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Effects of Serotonergic Agents on Food-Restriction–Induced Hyperactivity

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ALTEMUS, M., J. R. GLOWA, E. GALLIVEN, Y. LEONG, AND D. L. MURPHY. *Effects of serotonergic agents on food-restriction–induced hyperactivity.* PHARMACOL BIOCHEM BEHAV **53**(1) 123–131, 1996.—Rats that are fed for 90 min per day can stabilize their weight after an initial drop; however, if rats on this feeding schedule are also given access to a running wheel, they run excessively, eat less, lose weight, and often die. To investigate this phenomenon as a possible animal model of obsessive-compulsive disorder (OCD), rats were treated for 5 weeks with fluoxetine, an antidepressant that relieves OCD symptoms in humans (5 mg/kg, 2.5 mg/kg), or imipramine, an antidepressant that does not affect OCD symptoms (5 mg/kg), or saline prior to exposure to food restriction and the running wheel. In addition, because chronic fluoxetine treatment is thought to enhance serotonergic neurotransmission, for contrast an additional group of rats were treated with parachlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor that depletes serotonin. Rats treated with fluoxetine lost significantly less weight, ran significantly less, and increased food intake more rapidly during restriction of food availability than saline-treated rats. Rats treated with imipramine did not differ from those treated with saline on these parameters. Compared to saline-treated rats, rats treated with PCPA lost more weight, ate less food, and increased running more rapidly. These effects of pharmacological treatment indicate an inverse relationhip between central serotonergic activity and vulnerability to develop food-restriction-induced anorexia and compulsive running. In addition, like OCD in humans, this phenomenon in rats seems to be blocked by chronic treatment with a serotonin selective reuptake inhibitor but not a less selective monoamine reuptake inhibitor.

Serotonin Obsessive-compulsive disorder Anorexia nervosa Animal model Stress Serotonin reuptake inhibitor Adjunctive behavior

FOOD-RESTRICTION-INDUCED hyperactivity (FRIH) was first described in 1954 (32). Rats can stabilize their weight after an initial drop when food availablility is restricted to 1–2 h per day, but if rats also have access to a running wheel, they show a paradoxical reduction in food intake and also develop progressive weight loss and progressive increases in wheel running (21,40,63,70). If rats lose more than 30% of their body weight, they also develop gastric lesions or "activity-stress ulcers" (18). Once initiated, the FRIH syndrome is often fatal.

Although FRIH has long been considered an animal model of anorexia nervosa, a disease with cardinal symptoms of decreased food intake, weight loss, and hyperactivity (24,46), this phenomenon also has features analogous to obsessive-compulsive disorder (OCD). OCD is defined as the repetition of thoughts or behaviors that are senseless and maladaptive (4). Observable OCD-related compulsions in humans include repetition of movements, washing, and checking. Several lines of evidence suggest that anorexia nervosa and OCD may share some pathophysiological mechanisms. There is substantial comorbidity of these illnesses in individuals and in their families (33,44,64,65). In addition, both patient groups have elevated cerebrospinal fluid levels of corticotropin-releasing hormone and arginine vasopressin (2,28,36). OCD responds only to treatment with antidepressants that are selective serotonin reuptake inhibitors (29) and this also seems to be the case in anorexia nervosa, although the evidence in anorexia nervosa is more preliminary (31,43).

The most salient and consistent biological feature of OCD

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that distinguishes it from other psychiatric illnesses is the selective response of the illness to treatment with serotonin reuptake inhibitors. Behavioral animal models that show the same selective pharmacological response may be useful models for testing new treatment agents and for further investigation of the pathophysiology of OCD. To begin to validate FRIH as a drug-response model of OCD, we determined whether pretreatment with fluoxetine, a serotonin reuptake inhibitor effective for treatment of OCD in humans, would prevent development of the phenomenon. Control groups included rats pretreated with saline and rats pretreated with imipramine, an antidepressant not effective for OCD treatment. Finally, because chronic treatment with serotonin reuptake blockers is thought to enhance serotonergic neurotransmission (9,27), we also pretreated a group of rats with parachlorophenylalanine (PCPA), a serotonin-depleting agent. Because fluoxetine and imipramine generally require several weeks of treatment to produce antidepressant or antiobsessional effects in humans, rats were treated with drugs or saline for 5 weeks before exposure to food deprivation and the running wheel. We chose to initiate drug treatment before exposure to the wheel and food deprivation because the FRIH syndrome often leads to death within 2 weeks, an inadequate time period for these agents to have a therapeutic effect. We used a 5 mg/kg dose of imipramine because this dose has been shown to have behavioral and neuroendocrine effects after chronic administration in rats (6,7,11). We used two different doses of fluoxetine because there has been less definition of an effective chronic treatment dose for fluoxetine, and clinical doses of fluoxetine are 2–3 times lower than clinical doses of imipramine.

MATERIALS AND METHODS

Subjects

Female Sprague–Dawley rats (Taconic Farms, Germantown, NY) weighing 200 ± 2 g on arrival were individually housed during drug treatment in conventional polycarbonate cages with dry food (NIH 07 rat and mouse ration (23.5% protein, 4.5% fat, 4.5% fiber): Ziegler Brothers, Gardner, PA) and water ad lib. Temperature was kept at 24° with lights off from 1800 to 0600 h.

Apparatus

An activity wheel cage that consisted of a running wheel (1.1 m circumference) and an adjoining steel wire-mesh cage (Lafayette Instruments, Lafayette, IL) was used. A sliding door separated the wheel from the adjoining cage.

Procedure

Rats were treated IP daily for 5 weeks with either saline, fluoxetine (2.5 mg/kg and 5 mg/kg; Eli Lilly, Indianapolis, IN), or imipramine (5 mg/kg, Sigma, St. Louis, MO). Fluoxetine was dissolved in deionized water (1.0 ml/kg) and imipramine was dissoved in isotonic saline (1.0 ml/kg). Rats that received PCPA (Research Biochemicals Inc, Natick, MA) were first treated daily with saline for 4 weeks, then received a 300 mg/kg IP dose of PCPA 7 days prior to wheel exposure and then a 200 mg/kg dose on the fourth day prior to wheel exposure and 1 day prior to wheel exposure. This is a standard dosing regimen that has been demonstrated to cause a greater than 95% depletion of brain serotonin (5). PCPA (1.0 ml/kg) was dissolved in a 1% solution of Tween 80 and deionized water. These rats received saline injections on the days they did not receive PCPA.

Food restriction began the day prior to placement in the running wheel cage. After placement in the running wheel cages, rats with restricted food access were fed for 90 min in the middle of the light period. During the 90 min feeding period access to the wheels was closed for all rats, including the control group that had free access to food during the rest of the day. At the end of the 90 min feeding period rats were weighed and injected with drug or saline. Rats pretreated with PCPA continued to receive 200 mg/kg injections every 3 days and were treated with saline on intervening days. All rats were sacrificed on Day 10 after placement in the running wheel, 1 h after the end of the feeding period. All rats had free access to water throughout the study.

Rats were introduced to running wheel cages in groups of six with three to four control animals included in each group of six. Saline-treated control groups included 26 rats exposed to both food restriction and the wheel, 10 rats with food available ad lib and access to the wheel, 12 rats food restricted without wheel access, and 11 rats fed ad lib without wheel access. Drug-treated groups exposed to food restriction and the wheel included 13 rats treated with imipramine, 8 treated with PCPA, 10 treated with 2.5 mg/kg fluoxetine, and 9 treated with 5 mg/kg fluoxetine.

The research protocol was approved by the National Institute of Mental Health Animal Care and Use Committee.

Statistical Analysis

All results are expressed as means ± SE. Differences in weight, food intake, and wheel running were compared among the saline-treated control groups by ANOVA to clarify the effects of environmental manipulations on generation of the phenomenon. Differences in weight, food intake, and wheel running were also compared among the drug treatment groups, all of which were exposed to food restriction and the wheel, by a separate repeated measures ANOVA. Findings of significant main effects or interactions were followed by paired comparisons of single drug groups or control groups to the saline-treated food restricted group at individual time points using Bonferroni post hoc t-tests for multiple comparisons. Pearson's correlation coefficient was used to determine relationships between variables.

RESULTS

There were no significant differences among starting weights in the drug treatment groups and the control groups. The mean (±SD) body weight on the day of transfer to the running wheel cage was 256 ± 1 g.

Control Groups

Figures 1–3 illustrate the differences among the saline-treated control groups exposed to different combinations of food restriction and wheel availability. As expected, there was a significant main effect of environmental condition (food/wheel availability) on body weight ($F[3,51] = 8.65$, $p < 0.0001$) and a significant interaction between environmental condition and time ($F[30,510] = 17.4$, $p < 0.0001$). Exposure to the combination of food restriction and the wheel caused a significantly greater drop in weight compared to each of the other three control conditions. Body weight was also significantly reduced in freely fed rats exposed to the wheel compared to freely fed rats without wheel access on the fourth and fifth days after exposure to the wheel (Fig. 1).

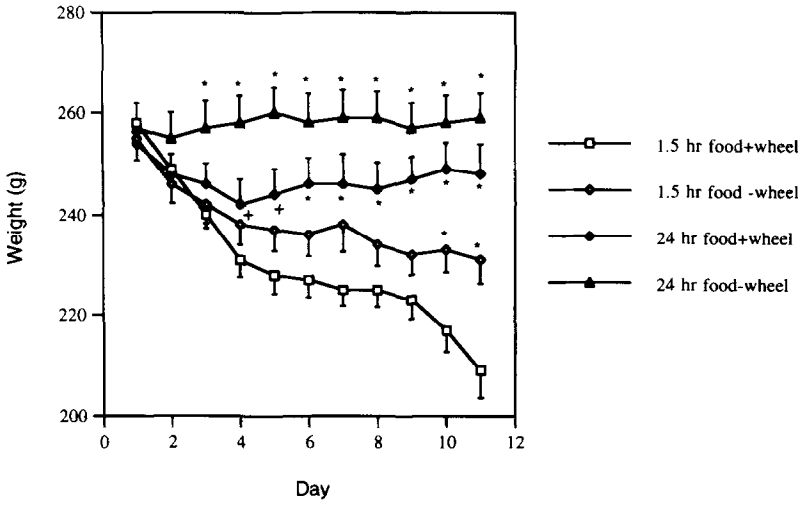

FIG. 1. Weight loss is enhanced in food-restricted rats with access to a running wheel compared to food-restricted rats without wheel access, freely fed rats with wheel access and without wheel access. (*Different from food-restricted, saline-treated rats, $p < 0.05$.) Weight loss is enhanced in freely fed rats with access to a running wheel compared to freely fed rats without access to a running wheel ($+p < 0.05$).

There was also a significant main effect of food/wheel availability on food intake ($F[3,51] = 126.4$, $p < 0.0001$) and a significant interaction between environmental condition and time ($F[27,459] = 4.98$, $p < 0.0001$). Food-restricted rats with and without access to the wheel had markedly reduced daily food intake compared to freely fed rats both with and without access to the wheel. Among freely fed rats, food intake was reduced in rats with access to the wheel, compared to rats without wheel access, but this diffence was only significant during the first 3 days of wheel exposure. Among food restricted rats, food intake was significantly reduced on Days 3, 5, 6, and 7 in rats exposed to the wheel compared to those without wheel access (Fig. 2).

There was no main effect of food availability on running activity ($F[1,240] = 0.21$, $p = 0.99$) and no significant interaction between food availability and time ($F[8,240] = 0.21$, $p = 0.98$) (Fig. 3).

Drug Treatment Groups

Figures 4–6 describe the differences between the saline-treated group exposed to food restriction and the wheel and

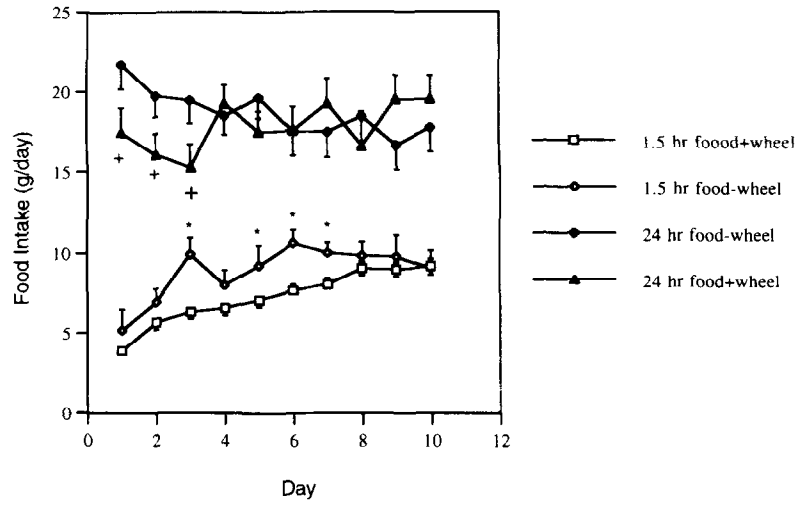

FIG. 2. Food intake is reduced in freely fed rats with access to a running wheel compared to freely fed rats without access to a running wheel ($+p < 0.05$). Food intake is reduced in food-restricted rats with access to a running wheel compared to food-restricted rats without access to a running wheel ($*p < 0.05$).

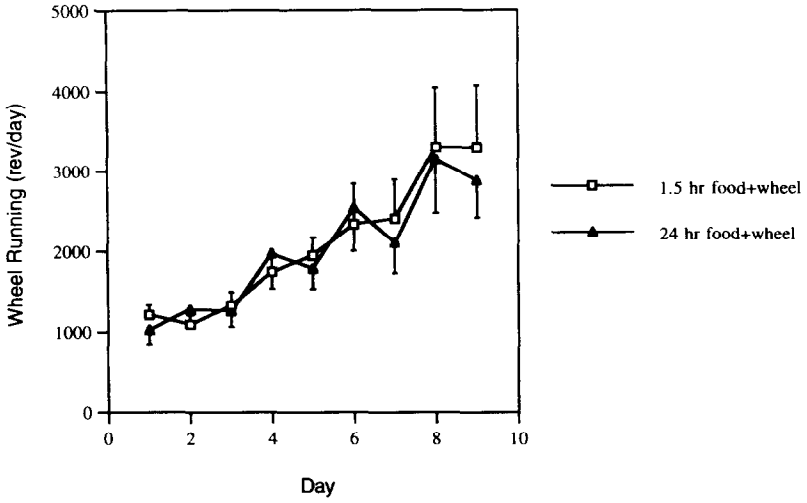

FIG. 3. Wheel running is similar in saline-treated freely fed rats and food-restricted rats.

rats pretreated with drugs, all of which were exposed to food restriction and the wheel. There was a significant main effect of drug treatment on weight (F[4,57] = 2.7, $p < 0.05$) and a significant interaction between drug treatment and time F[40,570] = 7.7, $p < 0.0001$). Post hoc testing revealed that compared to saline treatment, both doses of fluoxetine attenuated weight loss and weight loss was exacerbated in the PCPA treatment group. There was no significant difference between the saline-treated group and the group treated with imipramine (Fig. 4).

There also was a significant main effect of drug treatment on food intake (F[4,57] = 6.5, $p < 0.0002$) and a significant interaction between drug treatment and time (F[36,513] = 3.4, $p < 0.0001$). Compared to saline treatment, both doses of fluoxetine enhanced food intake and food intake was attenuated in the PCPA treatment group. There was no significant difference between the saline-treated group and the group treated with imipramine (Fig. 5).

There also was a significant main effect of drug treatment on running activity (F[4,57] = 2.6, $p < 0.04$) and a significant interaction between drug treatment and time (F[32,456] = 3.0, $p < 0.0001$). Compared to saline treatment, both doses of fluoxetine suppressed wheel running and wheel running was enhanced in the PCPA treatment group. There was no significant difference between the saline-treated group and the group treated with imipramine (Fig. 6).

Figure 7 describes the significant positive correlation between weight loss and peak wheel revolutions per day among all rats exposured to both food restriction and the wheel (N = 63, r = 0.61, $p < 0.01$). Only half of the saline-treated rats exposed to both food restriction and the wheel developed extreme degrees of running.

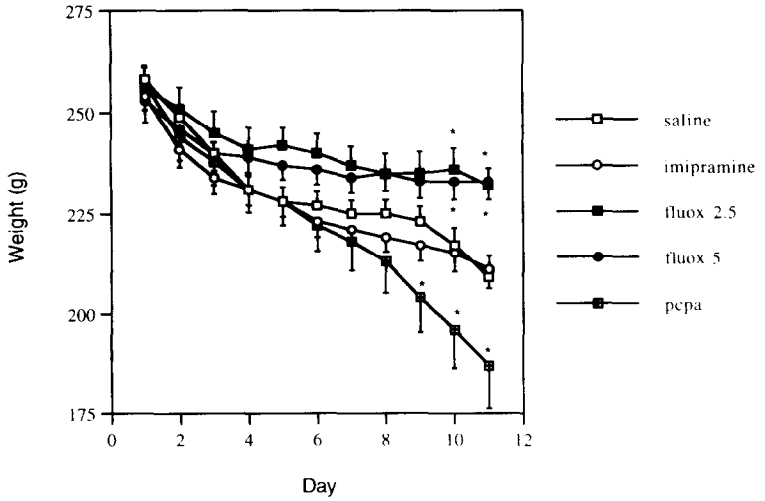

FIG. 4. In food-restricted rats with access to a running wheel, weight loss is attenuated in rats pretreated with fluoxetine 5 mg/kg and 2.5 mg/kg, enhanced in rats pretreated with PCPA (200 mg/kg Q3 days), and unchanged in rats pretreated with imipramine (5 mg/kg). (*Different from saline treated rats, $p < 0.05$.)

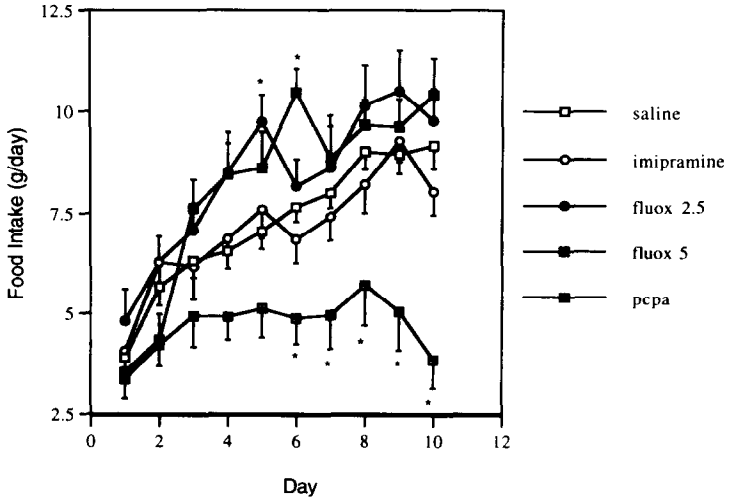

FIG. 5. In food-restricted rats with access to a running wheel, food intake is enhanced in rats pretreated with fluoxetine 5 mg/kg and 2.5 mg/kg, reduced in rats pretreated with PCPA (200 mg/kg Q3 days), and unchanged in rats pretreated with imipramine (5 mg/kg). (*Different from saline-treated rats, $p < 0.05$.)

DISCUSSION

Fluoxetine, a selective serotonin reuptake inhibitor effective for treatment of OCD, was able to attenuate development of the FRIH syndrome. In contrast, imipramine, a less serotonin-selective antidepressant ineffective for treatment of OCD did not affect development of the syndrome. These effects of pharmacological treatment resemble the preferential response to serotonin reuptake inhibiting antidepressants seen in humans with OCD, suggesting that FRIH may be a useful drug response animal model of OCD. The similar effects found with two different doses of fluoxetine are consistent with clinical studies showing similar anti-obsessive efficacy across a wide range of fluoxetine doses (77). Furthermore, exacerbation of the syndrome by serotonin depletion using PCPA suggests that the proposed enhancement of serotonergic neurotransmission by fluoxetine (9,27) may be important to its mechanism of action in attenuating the syndrome. Of course, presynaptic depletion of serotonin by PCPA administered for 10 days before and during running wheel exposure may not lead to a simple "opposite" state of central nervous system serotonin function compared to that produced by treatment with fluoxetine for 5 weeks, given the more than 13 molecularly identified serotonin receptors that serve separate and

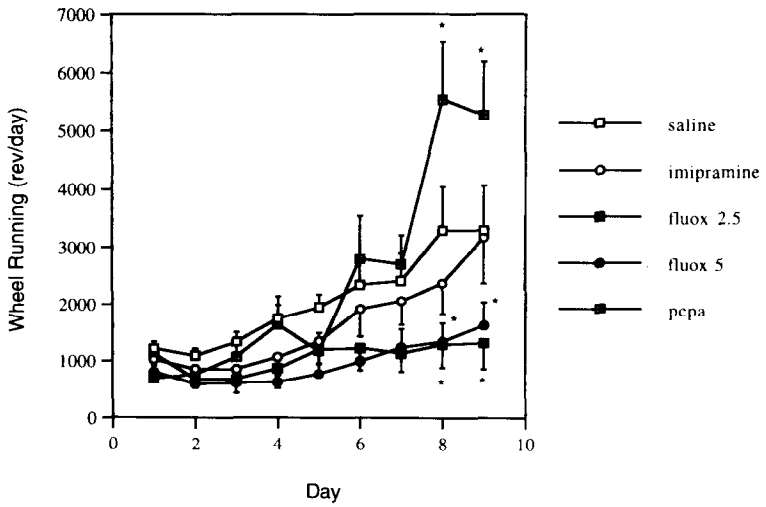

FIG. 6. In food-restricted rats with access to a running wheel, wheel running is attenuated in rats pretreated with fluoxetine 5 mg/kg and 2.5 mg/kg, enhanced in rats pretreated with PCPA (200 mg/kg Q3 days), and unchanged in rats pretreated with imipramine (5 mg/kg). (*Different from saline-treated rats, $p < 0.05$.)

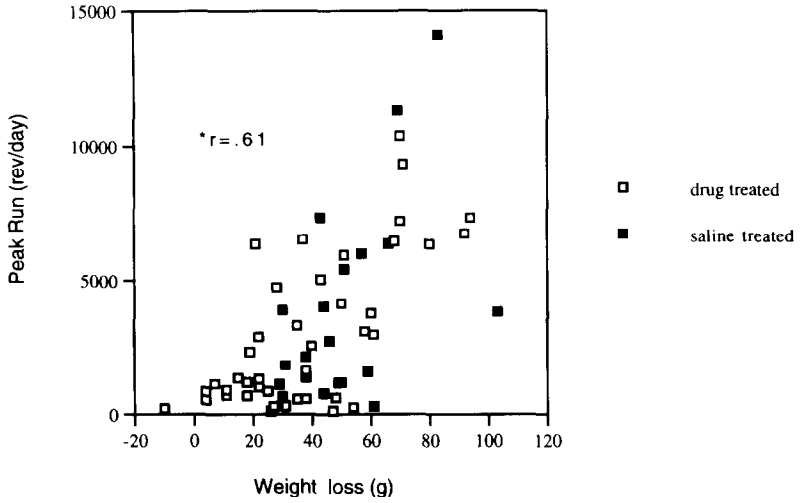

FIG. 7. Relationship of weight loss to peak wheel running in all food-restricted rats with access to the wheel ($N = 63$, $r = 0.61$, $p < 0.001$). Filled squares are saline-treated rats.

sometimes opposing functions and that in addition interact with dopamine, norepinephrine, acetylcholine, and other central nervous system modulatory systems (37). Moreover, the involvement of secondary, adaptational events leading to serotonin subsystem-specific receptor and postreceptor regulation (50,80) also require consideration in the antidepressant and antiobsessional effects of fluoxetine and related agents.

Our findings are consistent with a recent report that chronic administration of tryptophan, a serotonin precursor, attenuates development of FRIH, while serotonin depletion with 5,7-dihydroxytryptamine exacerbates the syndrome (3). On the other hand, development of FRIH was not affected by treatment with fenfluramine, a serotonin-releasing agent, beginning 5 days prior to wheel exposure (59). Fenfluramine and fluoxetine have a number of different pharmacological effects and there is no evidence that fenfluramine has any efficacy as a sole treatment agent for OCD.

Unlike other reported studies using this paradigm, extreme degrees of running and weight loss occured in only half of our saline-treated controls exposed to both restricted food access and the running wheel. Most likely this is due to our termination of the study at a relatively mild degree of weight loss. Our data and other studies of the relationship between amount of running and weight loss indicate a positive correlation, with extreme elevations in running occuring when weight drops below 80% of free-feeding weight (52,55). To comply with animal care committee guidelines that animal weights not drop below 80% of free-feeding weight, rats in our study were sacrificed after 10 days exposure to the running wheels, a time point at which few rats had fallen below 80% of original body weight. It is also possible that 5 weeks of daily handling and injection prior to exposure to food deprivation and the wheel contributed to the reduced degree of running behavior and weight loss in our controls.

The degree of novelty or stress seems to be important for development of the FRIH sydrome. Data from our study and others (48,61,62,76) indicate that both the novelty of change to a restricted feeding schedule without wheel access or introduction to the wheel apparatus without food restriction causes some initial decrease in food intake, but animals adapt to these manipulations within a few days. Moreover, rats that have a longer (less stressful) 3–4 h access to food each day in association with wheel availability show a few days of anorexia and weight loss but then do not continue to lose weight, and excessive wheel running is transient, decreasing after 7–10 days to levels seen in freely fed rats (79). Also, adaptation to the restricted feeding schedule prior to presentation of the combination of both conditions reduces the severity of the syndrome (82). There is evidence that the stress of water deprivation may also set off excessive wheel running (60).

We can only speculate why rats exposed to the combination of these two novel mildly stressful conditions are unable to adapt and regulate their activity, food intake, and weight. Food restriction has been shown in a number of paradigms to induce hyperactivity in rodents (16,19,26,32). Previous work has also shown that in conditions of food deprivation, wheel running increases much more than activity in a stationary cage (73,81). Conversely, there is evidence from studies of the effects of forced exercise in rats that once excessive running is set in motion, this in turn produces depressed food consumption and depressed body weight gain (42,72,75). Suggested physiological mediators of this effect include lactic acid production (8), catecholamine release (17,66), increased core temperature (12,72), and hypothalamic pituitary adrenal axis activation (82).

Although the feeding period could be construed as an adventitious reinforcer of wheel running, in one study, rats that were prevented from running for 2 h before and 2 h after the feeding period still developed the syndrome (63). Another study that argues against running developing as a reinforced behavior showed that complete starvation led to progressive increases in running behavior over a 72 h period (26). Similarly, Falk (22,23) has argued that schedule-induced drinking in rats is not reinforced or due to "superstitous" pairing of drinking with food delivery.

It may be more accurate to view excessive running instead as a displacement behavior or an adjunctive behavior. In animals, stressors such as novelty, conflict, or frustration are

known to cause inappropriate or "displaced" expression of normal behaviors (47,49,69). Such inappropriate, stereotypic, or displacement behaviors are seen in most species and include behaviors such as grooming, rocking, hoarding, foraging, and attack behavior. Similarly, schedule-induced behavior or "adjunctive behaviors," such as excessive water drinking and attack behavior (22,53,71), can be generated when reward presentation is regularly scheduled and dissociated from the behavior of the animal. Availability of environmental stimuli seem to determine the type of displacement or adjunctive behavior that develops in laboratory situations. In the FRIH paradigm, the wheel may serve as a stimulus, so that running develops rather than grooming, foraging, or aggression. Other displacement and adjunctive behaviors have been shown to respond selectively to chronic treatment with serotonin reuptake blockers, including acral lick dermatitis in dogs (57), feather picking in birds (30), and schedule-induced polydipsia in rodents (83).

Swedo (74) and others (35,56) have proposed that OCD symptoms in humans, which are exacerbated by environmental stress, are analogous to displacement behaviors in animals. Repetitive motor behaviors in humans that seem to respond to serotonin reuptake blockers include include checking, washing, repeating movements, face picking, hair pulling, and nail-biting.

There has been some investigation of the neurotransmitter changes that accompany the FRIH syndrome. For example, it has been suggested that FRIH may mitigate the reductions in serotonergic and noradrenergic activity brought on by food restriction (13,14,55). Consistent with this hypothesis are reports that repetitive motor behavior such as running or grooming increased the firing of a group of dorsal raphe neurons (38), and that central levels of 5-HIAA were increased in freely fed rats forced to exercise (1,15). Measures of 5-HT and 5-HIAA brain content in rats during food restriction and FRIH are not consistent and seem to depend on diet composition, sampling location, and time from last meal (14,34,41, 67). The data are more clear regarding catecholamines. FRIH phenomenon is reliably associated with increased brain turnover of norepinephrine and dopamine (13,58,78), which contrasts with the reduced brain levels of catecholamines found after food restriction (13,54,68). It is less certain whether a change is seen in NE turnover with exercise and ad lib feeding (20). It should be noted, however, that postsynaptic receptor and second messenger adaptations may occur during chronic stress, in which case monoamine turnover measures would be relatively poor reflections of neurotransmission.

The effect of food deprivation to lower central catecholamine and possibly serotonin turnover may be buffered more by treatment with selective serotonin reuptake blockers such as fluoxetine than other antidepressants, and thus preferentially reduce vulnerability to develop the FRIH syndrome. A number of preliminary reports suggest that in contrast to tricyclic antidepressants, selective serotonin reuptake blockers may increase serotonergic neurotransmission (9,27), increase total body basal metabolic rate (25), and increase tyrosine hydroxylase mRNA in the locus ceruleus (10).

In addition, fluoxetine may differentially mitigate the stress of isolation housing. Isolation after weaning has been shown to prouce an increase in spontaneous and conditioned locomotor activity (39) and resistance to extinction in adulthood (51).

Face validity of the FRIH model for OCD is weakened by the fact that although compulsive running occurs in humans, sometimes in association with eating disorders or weight loss, this has not been defined as a variant of OCD. Also, as with any animal model, we cannot assess whether the "compulsive" behavior is a response to an "obsessive" anxiety or fear. Face validity is also weakened by the use of fluoxetine to prevent development of FRIH, rather than to reverse FRIH once it had been established. On the other hand, FRIH is stress-induced, which parallels stress-induced exacerbation of OCD symptoms in humans. Like OCD and unlike AN, FRIH is reliably produced in both male (82) and female rats (79). Also similar to OCD, the behavior in FRIH is sustained and is problematic for the functioning of the animal. In addition, there is some evidence in humans that food restriction is associated with increased incidence of obsessions and compulsions (45) and, although cause and effect is unclear at this point, there is an increased incidence of OCD and OC symptoms in patients with eating disorders (44,64). Predictive validity of FRIH as an animal model of OCD is demonstrated by the current study. Testing of other pharmacological agents known to be effective or ineffective treatments for OCD would strengthen the predictive validity of the model. Construct validity remains to be explored.

One advantage of this animal model of OCD, compared to acral-lick dermatitis in dogs and feather picking in birds, is that it can be readily produced in the laboratory. If pretreatment with other serotonin reuptake blockers known to be effective in OCD also blocks development of FRIH, this model may be useful as a screen for new anti-OCD agents. In addition, examination of central nervous system changes in these animals may suggest further investigations of possible pathogenic factors in OCD and the mechanism of action of anti-OCD medications.

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