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The antipsychotic drug sulpiride does not affect bodyweight in male rats. Is insulin resistance involved?

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Abstract

Previous studies have shown that prolonged administration of antipsychotic drugs induces obesity in female but not in male rats. To explore the mechanisms involved in this sex-dependent effect, we administered the dopamine antagonist sulpiride (20 mg/kg i.p.) or vehicle (0.1 N HCl) to adult male rats during 21 days and daily assessed bodyweight and food intake. Then, we evaluated the glucose tolerance and the serum levels of insulin, leptin, total testosterone, dehydroepiandrosterone-sulfate (DHEA-S), thyroid hormones and blood lipids. In another experiment, food intake and water intake were assessed after acute injections of sulpiride or vehicle into the perifornical lateral hypothalamus. Lastly, the dopamine metabolites dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA) in the lateral hypothalamus were assessed by in vivo microdialysis after acute systemic injections of sulpiride and vehicle. Chronic sulpiride administration did not affect bodyweight gain and food intake. However, prolactin levels and the area under the glucose and insulin curves were significantly elevated. Acute sulpiride significantly increased food intake, water intake, DOPAC and HVA levels. The acute effects of sulpiride show that this drug is active at the perifornical lateral hypothalamus, which is a brain area where blockade of dopamine receptors stimulates feeding. However, after prolonged administration, sulpiride did not affect body weight. This lack of effect may be related to the impairment of insulin sensitivity, which may prevent body weight gain, and counteract other effects of sulpiride that promote adiposity such as hyperprolactinemia. These findings noticeably contrast with those observed in sulpiride-treated female rats that appear to display enhanced insulin sensitivity. The changes in insulin sensitivity do not appear related to a decrease in androgenic activity, because testosterone and DHEA-S levels were not affected by sulpiride. However, these results should be considered as preliminary because other relevant endocrine variables such as free testosterone, steroid binding globulin and pituitary gonadotrophin levels were not evaluated. Since the same sex-dependent effect on body weight and food intake in rats has been observed during administration of risperidone, which has a different pharmacological profile than sulpiride, future studies must evaluate other neurotransmitters involved in food intake regulation such as serotonin, noradrenaline and histamine.

Keywords: Antipsychotic drugs; Dopamine; Feeding; Glucose; Insulin; Lateral hypothalamus; Leptin; Obesity

1. Introduction

The propensity of antipsychotic drugs to induce excessive body weight gain, obesity and glucose intolerance was reported in the late 1950s (Baptista, 1999). However, the interest in this subject considerably increased after 1990 due to the strong tendency of some new antipsychotics to induce those side effects (Allison et al., 1999; Taylor and McAskill, 2000; Wetterling, 2001).

Experimental studies have faced a difficulty in reliably inducing body weight gain in rodents. In the early studies of Baptista et al. (1987, 1988, 1990, 1993a), Parada et al. (1988, 1989) and Shimizu et al. (1990), significant weight gain during treatment with typical antipsychotics was observed in adult females and prepubertal males, but not in adult male rats, which often tended to display a non-significant body weight loss. Preliminary studies conducted with the new atypical agents such as olanzapine and risperidone have also reported weigh gain only in female rats (Baptista et al., in preparation; Janssen-Ortho Inc., 2000; Lilly Research Laboratories, 2001).

The mechanisms of weight gain have been studied in female rats chronically treated with sulpiride, a dopamine

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D_2–D_3 receptor antagonist that is devoid of significant motor effects (Wagstaff et al., 1994). The following effects of sulpiride have been proposed to induce weight gain in female rats: (1) the blockade of dopamine D_2 receptors in the perifornical lateral hypothalamus (Baptista et al., 1987, 1990, 1993b, 1997a,b); (2) a decrease in serum estradiol levels due to hyperprolactinemia or to a direct drug effect in the hypothalamus (Baptista et al., 1997a; Parada et al., 1989); and (3) sulpiride-induced changes in insulin sensitivity (Baptista et al., 1998a,b, 1999; Lacruz et al., 2000).

As regards the effects in the lateral hypothalamus in females, it has been shown that local injections of sulpiride induce strong feeding and drinking in satiated animals (Baptista et al., 1993b, 1997b; Parada et al., 1988). In addition, systemic sulpiride administration increases the levels of homovanilic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) (the main metabolites of dopamine) in that hypothalamic area (Baptista et al., 1990). These results may be considered as indirect evidences that the dopamine system at the perifornical hypothalamus may be involved in the effects of antipsychotic drugs on body weight and feeding.

In relation to the mechanism involving prolactin and gonadal steroids, it has been demonstrated that excessive weight gain is often observed during hyperprolactinemic states in humans (Greenman et al., 1998) and rats (Moore et al., 1986; Gerardo-Gettens et al., 1989; Sauve and Woodside, 2000). Parada et al. (1989) showed that sulpiride-induced obesity in female rats was prevented by simultaneous administration of estradiol. Baptista et al. (1997a) also showed that tamoxifen (an agonist of estradiol as regards feeding behavior) and bromocriptine (which decreased prolactin levels) also counteracted antipsychotic drug-induced body weight gain (Baptista et al., 1987, 1997a,b).

Regarding insulin regulation, female rats rendered obese after sulpiride administration displayed normal leptin levels and normal or low glucose and insulin levels (Baptista et al., 1998a,b, 1999; Lacruz et al., 2000). This metabolic pattern suggests enhanced insulin sensitivity, which may promote weight gain (Ravusin and Bouchard, 2000).

The reasons why male rats do not gain (or tend to lose) body weight during antipsychotic administration have not been explored in detail. Parada et al. (1989) hypothesized that hyperprolactinemia-induced decrease in testosterone levels may explain those findings, as it occurs with castrated males. Okonmah et al. (1986) reported that haloperidol at a dose of 10 mg/kg significantly decreased testosterone levels in adult Sprague–Dawley male rats. Unfortunately, these authors did not report body weight changes.

This study aimed to explore whether some postulated effects of sulpiride that induce weight gain in female rats are also observed in males. Specifically, we evaluated (1) the acute effect on food intake of sulpiride injections in the perifornical lateral hypothalamus and (2) the dopamine turnover in this brain area after acute systemic sulpiride administration. In addition, we assessed the effects of chronic sulpiride treatment on bodyweight, food intake, water intake and the following hormones that are involved in weight regulation: prolactin, testosterone, dehidroepiandrosterone-sulfate (DHEA-S), tetraiodothyroxine (T_4), thyrotropic hormone (TSH) and leptin, and blood lipids.

2. Methods

Adult male rats of the Wistar strain weighing 250–300 g were housed two per cage (Experiment 1) or individually (Experiments 2 and 3). The cycle light/dark was 12:12 h with lights on at 7:00. Animals were treated according to the NIH Guide for Care and Use of Laboratory Animals.

Experiment 1: Effects of chronic sulpiride administration on body weight, food intake, water intake, serum hormone and lipids

2.1. Subjects

Eighty rats were divided into two groups of 40 subjects each, which received either racemic sulpiride (Sigma, 20 mg/kg i.p. during 21 days) or vehicle (0.1 N HCl adjusted to pH 7, 1 cm^3/kg i.p.). Injections were done at 9:00. A high fat diet (66.6% powered chow pellets, 33.3% corn oil placed in spillage-proof feeders) and water were freely available.

2.2. Procedure

Bodyweight and food intake were daily recorded to the nearest 0.1 g. After 21 days of treatment, it was conducted a glucose tolerance test. For that purpose, animals were fasted for 8 h, received an i.p. glucose injection (2 g/kg) and were decapitated by groups of 10 subjects in every treatment group at the following times (minutes): 0 (pre-injection), 30, 60 and 90. Blood was collected from the trunk vessels in ethylenediaminetetraacetic acid (EDTA)-coated tubes. Plasma was stored at −40 °C until analysis. Glucose (mg/dl), insulin (mIU/ml) and leptin (ng/ml) were measured in all blood samples. Prolactin (ng/ml), testosterone (ng/dl), T_4 (ng/dl), DHEA-S (μg/dl), TSH (μIU/ml) and lipids (mg/dl) were only assessed in the pre-injection samples (basal conditions). Hormones were assessed by radioimmunoassay with commercial kits (DPC, Los Angeles, CA) and Lipco (St. Charles, MO) for leptin. Glucose and lipids were measured by an enzymatic method from Boehringer (Mannheim, Germany). The inter- and intra-assay variability was below 10% for all hormone determinations.

2.3. Statistical analysis

The figure for bodyweight gain was obtained by subtracting daily values from the initial bodyweight. As previous experiments in females have shown that changes in food intake are mainly detected during the second week of treatment, the 21-day treatment period was divided into three periods of 1 week each.

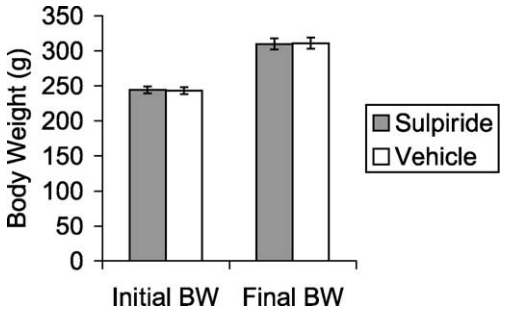

Fig. 1. Bodyweight gain during chronic sulpiride administration (20 mg/kg i.p.). Bodyweight gain (grams, mean ± S.E.M.) was similar after 21 days of sulpiride (79.6 ± 3.4) or vehicle administration (68.8 ± 3.2): $t(78) = 1.6$, $P = 0.1$; $n = 40$ in each treatment group.

Bodyweight gain, food intake for specific weeks, serum variables and areas under the insulin and glucose curves were compared *between* the groups by a two-tailed *t*-test for unrelated samples. Differences were considered significant when $P \leq 0.05$.

Experiment 2: Effects of local injections of sulpiride in the perifornical hypothalamus on food intake and water intake.

2.4. Subjects

Nine adult males weighing 300–350 g were individually housed with food (Purina Pellets) and water available ad libitum.

2.5. Surgery

Under ketamine anesthesia (100 mg/kg i.p.), bilateral 26-gauge stainless guide cannulae aimed 2 mm above the perifornical lateral hypothalamus were implanted. The stereotaxic coordinates were: 6.5 mm anterior to the interaural line, 1.6 mm lateral to the midsagittal sinus and 5.7 mm ventral to the cortical surface. The animals recovered for at least 1 week before starting the experiment. The injectors were 33-gauge stainless steel tubes connected by polyethylene tubing (PE 20) to a 10-ml syringe mounted on a syringe pump. They protruded 2 mm off the tip of the guide shafts. The injection rate was 0.5 μl in 30 s.

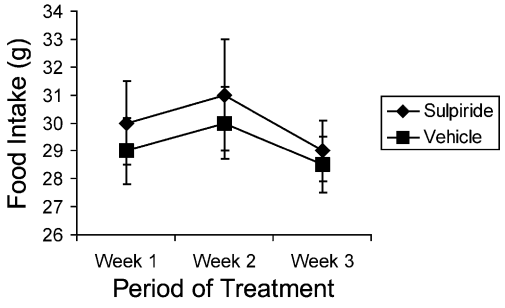

Fig. 2. Food intake during chronic sulpiride administration. Food intake (grams) was not significantly affected by sulpiride. Data represent daily average ± S.E.M.; $P > 0.1$ for comparisons between sulpiride and vehicle groups within similar weeks; $n = 40$ in each treatment group.

Table 1
Serum hormone and blood lipids in male rats treated with sulpiride or vehicle during 21 days

	Sulpiride	Vehicle	$t(18)$	P
Prolactin	46.2 ± 10.5	11.2 ± 5.5	2.0	0.0086
Testosterone	55.5 ± 8.9	39.7 ± 9.8	1.1	0.25
DHEA-S	4.88 ± 0.39	5.34 ± 0.68	0.59	0.56
T_4	0.80 ± 0.07	0.92 ± 0.11	0.84	0.41
TSH	0.27 ± 0.07	0.19 ± 0.07	0.45	0.76
TC	71.7 ± 6	77.4 ± 3.2	0.8	0.4
LDLC	17.8 ± 4.2	21.8 ± 2.5	0.8	0.42
HDLC	38.6 ± 2.5	41.2 ± 2.5	0.7	0.45
TG	76.3 ± 5.5	71.9 ± 5.9	0.5	0.6

Values represent mean ± S.E.M. DHEA-S = dehydroepiandrosterone sulfate; T_4 = tetraiodothyroxine; TSH = thyrotropic hormone; TC = total cholesterol; LDLC = low-density cholesterol; HDL = high-density cholesterol; TG = triglycerides; t = statistic of the Student's test with degree of freedom in brackets.

2.6. Procedure

In this experiment, we evaluated food intake and water intake after sulpiride or vehicle injections. For this purpose, each animal received two injections (sulpiride and vehicle) in a counterbalanced order and 3 days apart. Rats had free access to food and water before and during the test. Injections were conducted at 9:00 am, and food intake and water intake were assessed after 1, 4 and 24 h of treatments. Racemic sulpiride (Sigma) was dissolved in 0.1 N HCl. The amount of drug injected into the brain was 15 μg/0.5 μl/30 s bilaterally. The same volume of vehicle was used as a control. Placement of cannulae was verified by histological examination according to the atlas of Paxinos and Watson (1986).

2.7. Statistical analysis

Food intake and water intake after sulpiride and vehicle administration were compared by a two-tailed *t*-test for

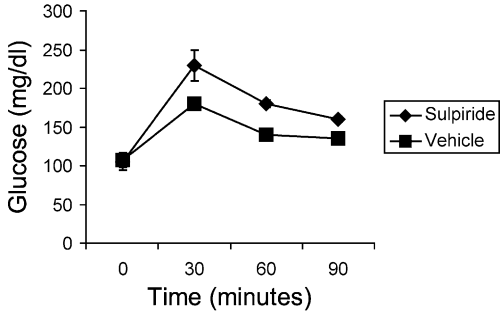

Fig. 3. Serum glucose levels after chronic sulpiride administration. The area under the curve (mg/dl, mean ± S.E.M.) was significantly higher after sulpiride (318.1 ± 17.4) than after vehicle administration (274.6 ± 5.1): $t(16) = 2.4$, $P = 0.028$. No significant differences were observed at specific points of the curve: $P > 0.1$ for all comparisons; $n = 10$ in each treatment group.

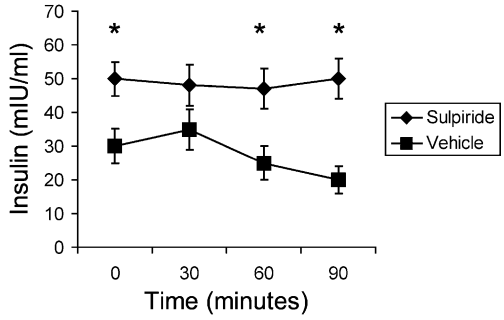

Fig. 4. Serum insulin levels after chronic sulpiride administration. The area under the curve (mIU/ml, mean ± S.E.M.) was significantly higher after sulpiride (83.4 ± 5.0) than after vehicle administration (52.8 ± 6.4): $t(16) = 3.6$, $P = 0.0021$. (*) = $P < 0.01$; $n = 10$ in each treatment group.

unrelated samples. Results were considered significant when $P \leq 0.05$.

Experiment 3: Effects of acute systemic sulpiride on dopamine metabolites in the perifornical lateral hypothalamus.

2.8. Subjects

Five adult males weighing 300–350 g were individually housed with food (Purina Pellets) and water available ad libitum.

2.9. Surgery

Under general anesthesia with i.p. ketamine hydrochloride (100 mg/kg), rats were implanted with 10-mm long, 21-gauge guide cannulas aimed at the right perifornical lateral hypothalamus. Stereotaxic coordinates for unilateral guide shafts were similar to those in Experiment 2. The animals recovered for at least 1 week following surgery before the experiments were conducted.

2.10. Probe design

Microdialysis probes were made by attaching 200 μm outside diameter, 10 μm wall thickness, reconstituted cellulose hollow fiber to the tip of a 26-gauge stainless steel tube.

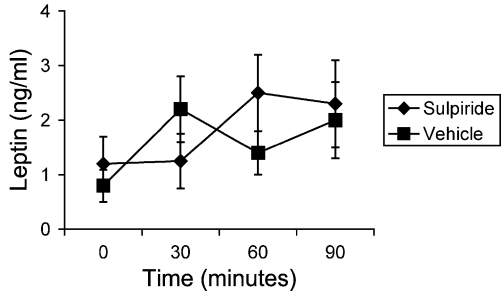

Fig. 5. Serum leptin levels after chronic sulpiride administration. Leptin levels were similar in both treatment groups, in basal conditions and after the glucose overload; $P > 0.1$ for all comparisons.

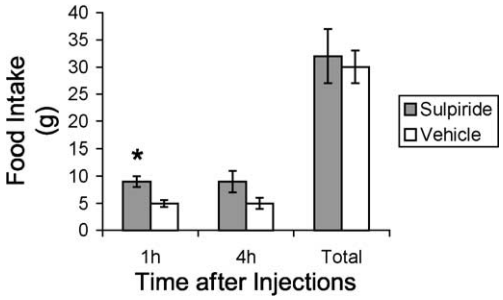

Fig. 6. Food intake after acute sulpiride administration in the perifornical hypothalamus. Food intake (grams, mean ± S.E.M.) was significantly higher after 1 h of sulpiride administration: $t(8) = 2.8$, $P = 0.049$; $n = 9$.

The cellulose fiber was sealed with epoxy at its distal end. Then, a 20-cm long, 150 μm outside diameter polimide covered fused silica capillary was inserted into the stainless tube until reaching the epoxy seal of the cellulose fiber. The effective length of the cellulose fiber was 2 mm. The probes were perfused at a rate of 1 μl/min through a swivel joint connected to a gas-tight syringe loaded with artificial cerebral spinal fluid (146 mM NaCl, 3.7 mM KCl and 1.2 mM $CaCl_2$). Samples were taken every 20 min, with a volume of 20 μl.

2.11. Neurochemical detection

Samples were analyzed by high-pressure liquid chromatography (HPLC) and electrochemical detection. The HPLC system was a double piston model 510 Waters pump with a standard head, with a model 7125 Rheodyne valve equipped with a 20-μl loop. Separation was done in 10-cm long, 3.2-mm bore, 3-μm particles, ODS Brownlee column. The mobile phase was a 153 mM acetate buffer at pH 3.1 with 0.1 mM EDTA, 1 mM octanesulfonic acid and 4% acetonitrile on a volume to volume basis.

The chemicals were detected in a model 400 EG and G electrochemical detector equipped with a glassy carbon electrode, a stainless steel auxiliary electrode and an Ag–AgCl reference electrode. The chemicals were oxidized at

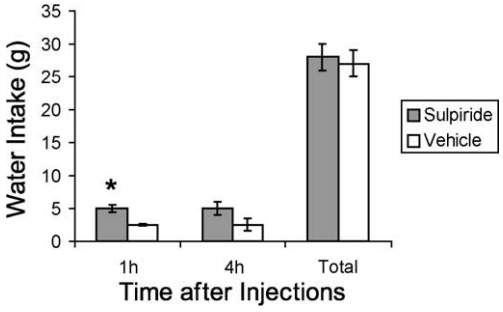

Fig. 7. Water intake after acute sulpiride administration in the perifornical lateral hypothalamus. Water intake (grams, mean ± S.E.M.) was significantly higher after 1 h of sulpiride administration: $t(8) = 5.8$, $P = 0.0004$; $n = 9$.

705 mV applied between the working and the reference electrode.

2.12. Procedure

The microdialysis probes were inserted in the animals 24 h before the experiment. When three consecutive samples showed a variation of less than 10%, the rat received an injection of vehicle (1 cm^3/kg i.p.). After sample number 10 was collected, sulpiride (20 mg/kg i.p.) was administered.

2.13. Statistical analysis

The peak heights were normalized according to the average of the first three samples, which was considered as 100%. Data were analyzed by the Kruskal–Wallis non-parametric analysis of variance (ANOVA) followed by the Dunn's test as a post hoc analysis. Results were considered significant when $P \leq 0.05$.

3. Results

3.1. Experiment 1

No significant differences were observed in bodyweight gain and food consumption between the treatment groups (Figs. 1 and 2). Water intake was not affected either (data not shown).

Serum prolactin levels and the areas under the glucose and insulin curves were significantly higher in the sulpiride group (Table 1; Figs. 3 and 4). No significant differences were observed in the serum levels of leptin (Fig. 5), testosterone, DHEA-S, T_4, TSH and lipids (Table 1).

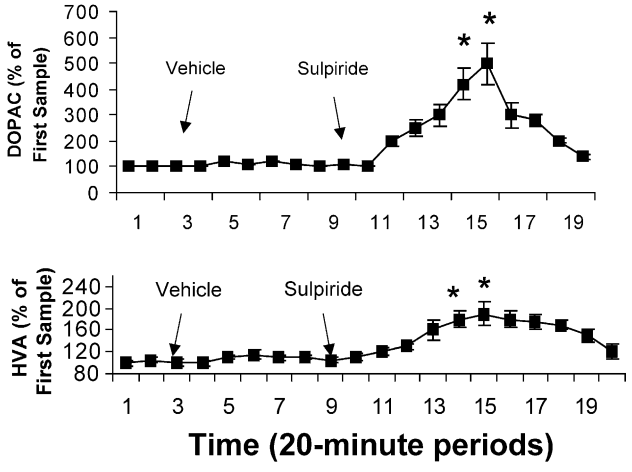

Fig. 8. DOPAC and HVA levels at the perifornical lateral hypothalamus after acute systemic sulpiride administration. DOPAC and HVA significantly increased after sulpiride administration (20 mg/kg i.p.). For DOPAC: $H = 50.7$, $P = 0.0001$; for HVA: $H = 73.5$, $P = 0.0001$. (*) = $P < 0.05$ compared to basal levels; $n = 5$.

3.2. Experiment 2

Food intake and water intake were significantly higher after 1 h of sulpiride injections in the hypothalamus. However, the 24-h consumption was similar in both treatment groups (Figs. 6 and 7).

3.3. Experiment 3

Dopamine levels were undetectable. However, the metabolites DOPAC and HVA significantly increased after sulpiride but not after vehicle administration (Fig. 8).

The cannulae tracks for Experiments 2 and 3 were located in the lateral hypothalamus in the planes 27–29 of Paxinos and Watson (1986).

4. Discussion

In this study, we administered sulpiride to adult male rats at a dose that consistently induces significant weight gain in female rats (Baptista et al., 1987, 1988, 1993b, 1997a,b, 1998a,b, 1999). We replicated here previous studies reporting absence of weight gain and hyperphagia in male rats chronically treated with antipsychotic drugs (Baptista et al., 1987, 1988; Parada et al., 1989; Shimizu et al., 1990). Notwithstanding, acute sulpiride administration in the perifornical lateral hypothalamus significantly increased food intake and water intake. In addition, systemic sulpiride injections acutely elevated the dopamine metabolites DOPAC and HVA. These results of acute sulpiride administration confirm that this agent is active in the lateral hypothalamus, which is a brain area where blockade of dopamine D_2 receptors is known to stimulate appetite in rats (Baptista et al., 1993b). As it was observed in female rats, the 24 h and total food intake and water intake were similar after local sulpiride or vehicle administration, which shows that appetite stimulation is short lasting. By contrast, female rats chronically treated with systemic sulpiride developed obesity and hyperphagia, which was noticeable when assessing the daily food consumption (Baptista et al., 1987, 1988, 1993b, 1997a,b, 1998a,b, 1999). Collectively, results in males show that even though sulpiride injections in the lateral hypothalamus acutely stimulate appetite, chronic treatment with systemic sulpiride is devoid of significant effects on bodyweight and food intake.

As expected from a dopamine receptor antagonist, sulpiride-treated rats displayed hyperprolactinemia. However, contrarily to our hypothesis, serum testosterone levels (and the other hormones and blood lipids) were similar in both treatment groups.

Interestingly, the area under the glucose and insulin curves was significantly higher in sulpiride-treated rats than in control animals. These results were replicated two times with the same findings (only one set of data is reported here). They contrast with those obtained in female rats during

sulpiride administration, which significantly gained bodyweight and rather displayed lower serum glucose levels and area under the insulin curve than controls (Baptista et al., 1998a,b, 1999; Lacruz et al., 2000). This has been interpreted as an increased insulin sensitivity that may be one mechanism involved in the weight gain observed in female rats. The high levels of glucose and insulin observed in male rats rather point to an increased insulin resistance (or decreased insulin sensitivity).

Insulin resistance is a complex phenomenon that impairs the cells ability to uptake glucose from the blood (Kahn and Lier, 2000). Bodyweight gain or loss may be observed during insulin resistance states, and it will depend on a fine interplay between the insulin effects on lipid, protein and carbohydrate metabolism, water and electrolyte regulation and endocrine profile (Kahn and Lier, 2000). Eckel (1992) proposed that insulin resistance is an adaptive mechanism that prevents additional weight gain. We thus speculate that sulpiride promoted insulin resistance in male rats. It may prevent weight gain by itself, and counteract other drug effects that increase appetite and adiposity such as hyperprolactinemia and the local effects in the hypothalamus.

Insulin resistance (defined as hyperglycemia and hyperinsulinemia) is often detected in people treated with typical and atypical antipsychotics (Baptista et al., 2001; Brambrilla et al., 1976; Hagg et al., 1999; Henderson et al., 2000). As many of these subjects have gained weight, it is unclear whether insulin resistance is a direct drug effect or it is related to weight gain. The few studies that have attempted to explore this phenomenon in people (Erle et al., 1977) and animals (Ammon et al., 1973; Melkerson et al., 2001) treated with antipsychotics have rather reported contradictory effects on insulin secretion. However, most of these studies were conducted in acute or in vitro conditions, where bodyweight changes were not assessed.

The present study does not provide direct information on the mechanisms by which sulpiride impaired the glucose tolerance in male rats. We have speculated that it may be related to hyperprolactinemia, which has been shown to impair insulin effects on glucose metabolism in humans (Foss et al., 1995), mice (Matsuda and Mori, 1996) and rats (Cabrera et al., 1988; Reiss et al., 1996). These latter studies have been conducted during hyperprolactinemia induced by methods others than antipsychotic administration, such as pituitary implants and exogenous prolactin administration. Therefore, it is presently unknown whether the molecular mechanisms underlying insulin resistance are the same in those dissimilar experimental conditions.

As castrated male rats showed insulin resistance, which is improved with low dose of testosterone (Holmång et al., 1990), and haloperidol-treated male rats displayed low serum testosterone levels (Okonmah et al., 1986), we expected a similar endocrine profile in sulpiride-treated males. Additional support for this hypothesis was that hyperprolactinemia induces hypogonadism in men (Loh et al., 1996). However, testosterone levels were not affected by administration of this agent. This result must be considered as preliminary, since other androgenic parameters such as free testosterone, pituitary gonadotrophins and steroid binding globulin levels were not assessed. In any case, future studies on insulin resistance in antipsychotic-treated rats should explore mechanisms other than those involving gonadal steroids. Lastly, it should be clarified how sulpiride induces opposite metabolic profiles in males (hyperglycemia and hyperinsulinemia) and in female rats (hypoinsulinemia and a trend towards hypoglycemia) (Baptista et al., 1998a,b, 1999; Lacruz et al., 2000). Since sulpiride induces hyperprolactinemia in both sexes, and prolactin modulates insulin sensitivity (Cabrera et al., 1988; Foss et al., 1995; Matsuda and Mori, 1996; Reiss et al., 1996; Schernthaner et al., 1985; Serri et al., 1986), future studies should explore how gonadal steroids influence prolactin effects on carbohydrate metabolism.

The serum leptin levels were similar in the sulpiride and vehicle groups, in basal conditions and after the glucose overload. This is consistent with the absence of bodyweight gain and hyperphagia during sulpiride administration. However, given the close association between leptin and insulin (Harris, 2000), the high insulin levels induced by sulpiride should have increased leptin levels. Interestingly enough, we have previously shown that female rats receiving sulpiride displayed less than expected serum leptin elevation (along with low or normal insulin levels) in spite of increased bodyweight gain (Lacruz et al., 2000). Contrarily, leptin is significantly increased along with bodyweight in AP-treated patients (Baptista et al., 2001; Brömel et al., 1998; Kraus et al., 1999; Pollmächer et al., 2000).

In summary, we corroborated that, contrarily to female rats, chronic sulpiride administration does not affect bodyweight, food intake and water intake in adult males. In addition, we found that after prolonged sulpiride treatment, male rats displayed a metabolic pattern suggestive of insulin resistance. It may be one mechanism that counteracts other effects of sulpiride that promote weight gain such as hyperprolactinemia and direct effects on feeding and water intake in the lateral hypothalamus.

A similar sex-dependent effect on bodyweight gain has also been observed in rats treated with risperidone (Baptista, in preparation) or lithium (Baptista et al., 1995). Interestingly, a preliminary study recently reported that significant weight gain was observed in male rats chronically treated with haloperidol, which was delivered through subcutaneous mini pumps (Pouzet and Sonne-Hansen, 2002). Future studies with atypical antipsychotics should also consider alternative ways of drug delivery. Direct assessment of insulin sensitivity and the evaluation of other neuroregulators involved in bodyweight regulation, such as neuropeptide Y, cholecistokinine and galanin, are also necessary. As sulpiride only interacts directly with dopamine D_2-D_3 receptors, other antipsychotics such as olanzapine, clozapine, risperidone and quetiapine that interact with histaminergic, noradrenergic and serotonergic receptors should be evaluated (Richelson, 1999). These studies are of clinical

relevance, because excessive bodyweight gain and glucose intolerance are important side effects of some agents in the new generation of antipsychotics (Allison et al., 1999; Taylor and McAskill, 2000; Wetterling, 2001; Hagg et al., 1999; Henderson et al., 2000).

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