/refeeding cycles did not alter the behavioral scores measuring depression-like behaviors in NH rats. Taken together, it is concluded that increased dopamine neurotransmission in the hippocampus is likely involved in the regulatory mechanisms underlying the improved depression-like behaviors of MS rats by repeated fasting/refeeding cycles.

Disruption of dopaminergic function within the nucleus accumbens (NAc) caused anhedonia, a core symptom of major depressive disorder, in rodents [41], and dopamine neurotransmission in the NAc responding to food was blunted by chronic mild stress, an animal model of depression [42]. Our previous studies have suggested that blunted mesolimbic dopaminergic activity responding to acute stress is associated with depression-like behaviors including anhedonia (decreased pleasure-seeking behavior) in our MS rat model [8, 19, 20]. In this study, repeated fasting/refeeding cycles did not significantly increase dopamine levels in the reward center NAc not only in NH rats but also in MS rats, suggesting that the improved depression-like behaviors in MS rats by repeated fasting/refeeding cycles may not comprise an improvement of hedonic behavior. Thus, the present result does not seem to support the idea that repeated fasting/refeeding cycles may increase the hedonic value of food consumed in MS rats, which may contribute to a sustained hyperphagia at refeeding days during the cycles as observed in our previous report [11]. However, this is not yet sure because either a hedonic behavior *per se* or dopamine release responding to food consumption was not measured in this study.

Negative emotions appear to be associated with eating behaviors. Eating has been viewed as a strategy to improve negative mood [43] and to mask stress [44]. Obese binge eaters experience an increased tendency to binge in response

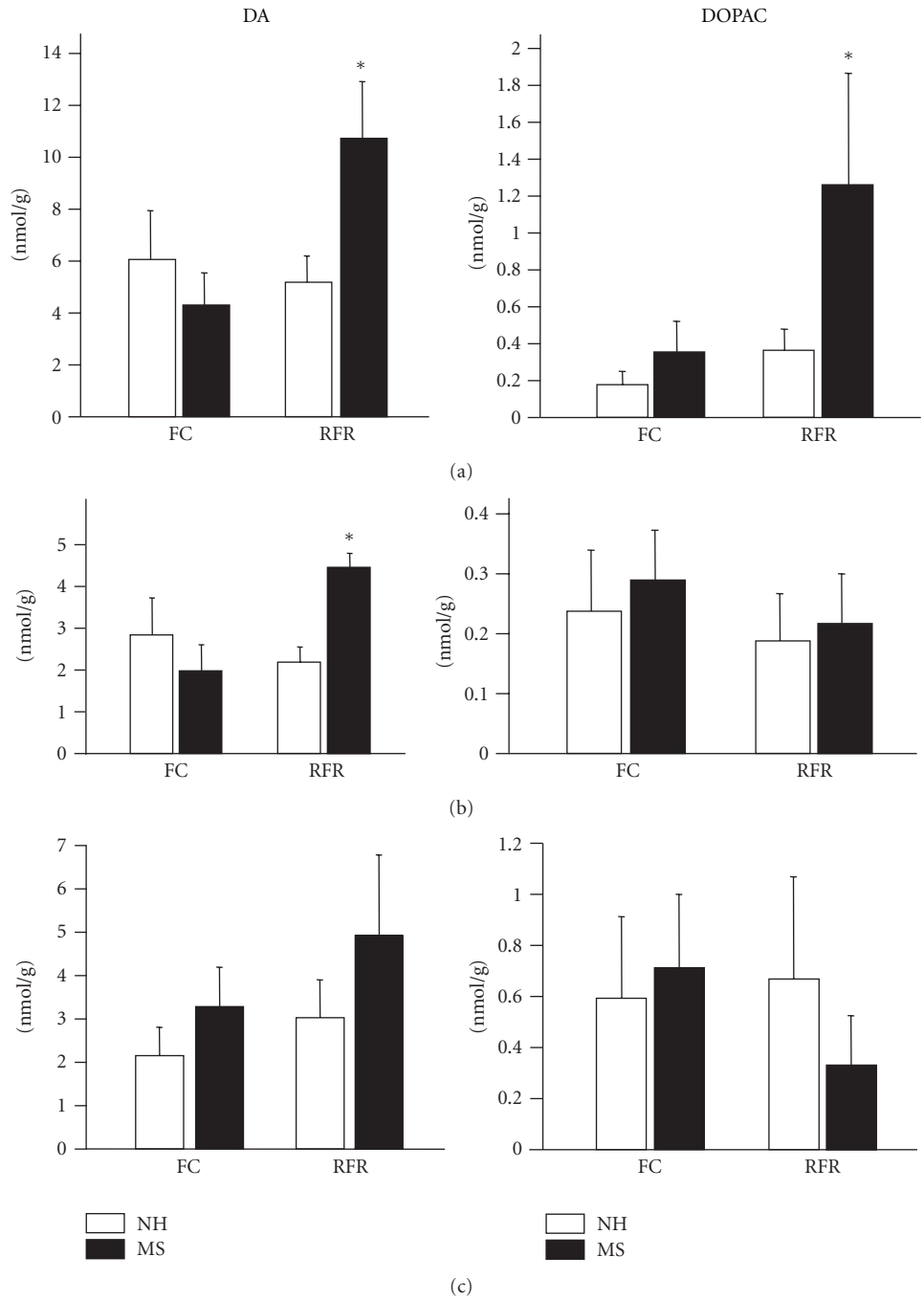

Figure 4: Tissue contents of dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) in the hippocampus (a), the ventral tegmental area and substantia nigra (b), and the nucleus accumbens (c). After the 21st refeeding session (PND 70), rats were rapidly decapitated, and the tissue contents of DA and DOPAC were analyzed by high-performance liquid chromatography. $^*P < 0.05$ versus MS/FC, NH: nonhandled, MS: maternal separation, FC: free fed control, RFR: repeated fasting/refeeding. Data are presented as means ± S.E.

to negative mood [45, 46]. Also, it was reported that even healthy, normal-weight persons regulate negative emotions by eating [47–49]. In a rat model of neonatal maternal separation, consumption of high fat diet reduced anxiety- and depression-like symptoms [50, 51], suggesting that negative emotions developed by early life stressful experience can be improved by eating. This is further supported by the present results demonstrating that depression-like behaviors, though not anxiety, of MS rats were improved during repeated fasting/refeeding cycles, and that the behavioral scores of NH rats were not changed by fasting/refeeding cycles. It should be noticed that rats were subjected to the behavioral assessments when satiated with refeeding, and MS rats showed binge-like eating on each refeeding day

[11]. Thus, it is plausible that the improved depression-like behaviors in MS rats subjected to fasting/refeeding cycles might be a consequence of binge-like eating during refeeding days which possibly occurred to cope with the metabolic stress challenges during fasting/refeeding cycles. Indeed, the depression-like behavioral scores of MS rats on the cycles when measured on fasting day were still higher than NH controls (data not shown).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors that regulate development, maintenance, and morphological plasticity of neuronal systems. It has been reported that BDNF promotes the survival and differentiation of cultured dopaminergic neurons [52, 53], enhances dopamine turnover in the brain [54], and elevates activity-dependent release of dopamine [55], suggesting that BDNF plays a crucial role in regulating dopaminergic tone. Previous studies have reported that BDNF expression is reduced [51] or increased [56] in the hippocampus of MS rats that subjected to a similar separation protocol used in this study, and consumption of high fat diet normalized the hippocampal BDNF expression in MS rats [51]. Also, increased hippocampal BDNF was shown to modulate depression-like behaviors induced by acute stress [57] or chronic unpredictable stress [58]. Furthermore, chronic antidepressant treatment in rats reduced depression-like behaviors and increased hippocampal BDNF mRNA [59]. Taken together, it is speculated that BDNF may play a role in the regulation of the mesohippocampal dopaminergic activity by repeated fasting/refeeding cycles in our MS rats. Studies on the regulatory mechanisms underlying the increased mesohippocampal dopaminergic activity by fasting/refeeding cycles are currently under our consideration.

In conclusion, fasting/refeeding cycles may increase the mesohippocampal dopaminergic activity and improve depression-like behaviors in rats with MS experience. Together with our previous report demonstrating that MS rats exhibit a binge-like eating behavior during fasting/refeeding cycles [11], it is suggested that increased dopamine neurotransmission in the hippocampus may be implicated in the underlying mechanisms by which the fasting/refeeding cycles induced binge-like eating and improved depression-like behaviors in MS rats. Underlying mechanisms by which fasting/refeeding cycles increase the mesohippocampal dopaminergic activity should be further studied.

Acknowledgments

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