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The selective serotonin reuptake inhibitor fluvoxamine suppresses post-feeding hyperactivity induced by food restriction in rats

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Abstract

Previous studies demonstrated that rats allowed access to running wheel with food restriction schedules run excessively. This hyperactivity consisted of a pre-feeding activity (an increase in running activity before the feeding time, also termed food-anticipatory activity: FAA) and a post-feeding activity (an increase in running activity after the feeding time, succeeding activity: SA). Here we evaluated the effect of fluvoxamine, a selective serotonin reuptake inhibitor, on food restriction-induced hyperactivity in rats. Furthermore, the effect of fluvoxamine on each of the FAA and the SA was also investigated. Rats were individually housed in a running-wheel cage under food restriction for 3 h per day, and running activity was measured for 7 consecutive days. This restricted feeding significantly increased the running activity and decreased body weight. Simultaneous administration of fluvoxamine (50 mg/kg/day, p.o.) for 7 days suppressed the increase in running activity ($P<0.05$) with no modification of the decrease in body weight or food intake. Analysis of each activity revealed that fluvoxamine's efficacy was observed only in the SA ($p<0.01$). These results suggest that repeated treatment with fluvoxamine attenuates the hyperactivity, which is exclusively dependent on the substantial reduction in the SA.

Keywords: Food restriction; Hyperactivity; 5-HT; Selective serotonin reuptake inhibitor; Fluvoxamine; Rat; Food-anticipatory activity; Succeeding activity

1. Introduction

As first reported by Hall and Hanford, food restriction-induced hyperactivity (FRIH) involved placing rats individually in a running-wheel cage and feeding them for 1 h per day (Hall and Hanford, 1954). These rats demonstrated a loss of body weight, decreased food intake, and increased running activity, and eventually died within 3 to 12 days (Altemus et al., 1996; Endou et al., 2001; Iwamoto et al., 1999; Morrow et al., 1997). Besides the increase in running activity, they developed gastric ulcer, atrophy of the spleen and thymus, and hypertrophy of the adrenal (Tsuda and Tanaka, 1990). Many of these phenomena are common features of anorexia nervosa or obsessive–compulsive disorder (OCD). Consequently, FRIH has been suggested to be a useful model for studies of gastric ulcer (Pare, 1975; Tsuda et al., 1982; Watanabe et al., 1990), anorexia nervosa (Beneke et al., 1995; Watanabe et al., 1992), or OCD (Altemus et al., 1996; Takeda et al., 2003). Alterations of the activities of the noradrenergic (Pirke et al., 1993; Rea and Hellhammer, 1984; Tsuda et al., 1983), serotonergic (Hellhammer et al., 1983; Izumisawa et al., 1994; Mayeda et al., 1989; Wilckens et al., 1992), and cholinergic systems (Izumisawa et al., 1994) in the brain were seen in animals showing FRIH. In particular, rats that suffered from FRIH showed a decrease in the levels of serotonin (5-HT) and its metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) in the midbrain and cerebellum (Izumisawa et al., 1994). Rats repeatedly treated with parachlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor that depletes 5-HT, showed a greater increase in FRIH compared with vehicle treatment (Altemus et al., 1996). These findings suggested that suppression of the serotonergic system plays an important role in the pathogenesis of FRIH.

Restricted feeding (RF) triggers hyperactivity prior to feeding time which is referred to as the pre-feeding activity (food-anticipatory activity, FAA) (Honma et al., 1983; Mistlberger, 1994; Richter, 1922). The FAA has been well investigated in view of circadian rhythmicity. Orexin neuron-ablated transgenic mice have

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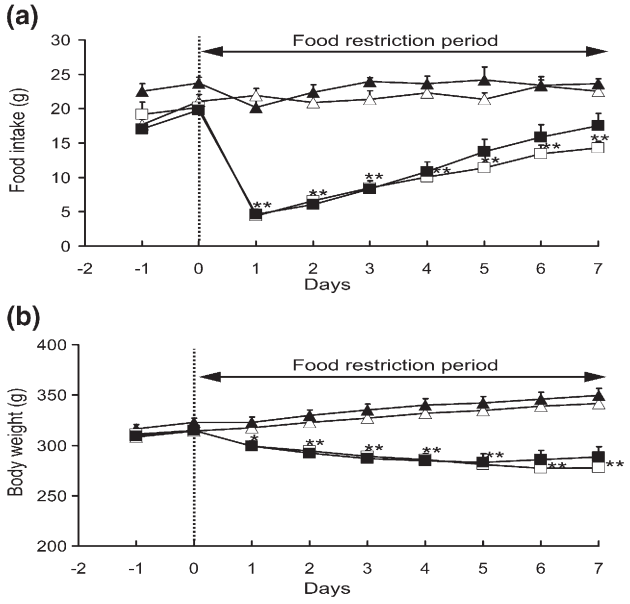

Fig. 1. Effect of repeated doses of fluvoxamine on the decrease in daily food intake and body weight in food-restricted rats. (a) Daily food intake. (b) Body weight. Each point represents the mean+S.E. of 9–14 animals. (open triangles): free feeding+vehicle, (closed triangles): free feeding+fluvoxamine 50 mg/kg, (open squares): 3 h feeding+vehicle, (closed squares): 3 h feeding+fluvoxamine 50 mg/kg. Repeated measurement of ANOVA followed by Student's *t*-test. $*p<0.05$, $**p<0.01$ compared with the free feeding+vehicle group.

a severe deficit in displaying the normal FAA observed in food-restricted wild-type mice (Mieda et al., 2004). Thus, orexin may be essential for the expression of the FAA. However, the detailed mechanisms are not yet fully understood. On the other hand, some rats under RF showed a post-feeding activity (a second bout of activity after feeding time, so-called the succeeding activity: SA) (Aschoff et al., 1983; Aschoff, 1991; Honma et al., 1983). Compared with the stable expression of the FAA, the SA is often less clearly separated from activity bouts of the free-running rhythm and hence, more difficult to define precisely, which might have impeded elucidation of the mechanistic understanding of this behavioral component.

Many molecules such as leptin (Exner et al., 2000), histamine (Endou et al., 2001), and 5-HT type2 receptor agonist (Wilckens et al., 1992), can attenuate FRIH. Altemus et al. showed that FRIH is suppressed in rats that has been treated for 5 weeks with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), but not with imipramine, a tricyclic antidepressant (Altemus et al., 1996). However, all of the studies reported so far evaluated only daily total wheel revolutions and did not clarify the effect of the drugs on each of the FAA and the SA. In the present study, we investigated the effect of fluvoxamine, the different type of SSRI, on FRIH in rats in terms of differences in the response between the FAA and the SA.

2. Material and methods

2.1. Animals

Male Sprague-Dawley rats (Clea Japan Co., Japan) weighing 220±20 g on arrival were housed individually in metal cages and supplied with powdered food (CRF-1, Oriental Yeast Co., Japan) and water ad libitum prior to the experiment. In an animal room, the temperature was kept at 23±3 °C, the humidity was 40–70%, and the light was on from 7:00 to 19:00. All studies were performed according to the guidelines of the Animal Care and Use Committee of the Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd.

2.2. Drug

Fluvoxamine maleate (Meiji Seika Kaisha, Ltd., Japan) was dissolved in distilled water, and a dosing volume was set at 5 ml/kg for oral administration.

2.3. Apparatus

A running-wheel cage (MED Co., USA) consisted of a clear plastic-made running wheel (36 cm in diameter, 11 cm width) and an adjoining plastic square cage (30.5×24×29 cm). The rats could enter the running wheel freely throughout the experiment. A feeding box was attached to the cage with a sliding door between them. Opening and closing of the sliding door was controlled with a computer system (AB System, Neuroscience Co., Japan). When the sliding door was open, the rats had access to food. The number of wheel revolutions was automatically

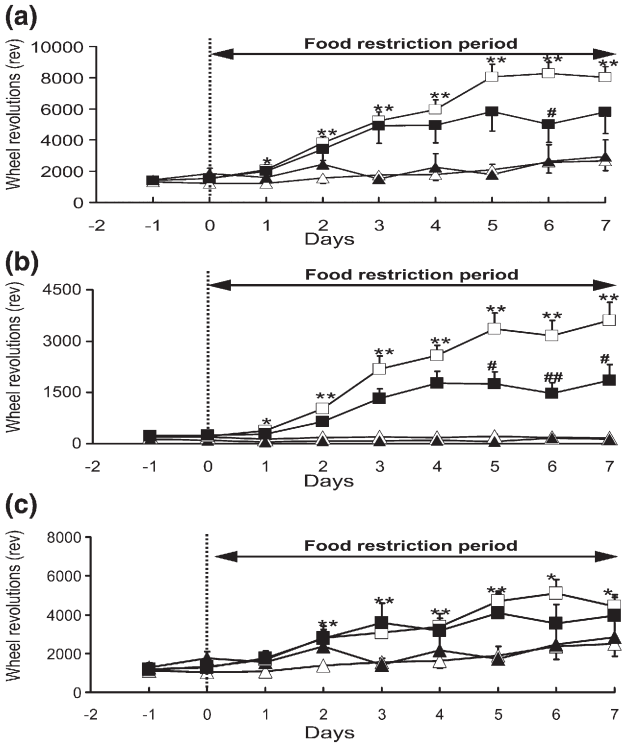

Fig. 2. Effect of repeated doses of fluvoxamine on the increase in wheel revolutions in the daily total (a), the light phase (b), and the dark phase (c) in food restricted rats. Each point represents the mean±S.E. of 9–14 animals. (open triangles): free feeding+vehicle, (closed triangles): free feeding+fluvoxamine 50 mg/kg, (open squares): 3 h feeding+vehicle, (closed squares): 3 h feeding+fluvoxamine 50 mg/kg. Repeated measurement of ANOVA followed by Student's *t*-test. $*p<0.05$, $**p<0.01$ compared with the free feeding+vehicle group. $\#p<0.05$, $\#\#p<0.01$ compared with the 3 h feeding+vehicle group.

recorded at one-minute intervals with the computer system (AB System, Neuroscience Co.).

2.4. Experimental procedure

All rats were individually housed in the running-wheel cage with food and water provided ad libitum during a 7-day acclimation period. A food restriction schedule started at the end of the acclimation period and lasted for 7 days. The rats were evenly assigned into groups to avoid differences among them with regard to body weight and the number of wheel revolutions recorded on the last day of the acclimation period. Rats were divided into four groups: (1) free feeding + vehicle group ($n = 13$); (2) free feeding + fluvoxamine (50 mg/kg) group ($n = 9$); (3) 3 h (between 12:00 and 15:00) feeding + vehicle group ($n = 14$); (4) 3 h (between 12:00 and 15:00) feeding + fluvoxamine (50 mg/kg) group ($n = 13$). In our preliminary studies, some rats under severe food restriction (less than 3 h) died within 1 week. Thus, we chose the 3 h feeding period. Also our preliminary studies indicated that this dose of fluvoxamine does not alter locomotion activity compared with vehicle treatment, and the lower dose (25 mg/kg) is ineffective in suppressing hyperactivity in any time periods. From these reasons, we tested the one dose of fluvoxamine this time. Body weight and food intake were daily measured between 15:00 and 16:00 throughout the experiment. The rats were orally given the drug or vehicle once daily immediately after the measurement of body weight from the start of RF. This procedure was decided

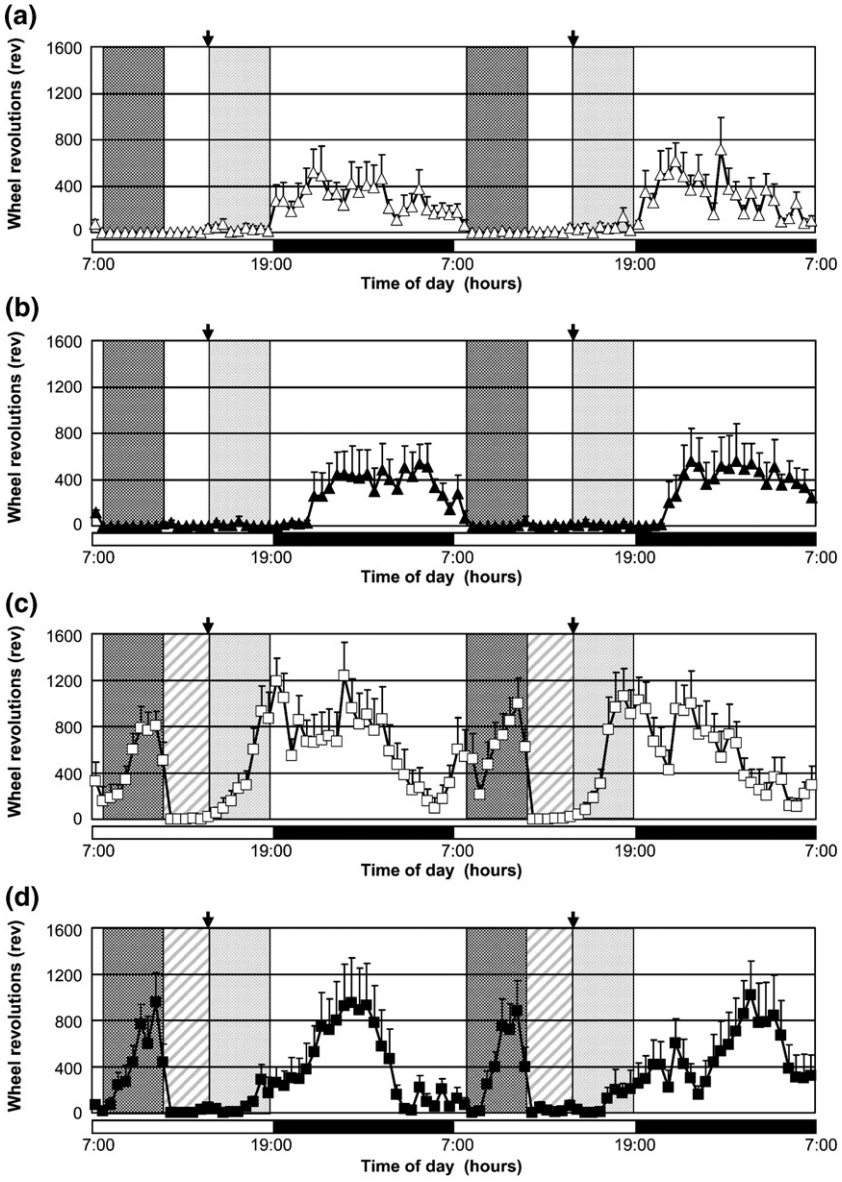

Fig. 3. Changes in wheel revolutions on day 6 and day 7. (a) free feeding + vehicle (open triangles). (b) free feeding + fluvoxamine 50 mg/kg (closed triangles). (c) 3 h feeding + vehicle (open squares). (d) 3 h feeding + fluvoxamine 50 mg/kg (closed squares). Each point represents the mean + S.E. The vertical arrows indicate the time of drug administration. The lighting cycle is shown by horizontal bar on the bottom of the figures; white denotes light (L) and black denotes darkness (D). The hatched vertical bars indicate the feeding time. The dark grey and the light vertical bars indicate the FAA and the SA, respectively.

with reference to the previous studies except for feeding and drug administration schedule (Altemus et al., 1996). Period of the FAA and the SA were defined as 4 h preceding meal access and 4 h after the end of feeding time, respectively (Davidson and Stephan, 1999).

2.5. Statistics

All results are expressed as means±S.E. Statistical analysis was performed with the SAS statistical package (SAS Institute Japan, Japan). Significant differences between two of four groups (see Section 2.4, Experimental procedure) were determined using the analysis of variance (ANOVA) for repeated measures (split-plot design). Student's *t*-test was performed if any significant interactions were detected by ANOVA. The data from day 1 to day 7 were used for the statistical analysis. Differences were considered significant at $p<0.05$.

3. Results

Fig. 1 shows the daily changes in food intake and body weight. In vehicle-treated rats under free feeding (FF), food intake did not significantly change during the experiment and body weight gradually increased until day 7. The rats in RF group displayed marked reduction in food intake on day 1 followed by restoration from day 2 to day 7 (Fig. 1a). There were significant differences in food intake between RF and FF treatment [group×time: $F(6, 150)=12.88$, $p<0.01$, group: $F(1, 25)=204.44$, $p<0.01$]. The RF-treated rats significantly decreased body weight compared with the FF group [group×time: $F(6, 150)=103.63$, $p<0.01$, group: $F(1, 25)=31.15$, $p<0.01$] (Fig. 1b). Fluvoxamine did not affect the decrease in food intake [group×time: $F(6, 150)=1.86$, n.s., group: $F(1, 25)=0.95$, n.s.] and body weight [group×time: $F(6, 150)=2.99$, $p<0.01$, group: $F(1, 25)=0.08$, n.s.] (Fig. 1a and b).

The RF treatment significantly increased daily wheel revolutions from day 1 to day 7 [group×time: $F(6, 150)=14.81$, $p<0.01$, group: $F(1, 25)=38.91$, $p<0.01$] which peaked on day 5 (Fig. 2a). Fluvoxamine significantly reduced the RF-induced increase in daily wheel revolutions on day 6 [group×time: $F(6, 150)=2.84$, $p=0.012$, group: $F(1, 25)=1.78$, n.s.] (Fig. 2a). The RF treatment also significantly increased wheel revolutions in the light [group×time: $F(6, 150)=20.80$, $p<0.01$, group: $F(1, 25)=51.43$, $p<0.01$] and dark phase [group×time: $F(6, 150)=2.96$, $p<0.01$, group: $F(1, 25)=12.61$, $p<0.01$] (Fig. 2b and c). Fluvoxamine reduced the RF-induced increase in wheel revolutions in the light phase from day 5 onward [group×time: $F(6, 150)=3.89$, $p<0.01$, group: $F(1, 25)=7.69$, $p=0.01$] (Fig. 2b). However, this drug had no significant effect on wheel revolutions in the dark phase [group×time: $F(6, 150)=1.01$, n.s., group: $F(1, 25)=0.19$, n.s.] (Fig. 2c).

Daily patterns of wheel revolutions from day 6 to 7 in each group were illustrated in Fig. 3. The rats in FF treatment turned a wheel not in the light but in the dark phase, showing a clear circadian pattern (Fig. 3a). Fluvoxamine treatment did not significantly change the distribution of wheel revolutions in FF rats (Fig. 3b). Under RF, the vehicle-treated rats revealed an explicit expression of the FAA (elevated running activity prior to the feeding time) and the SA (elevated running activity after feeding time) concomitant with enhancement of nocturnal activities (Fig. 3c). On the other hand, fluvoxamine-treated rats with RF increased running activity only prior to and not after the feeding time (Fig. 3d).

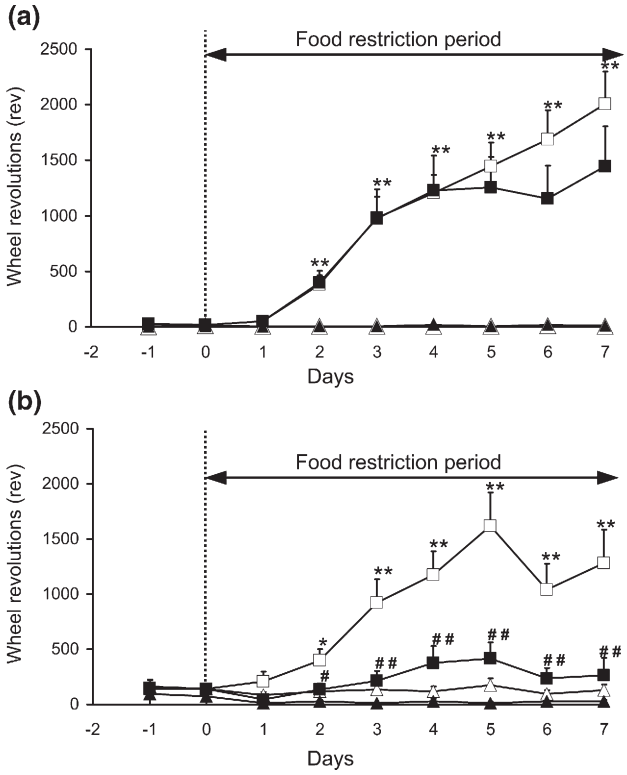

Fig. 4. Effect of repeated doses of fluvoxamine on the increase in wheel revolutions in the FAA and the SA in food-restricted rats. The number of wheel revolutions in the FAA (a) and the SA (b). Each point represents the mean+S.E. of 9–14 animals. (open triangles): free feeding+vehicle, (closed triangles): free feeding+fluvoxamine 50 mg/kg, (open squares): 3 h feeding+vehicle, (closed squares): 3 h feeding+fluvoxamine 50 mg/kg. Repeated measurement of ANOVA followed by Student's *t*-test. *$p<0.05$, **$p<0.01$ compared with the free feeding+vehicle group. #$p<0.05$, ##$p<0.01$ compared with the 3 h feeding+vehicle group.

Described in Fig. 4 is the number of wheel revolutions in the FAA and the SA. In the vehicle-treated RF group, wheel revolutions in the FAA significantly increased from day 2 to day 7 [group×time: $F(6, 150)=17.84$, $p<0.01$, group: $F(1, 25)=64.95$, $p<0.01$], and wheel revolutions in the SA also significantly increased from day 2 to day 7 [group×time: $F(6, 150)=8.68$, $p<0.01$, group: $F(1, 25)=20.18$, $p<0.01$] and peaked on day 5 (Fig. 4a and b). Fluvoxamine reduced the increase in wheel revolutions in the SA from day 2 to day 7 [group×time: $F(6, 150)=4.35$, $p<0.01$, group: $F(1, 25)=13.24$, $p<0.01$] (Fig. 4b). However, this drug had no significant effect on wheel revolutions in the FAA [group×time: $F(6, 150)=1.15$, n.s., group: $F(1, 25)=0.60$, n.s.] (Fig. 4a).

In the FF groups, as partly mentioned above, fluvoxamine did not affect food intake, body weight, wheel revolutions in daily, the light phases, and the dark phases, the FAA, and the SA.

4. Discussion

The present study demonstrated that food-restricted rats showed a decrease in body weight, a suppression of food intake, and an increase in daily running activity (Fig. 1 and 2). In addition, they developed the FAA and the SA (Figs. 3 and 4), which are consistent with the previous reports (Honma et al., 1983; Shido et al., 1986). Repeated administration of fluvoxamine from the onset of RF attenuated an increase in daily wheel revolutions. Moreover, this is the first study to indicate that fluvoxamine suppressed the elevated wheel revolutions in the SA. According to the earlier study by Altemus et al., long term treatment with fluoxetine can suppress FRIH in this similar experimental model (Altemus et al., 1996). However, they did not make clear in that study the efficacy of fluoxetine for the FAA and the SA. On this account, it is suggested that SSRIs may commonly share the FRIH-suppressing property which is possibly dependent on the SA inhibition. Considering that two SSRIs (fluvoxamine and fluoxetine) known to be effective in OCD in humans attenuated hyperactivity, this FRIH model may be useful to screen for new anti-OCD agents.

In our study, fluvoxamine did not modify the RF-induced changes in food intake and body weight (Fig. 1a and b). This result was unexpected, since it was reported that fluoxetine treatment reversed the decrease in food intake and body weight in the food-restricted rats (Altemus et al., 1996). This discrepancy might be derived from differences in experimental setup of the current and previous studies like duration of food access (3 h vs. 1.5 h) and drug administration (1 week vs. 5 weeks including 4 weeks of pretreatment), or gender (male vs. female). Indeed, fluoxetine single or repeated administration reduces food intake in rats (Halford and Blundell, 1996; Heisler et al., 1997), and fluvoxamine suppresses rebound hyperphagia induced by a restricted feeding schedule (Inoue et al., 1997). In the present study, however, fluvoxamine did not show hypophagia in the rats under FF and RF. It is possible that fluvoxamine administered 21 h before daily feeding access did not influence food intake. Coincident with this response, fluvoxamine was ineffective in altering the body weight in the food-restricted rats.

An abundance of data suggests a crucial role of 5-HT in pathophysiology of FRIH. Altemus et al. found a greater increase in FRIH in rats repeatedly treated with PCPA compared with control rats (Altemus et al., 1996). A previous study reported that rats with gastric lesions resulting from FRIH showed a decrease in the levels of 5-HT in the midbrain, cortex, hippocampus, and posterior hypothalamus, and also a decrease in the level of 5-HIAA in the posterior hypothalamus (Hellhammer et al., 1983). Similarly, another study reported that rats that suffered from FRIH showed a decrease in the levels of 5-HT and 5-HIAA in the midbrain and cerebellum, and a decrease in the level of 5-HIAA in the amygdala (Izumisawa et al., 1994). Bmax for ketanserin, a 5-HT2 antagonist, increased in the frontal cortical homogenates collected from rats with FRIH (Mayeda et al., 1989). Moreover, FRIH was suppressed by the 5-HT2 agonists m-chlorophenylpiperazine and 1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane (Wilckens et al., 1992). From these findings, it is evident that the function of central serotonergic systems including 5-HT2 receptor signaling is suppressed in rats that are hyperactive due to the RF treatment. Thus, the efficacy of fluvoxamine for attenuation of FRIH is probably caused by its action on the blockade of 5-HT reuptake (Hyttel, 1994) which increases 5-HT in the synaptic cleft (Bel and Artigas, 1992; Bosker et al., 1995) and subsequent stimulation of post-synaptic 5-HT2 receptor (Claassen et al., 1977).

Fluvoxamine significantly suppressed an increase in the number of wheel revolutions in the light phase but not in the dark phase (Fig. 2). In the light phase, fluvoxamine inhibited the increase specifically in the SA and not in the FAA (Figs. 3 and 4). Running activity in rats under no food restriction is thought to be regulated by circadian oscillator located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Stephan and Zucker, 1972). Meanwhile, food restriction causes the gradual development of the FAA (Honma et al., 1983; Mistlberger, 1994; Richter, 1922). As development of the FAA proceeds, the SCN-dependent phase of running activity drifts into the light phase and gets coupled to the SA (Aschoff et al., 1983; Aschoff, 1991; Honma et al., 1983). Thus, rats given food at the middle of light phase show the increase in running activity in the light phase. The FAA and the SA persist even when SCN function is physically or genetically ablated, indicating the presence of a food entrainable oscillator (FEO) that is separate from and independent of SCN (Davidson and Stephan, 1999; Marchant and Mistlberger, 1997). The dorsomedial hypothalamic nucleus (DMH) may be the site of FEO (Mieda et al., 2006), but recent evidence argues against this possibility (Landry et al., 2006). The chronically administered naloxone, opiate antagonist, increased the FAA, but not the SA (Shido et al., 1986). Accordingly, the endogenous opioid system may play a role in suppressing the excessive increase in the FAA. By contrast, the mechanisms of the SA remain unclear because of deficiency in drug efficacy in the previous reports. In our study, fluvoxamine completely blocked the increase in running activity after feeding period, but the FAA was not changed by this treatment (Figs. 3 and 4), suggesting that serotonergic systems may be involved in the development of the SA, but not the FAA. Our pilot studies indicated that fluvoxamine does not induce hypolocomotion during 4 hr from administration time. Thus, suppression of the SA by fluvoxamine is not derived from the sedative effect of this drug. Repeated treatment with fluvoxamine significantly raised the level of 5-HIAA in rat cerebrospinal fluid during the light and not dark phase (Egashira et al., 2000). Given that fluvoxamine may evoke enhancement of the diurnal physiological activity of serotonergic neurons, it is quite reasonable to interpret that this change greatly contributes to the substantial inhibition of the SA by fluvoxamine. However, the rats were treated with fluvoxamine once daily in the end of feeding period, and it would be likely that fluvoxamine does not exist in the brain to fully suppress the FAA. Thus, additional studies with different dosing conditions such as drug administration before feeding period or constant drug infusion using osmotic minipumps would be necessary to clarify this point.

Taken together, we here confirmed occurrence of the FAA and the SA in the experimental model of FRIH, not former but latter of which were suppressed by chronic treatment with fluvoxamine. Although the underlying mechanisms have not been elucidated, future studies using neurochemical and molecular biological techniques will lead to a full comprehension of the relationship between development of the SA and changes in serotonergic neurotransmision.

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