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Fluoxetine alters feeding behavior and leptin levels in chronically-stressed rats

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ABSTRACT

Stress-induced alterations in feeding behavior are sexually dimorphic and have been related to changes in monoamine levels. Fluoxetine is commonly used as an antidepressant and has also been suggested as an adjunct to other strategies to treat obese individuals. Leptin may interact with stress hormones and with the brain serotonergic system, possibly affecting the feeding behavior of stressed rats. The aim of this study is to evaluate the interaction between chronic fluoxetine treatment and leptin levels in adult female Wistar rats submitted to chronic variable stress. After 30 days of stress, control and stressed groups were subdivided into two groups that received daily injections of vehicle or fluoxetine (8 mg/kg, i.p.). Body weight was evaluated before and after fluoxetine treatment. The animals gained weight with time, signifying that there is a difference in weight gain over time when fluoxetine-treated animals are, or not, subjected to the stress model. Both fluoxetine and stress induced a decrease in sweet food consumption. On the 60th day of fluoxetine treatment, leptin levels were decreased in fluoxetine-treated animals and there was no effect of stress. We conclude that chronic fluoxetine treatment induced a decreased intake of sweet food, as well as a reduction in leptin levels, and that this result could represent a compensatory response to reduced food intake rather than a direct anorectic mechanism. No interaction with chronic stress was observed.

1. Introduction

Exposure to stress may cause either an increase or a decrease in food intake, depending on the nature of the stress (Ely et al., 1997; Gamaro et al., 2003; Silveira et al., 2000; Varma et al., 1999). For example, exposure to repeated restraint leads to increased consumption of sweet food (Ely et al., 1997; Torres et al., 2002). On the other hand, models of chronic variable or mild stress usually induce a decreased appetite for sweet food or palatable solutions (Baker et al., 2006; Bekris et al., 2005; D'Aquila et al., 1997; Gamaro et al., 2003; Grønli et al., 2005; Lu et al., 2006; Willner, 1991).

Chronic mild stress has been proposed as a model of depression in animal studies (Katz et al., 1981; Lu et al., 2006; Pucilowski et al., 1993; Willner, 1990, 1991, 2005). In this paradigm, rats are exposed to different weak stressors for several days. The response to rewarding stimuli is usually diminished, as demonstrated by tests showing reduced sucrose consumption, which is interpreted as anhedonia (Pucilowski et al., 1993; Willner, 1991). Stress has been shown to alter normal serotonergic and dopaminergic neurotransmission (Meijer and de Kloet, 1998; Piazza and Le Moal, 1996) and, in animal models of depression, the efficacy of drugs that act on the serotonergic system in reversing some of the stress-induced effects suggests that serotonin may be involved in their development or expression (Grippo et al., 2006; Li et al., 2007; Muscat et al., 1992; Willner et al., 1987).

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is commonly used as an antidepressant in psychiatry. Furthermore, it may be suggested as an adjunct to other strategies to treat obese individuals, because it causes weight loss both in laboratory animals and humans (Konkle and Bielajew, 1999; Mancini and Halpern, 2006; Mitchell et al., 2003; Ward et al., 1999). However, the mechanisms underlying the effect of fluoxetine in feeding behavior are affected by factors such as stress and hunger (Hsiao et al., 2006; Placidi et al., 2004).

Leptin is a hormone secreted mainly by the adipocytes and has a role in metabolic adaptation, acting in the regulation of body weight. It is believed to establish a feedback loop between the energy reserves and the hypothalamic centers that control food intake (Inui, 1999; Loftus, 1999; Prolo et al., 1998). Some data suggest that leptin also interacts with other endocrine systems to provide critical information about the size of the fat stores (Loftus, 1999; Sandoval and Davis, 2003). This peptide participates in the expression of hormones involved in the stress response, such as corticotrophin releasing hormone (CRH) in the hypothalamus, and interacts in the adrenals with adrenocorticotropic hormone (ACTH) (Ceballos et al., 2006; Oates et al., 2000; Spinedi and Gaillard, 1998). Leptin could limit the activity of the hypothalamo–pituitary–adrenal (HPA) axis by inhibiting CRH release and, during acute and chronic stress, leptin secretion may decrease and, thus, facilitate the responsiveness of the HPA axis (Ceballos et al., 2006; Heiman et al., 1997). Conversely, leptin is probably influenced by activation of the HPA axis, when animals are exposed to stress situations (Ceballos et al., 2006).

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An interaction between leptin and the serotonergic system has been suggested by several studies (Collin et al., 2000; Finn et al., 2001; Hastings et al., 2002). Serotonergic neurons present leptin receptor immunoreactivity and mRNA, indicating the possibility of a direct action of leptin on this neurotransmitter system (Finn et al., 2001; Hay-Schimidt et al., 2001; Telles et al., 2003), and leptin levels have been found to be altered in patients with depression (Esel et al., 2005; Moosa et al., 2003). Acute treatment with fluoxetine causes a decrease in leptin levels (Dryden et al., 1999); however, the effect of chronic fluoxetine administration on leptin levels and its possible interaction with chronic stress has not been studied. Since fluoxetine treatment is usually chronic, this is a subject that deserves further investigation.

Although affective and eating disorders are more prevalent in women than men (Kornstein, 2002; Oliver and Wardle, 1998), most of the studies in animal models have been performed in males (Harris et al., 2002; Kelly et al., 1999). Additionally, females are known to respond differently to stress (Jezova et al., 1996; Leuner et al., 2004; Rivier, 1999). Therefore, it is important to investigate parameters related to depressive models using female rats. Since leptin and the stress response may interact, in this study, we investigated leptin levels in rats under chronic variable stress submitted to chronic fluoxetine treatment (60 days); we also evaluated consumption of different types of food by these animals, as well as their body weights.

2. Methods

2.1. Animals

Twenty-nine adult, female Wistar rats (60 days old; 200–270 g weight) were used. The experimentally-naive animals were housed in groups of 4–5 in home cages made of Plexiglas material (65×25×15 cm) with the floor covered with sawdust. They were maintained under a standard dark–light cycle (lights on between 7:00 and 19:00 h) at a room temperature of 22±2 °C. The rats had free access to food (standard rat chow) and water, except for the stressed group during the period when the stressor applied required no food or water. After being randomized to assure all groups presented similar body weights, the animals were divided into two groups: control (15 animals) and stressed (14 animals). After 30 days of stress, sweet food consumption was evaluated, in order to confirm the ability of this stress treatment to induce altered consumption of palatable food. Afterwards, ten animals from each group were subdivided (n=5/group), receiving vehicle and fluoxetine for 60 days. Body weight was measured at different times during fluoxetine treatment. Standard lab chow consumption (from Nuvital, Brazil) was monitored by leaving a determined amount of food in the cage and checking the remainder the next day. Blocks of three measurements of consumption were used to evaluate consumption in each period of the treatment. Animal care followed the official governmental guidelines in compliance with the Federation of Brazilian Societies for Experimental Biology and was approved by the Ethical Committee of the Universidade Federal do Rio Grande do Sul, Brazil.

2.2. Stress model

The chronic variable stress (CVS) protocol was modified from other models of variable stress (Konarska et al., 1990; Murua and Molina, 1992; Papp et al., 1991; Willner et al., 1987), and followed the protocol already described (Gamaro et al., 2003; Manoli et al., 2000). The protocol involves repeated exposures to different mild stressors over a certain period of time (Gamaro et al., 2003; Katz et al., 1981, Willner et al., 1987). The animals were divided into 2 groups: Control and Stressed. Controls were handled daily. A variable-stressor paradigm was used for the animals in the stressed group. This protocol differs from other chronic stress protocols that use only one stressor in that the different stressors used diminish adaptation to stress. Animals were subjected to one stressor per day, at different times each day, in order to minimize predictability. The following stressors were used: a) 24 h of food deprivation, b) 24 h of water deprivation, c) 1 h to 3 h of restraint, as described below, d) 1.5 to 2 h of restraint at 4 °C, e) forced swimming during 10 or 15 min, as described below, f) flashing light during 120 to 210 min, g) isolation (2 to 3 days). Restraint was carried out by placing the animal in a 25×7 cm plastic tube and adjusting it with plaster tape on the outside, so that the animal was unable to move. There was a 1 cm hole at the far end for breathing. Forced swimming was carried out by placing the animal in a glass tank measuring 50×47×40 cm with 30 cm of water at 23±2 °C. Exposure to flashing light was made by placing the animal in a 50 cm-high, 40×60 cm open field made of brown plywood with a frontal glass wall. A 40 W lamp, flashing at a frequency of 60 flashes per minute, was used.

2.3. Consumption of palatable food

At 25 days of stress, animals were food deprived (receiving 80% of their normal consumption of rat chow) and submitted to 3-min trials, one per day, during five days, in order to become familiarized with the type of food used (Froot loops, Kellogg's® — pellets of wheat and corn starch and sucrose; see Table 1 for composition of this food). In each trial, the animals were placed in a lightened rectangular box (40×15×20 cm) with a glass ceiling, floor and side walls made of wood. Ten Froot loops were placed in one extremity of the box. After being habituated, the animals received rat chow ad libitum and, on the next day (30th day of stress), they were exposed to a 3-min test session, when the number of ingested pellets was counted. A protocol was established so that when the animal ate part of the Froot loops (e.g.: 1/3 or 1/4), this fraction was considered (Ely et al., 1997; Gamaro et al., 2003). During these days of evaluation of feeding behavior, food or water deprivation were not used as stressors. The 3 min test to evaluate sweet food consumption was repeated after fluoxetine treatment. A few days later, animals were submitted to two trials, one per day, using another palatable food, peanuts. The first trial was carried out to habituate the animal to the novel food. The measurement of consumption was made during the second trial.

2.4. Pharmacological treatment

After 30 days of chronic stress treatment, each group (control and stressed) was subdivided into two other groups: Fluoxetine (8.0 mg/kg) or vehicle (10% tween 80 in saline), which were administered daily i.p., between 9:00 and 10:00 a.m., for a total of 60 days, in animals subjected, or not, to chronic stress. This dose of fluoxetine was chosen according to the literature (Beaufour et al., 1999).

2.5. Control of estrous cycle and leptin measurement

The stage of the estrous cycle was determined by vaginal swabs, starting on the 53th day of fluoxetine treatment. The observed phases were: diestrus, when mucus, leukocytes and some nucleated cells were present (2–3 days on average); proestrus, when only nucleated cells were present (12 h); estrus, when only cornified cells were observed (24 h), and metaestrus, when leukocytes, cornified cells and

Table 1
Nutritional composition/100 g of the palatable food and standard rat chow used in the studies performed

Food	Energy (kcal)	Total protein (g)	Total carbohydrate (g)	Total fat (g)	Crude fibre (g)
Froot loops Kellogg's ®	390	6	85 (54% simple, 46% complex)	3	2
Rat chow Nuvital®[a]	411	22	56 (mainly starch)	11	3

[a] Commercial non-purified diet, Nuvilab-CR1 (Curitiba, Brazil). Additionally, this chow contains ashes (6%) and vitamins (2%).

some nucleated cells were present (Baker et al., 1979). Animals were sacrificed between 9:00 and 10:00 a.m, after at least 60 days of treatment; all females were in the diestrus phase at the time of decapitation, which occurred 24 h after the last stress session. Trunk blood was collected and serum separated and frozen until the day of the analysis. Measurement of serum leptin was performed with a commercial leptin ELISA kit (Crystal Chem. Inc., Chicago, IL, USA).

2.6. Statistical analysis

Data were expressed as mean ± standard error of the mean (S.E.M.). Consumption of sweet food after 30 days of stress was analyzed using Student's *t* test for independent samples. To analyze sweet food consumption or leptin levels after 60 days of fluoxetine treatment, a two-way ANOVA was used. A post-hoc Duncan multiple range test was used when indicated. Body weight and regular rat chow consumption were analyzed using repeated measures ANOVA. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software. P values ≤ 0.05 were considered statistically significant.

3. Results

After 30 days of stress, body weight was evaluated. Stressed animals presented a slightly lower body weight [Student's *t* test, $t(18)=4.005$; $P<0.01$; data not shown]. At this time of the treatment, sweet food consumption was decreased in chronically-stressed animals (mean ± SEM: 4.1 ± 0.4 for controls, and 2.3 ± 0.3 for stressed animals), confirming the effect of this type of stress in this parameter (Student's *t* test, $t(37)=3.80$; $P<0.05$). Animals were then subdivided and treated with vehicle or fluoxetine (8 mg/kg, i.p.), resulting in four groups (control + vehicle; control + fluoxetine; stressed + vehicle; stressed + fluoxetine). Body weight was evaluated in the four groups before fluoxetine treatment and after 2, 4 and 8 weeks of treatment. Body weight during this treatment is shown in Fig. 1. A repeated measures ANOVA indicates that the animals gained weight with a significant effect of time [$F(1,16)=503.08$; $P<0.01$] and also significant stress × time interaction [$F(1,16)=39.89$; $P<0.01$], and fluoxetine × time × stress interaction [$F(1,16)=4.56$; $P<0.05$], signifying that there is a difference in weight gain over time when animals subjected to the stress model are, or not, treated with fluoxetine.

Consumption of regular rat chow was reduced by fluoxetine treatment during the first days of treatment, as observed in Fig. 2 [Repeated measures ANOVA, $F(1,8)=17.35$, $P<0.01$]. After the first week of fluoxetine treatment, rat chow consumption reached a steady state, and no effects of fluoxetine or stress were observed in this parameter [e.g., for the 3rd week of treatment, Repeated measures ANOVA, stress effect: $F(1,8)=0.088$, $P>0.05$, and fluoxetine effect: $F(1,8)=0.059$, $P>0.05$]. Data from days when the stressor applied was deprivation of food and the next day were not considered.

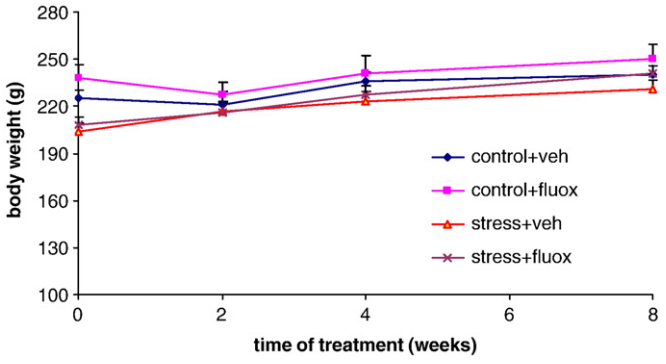

Fig. 1. Mean body weight during chronic fluoxetine treatment (8 mg/kg), measured during 60 days of treatment. Data expressed as mean ± S.E.M. $N=5$ animals/group. Repeated measures ANOVA presented a marginal effect of stress treatment [$F(1,16)=4.12$; $P=0.059$]. There was no effect of fluoxetine. There was a significant effect of time [$F(3,48)=115.48$; $P<0.01$] and also a significant stress × time interaction [$F(3,48)=17.95$; $P<0.01$], and a fluoxetine × time × stress interaction [$F(3,48)=3.59$; $P<0.05$].

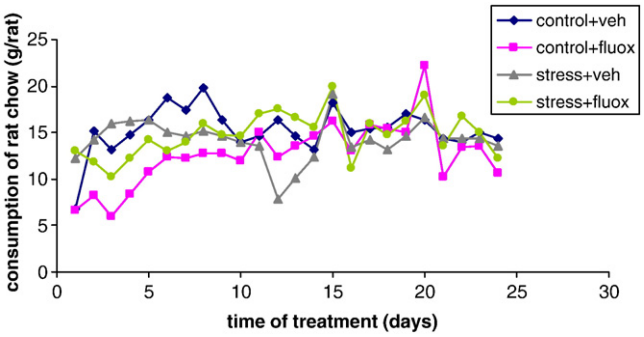

Fig. 2. Consumption of regular rat chow during fluoxetine treatment, in control and chronically-stressed animals ($N=5$ animals/group). Data expressed as mean of consumption/day/rat in grams. A repeated measures ANOVA showed a reduction of consumption by fluoxetine [$F(1,8)=17.35$, $P<0.01$] during the first days of treatment. After the first week of fluoxetine treatment, rat chow consumption reached a steady state, and no effects of fluoxetine or stress were observed on this parameter [Repeated measures ANOVA, stress effect: $F(1,8)=0.088$, $P>0.05$, and fluoxetine effect: $F(1,8)=0.059$, $P>0.05$].

Consumption of sweet food was analyzed after 60 days of fluoxetine treatment. As shown in Fig. 3A, both chronic stress and chronic fluoxetine significantly reduced consumption of this type of food [two-way ANOVA, $F(1,15)=8.35$, $P<0.02$ for stress, and $F(1,15)=5.72$, $P<0.05$ for fluoxetine], and no interaction was observed. Later, these same animals were tested for consumption of peanuts. A significant effect of stress was observed, as shown in Fig. 3B [two-way ANOVA, $F(1,15)=$

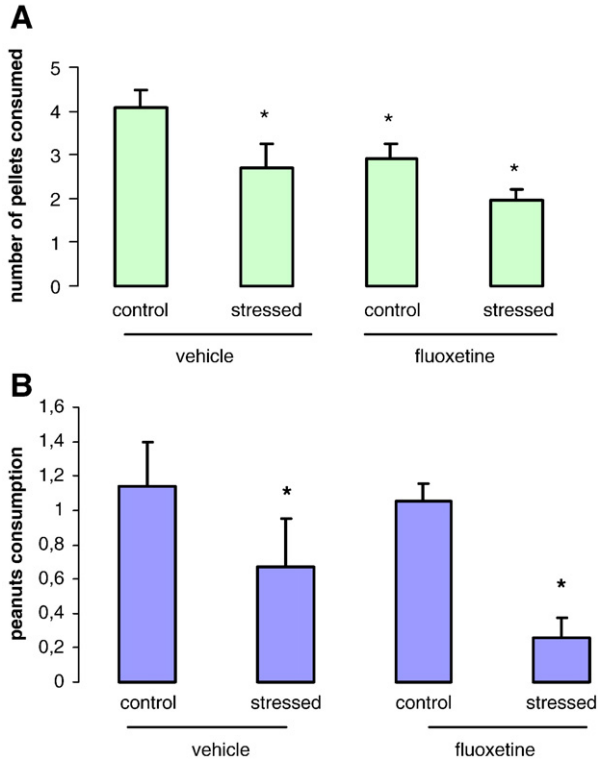

Fig. 3. Consumption of palatable food in female rats after 60 days of fluoxetine treatment (90 days of stress). Data expressed as mean ± S.E.M. Group control-vehicle ($N=4$), stress-vehicle ($N=5$), control-fluoxetine ($N=5$), stress-fluoxetine ($N=5$). (A) Consumption of sweet food. A two-way ANOVA showed a significantly reduced consumption of sweet food [$F(1,15)=8.35$, $P<0.02$ for stress, and $F(1,15)=5.72$, $P<0.05$ for fluoxetine]. (B) Consumption of peanuts (in g). A two-way ANOVA [$F(1,15)=9.69$, $P<0.01$] showed a significant effect of stress. *Significantly different from control + vehicle group (Duncan multiple range test, $P<0.05$).

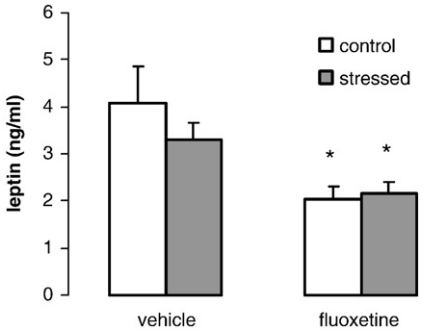

Fig. 4. Serum leptin levels in female rats subjected to chronic variate stress during 90 days, with the concomitant administration of i.p. fluoxetine (8 mg/kg) during the last 60 days. Data expressed as mean±S.E.M. $N=5$ animals/group. A two-way ANOVA revealed a significant effect of fluoxetine treatment [$F(1,16)=7.49$; $P<0.02$]. There was no effect of stress treatment [$F(1,16)=1.16$; $P>0.05$], and no interaction between stress exposure and fluoxetine treatment [$F(1, 16)=0.155$, $P>0.05$]. *Significantly different from control+vehicle group (Duncan multiple range test, $P<0.05$).

9.69, $P<0.01$]. No effect was observed for fluoxetine treatment, as well as no interaction ($P>0.05$ in both cases).

The effect of chronic fluoxetine treatment on serum leptin levels, both in controls and in animals subjected to variable stress is shown in Fig. 4. A two-way ANOVA revealed a significant effect of fluoxetine treatment [$F(1,16)=11.85$; $P<0.005$], with no effect of the stress treatment [$F(1,16)=0.534$; $P>0.05$], and no interaction between stress exposure and fluoxetine treatment was observed [$F(1, 16)=0.965$, $P>0.05$].

4. Discussion

In the present study, rats chronically-stressed during 30 days presented a reduced ingestive behavior, particularly for sweet food, in agreement with other reports (Baker et al., 2006; Bekris et al., 2005; D'Aquila et al., 1997; Gamaro et al., 2003; Grønli et al., 2005; Lu et al., 2006; Willner, 1991). This reduced sucrose consumption after chronic mild stress has been observed in several studies, although in certain cases some authors have not observed a reliable decrease in sucrose consumption (Baker et al., 2006; Matthews et al., 1995; Nielsen et al., 2000; Sampson et al., 1992), this variability has been attributed to methodological differences in the choice of stressors and to the application of the measurement procedures.

After 60 days of receiving fluoxetine, the animals ate less sweet food when exposed to it, while peanut consumption was affected by variable stress exposure (as shown by two-way ANOVA), with no effect of chronic fluoxetine treatment. This behavior is related to the anorectic effect of fluoxetine. Fluoxetine preferentially inhibits the ingestion of carbohydrate, more than fat or protein (Weiss et al., 1991). A negative feedback loop exists between the consumption of carbohydrates and the turnover of 5-HT in the hypothalamus: carbohydrate ingestion enhances the synthesis and release of hypothalamic 5-HT, which in turn serves to control the size of carbohydrate-rich meals (Wurtman and Wurtman, 1995). In the present study, the anorectic effect of fluoxetine was observed even after a long treatment, at least for sweet food ingestion, when female rats were exposed to this food during short periods. Interestingly, the stress+fluoxetine group presented no significant difference from the stress+vehicle group, when analyzed by a post-hoc test. This may be due to the fact that fluoxetine could reverse stress effects, since this model of stress has been used as a model of depression in animals, but still has effects per se. Fluoxetine-induced anorectic effects have been described in rodents, in both normal and genetically-obese rats, after chronic administration (Churruca et al., 2004; Gutiérrez et al., 2002; Hsiao et al., 2006; Van de Kar et al., 2002), consistent with the present findings.

In this study, the control+fluoxetine-treated group appeared to loose weight in the first two weeks of treatment. Later, this group gained weight normally, in agreement with some reports from human patients and animal studies using fluoxetine (Gutiérrez et al., 2002; Ward et al., 1999). The results from the present study suggest that some effects of fluoxetine on body weight and on appetite may disappear during chronic treatment, but that effects of this substance on sweet food intake remain. Although chronic fluoxetine-treated animals are able to gain weight normally, they will eat less when exposed to sweet food in the absence of food deprivation, suggesting that this long-lasting effect of fluoxetine is specific to sweet food. It is possible that, in fluoxetine-treated animals, the hedonic impact and the incentive value of sweet food may be reduced. It should be taken into consideration that gonadal hormones affect serotonergic neurotransmission (Moses et al., 2000; Raap et al., 2000; Van de Kar et al., 2002). Therefore, neurochemical and molecular mechanisms of action of SSRIs could be differently affected in females and males.

The interaction between time and stress on body weight indicates that stressed females gain weight differently when compared to non-stressed females, and this is consistent with other studies (Bowman et al., 2002; Ceballos et al., 2006; Harro et al., 2001; Konarska et al., 1990). In addition, fluoxetine-treated animals gained weight differently, depending on whether or not they were stressed, although at the end of the treatment fluoxetine-treated animals presented similar body weights to those of saline-treated animals. Interestingly, in the stressed group, body weight was restored to control levels by fluoxetine treatment, but remained below control levels in animals treated with saline.

The present results showed no significant effect of chronic variable stress on leptin levels after 90 days of treatment. It has also been shown that chronic fluoxetine administration decreases serum leptin levels, both in control rats and in rats subjected to chronic variable stress. This observation agrees with those of other authors (Dryden et al., 1999), who observed that acute or sub-acute (7 days) administration of fluoxetine reduced leptin levels. Thus, these results suggest that chronic fluoxetine treatment is able to induce a pronounced suppressive effect upon the release of leptin to the serum, and that this effect is not affected by exposure to chronic stress. Taking into account that a reduction in leptin levels stimulates appetite, these results could represent a compensatory response to reduced food intake, rather than a direct anorectic mechanism. Future studies concerning effects of chronic fluoxetine in comparison with other drugs affecting the serotoninergic system that present different effects on feeding behavior, and their effects on leptin release, would help to clarify this point. Although some studies have been performed concerning this question (Esel et al., 2005; Hinze-Selch et al., 2000), results are still inconclusive.

Stress hormones may modulate leptin levels. During the stress response, there may be opposing signals to leptin secretion; for example, the HPA axis stimulates while sympathetic activation inhibits leptin release (Sandoval and Davis 2003). Conversely, leptin stimulates sympathetic outflow (Tataranni, 1998) and inhibits the HPA axis response to stress (Heiman et al., 1997). During acute and chronic stress, a decreased leptin secretion may thus facilitate the responsiveness of the HPA axis (Ceballos et al., 2006; Gomez et al., 2002; Heiman et al., 1997; Harris et al; 2002). In the present study, however, chronically-stressed animals presented similar leptin levels to the control group. These results agree with those described by Kim et al. (2006). The impact of stress on leptin levels probably depends on the type, intensity, and duration of stress and more prolonged and/or higher intensity stress may cause a reduction in leptin levels (Sandoval and Davis, 2003).

An interaction between leptin and the serotonergic system has been suggested by studies showing that i.p. leptin administration increases serotonin metabolism in the rat hypothalamus (Hastings et al., 2002). Leptin appears to have a direct role in the cells of the dorsal raphe nucleus (Collin et al., 2000; Finn et al., 2001). Therefore, apart from directly affecting hypothalamic neurons and, thereby, regulating body weight, leptin may also affect behavior mediated via the brain serotonergic system. Thus, leptin may affect body weight indirectly via projections from the serotonergic raphe neurons to several

hypothalamic regions containing multiple serotonergic receptors. The results from all these studies suggest that the regulation between leptin levels and central serotonin is a two-way regulation. On the other hand, the mechanism by which chronic treatment with fluoxetine (which increases extracellular serotonin by preventing its reuptake) is able to decrease leptin levels is not known, although it has been suggested that the effect of serotonin on food intake, besides being mediated through NPY neurons, could also involve an inhibitory action on leptin secretion in the white adipose tissue (Dryden et al., 1999).

These reduced levels of leptin could be a reflection of a reduced food ingestion in fluoxetine-treated animals, since leptin provides information about the size of the fat stores (Loftus, 1999; Sandoval and Davis, 2003), establishing a communication between the energy reserves and the hypothalamic centers that control food intake (Inui, 1999; Loftus, 1999; Prolo et al., 1998). Additionally, administration of D-fenfluramine, which also increases extracellular 5HT, has been shown to increase lipid oxidation in obese rats (Boschmann et al., 1996). As a result of these events (decreased appetite and increased lipid oxidation), leptin levels must be decreased. In this study, however, all animals gained weight over time during fluoxetine treatment, although the weight gain differed among the groups and, at the end of the treatment, no weight differences were observed between groups treated or not with fluoxetine. Therefore, decreased fat stores are probably not the direct explanation for reduced leptin levels under these circumstances. Additionally, these reduced levels of leptin are not involved in the decreased appetite for sweet food observed in the present study.

In conclusion, chronic fluoxetine induced a reduction in leptin levels, even after 60 days of treatment, besides inducing a strong reduction in the consumption of a type of food rich in simple carbohydrates. Both effects were independent of exposure to chronic stress. These results support the utility of an animal model to elucidate the effects of fluoxetine on food consumption, in order to improve the treatment of eating disorders.

Acknowledgments

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