Comparative effects of the antipsychotics sulpiride or risperidone in rats
I: Bodyweight, food intake, body composition, hormones and glucose tolerance

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Accepted 10 September 2002

Abstract

Obesity and related metabolic disorders are important side effects of some antipsychotic drugs (APs). The currently available animal model of AP-induced bodyweight gain (BWG) in rats is based on administration of sulpiride (SUL). However, this model has important limitations. For example, SUL is a pure dopamine antagonist, whereas most APs in current clinical use interact with multiple neurotransmitter receptors involved in food intake (FI) and metabolism regulation. Therefore, we evaluated the effects of risperidone (RIS, 0.125, 0.25 or 0.5 mg/kg during 16 days) on BWG and FI in male and female rats. Comparison between RIS (0.5 mg/kg), SUL (20 mg/kg) and vehicle (VEH) during 12 days was also conducted in females. In male rats, RIS did not significantly affect BWG, FI, glucose tolerance or leptin levels, even though prolactin and corticosterone were significantly elevated. In females, both APs significantly increased BWG and FI, but the effect was stronger with SUL. The BWG was significantly associated with an increase in body fat. Serum leptin levels were increased only in SUL-treated rats. The area under the curve for glucose (AUGC) was significantly lower in the SUL group, but it was similar for insulin in all treatment groups. The area under the curve for insulin (AUIC) and BWG positively correlated only in the RIS group. Prolactin and corticosterone were significantly increased by both APs. Serum estradiol levels were significantly increased by RIS but not by SUL, but progesterone levels were similar in both groups. The observed positive correlation between BWG and the AUIC during RIS administration suggests that this agent may represent a better model of AP administration in humans. The animal model of RIS-induced obesity in rats might be improved by testing other doses, route of administration and type of diet.

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In humans, APs appear to promote BWG and obesity by several mechanisms comprising either direct appetite stimulation (through interaction with histamine, acetylcholine, dopamine and serotonin receptors) or endocrine/metabolic effects associated with hyperprolactinemia and gonadal dysfunction [2,17,14,31]. The heterogeneous effects of APs on appetite and the endocrine system have hampered a full description of the hormonal and metabolic profile of people with AP-induced obesity. For example, sustained hyperprolactinemia is generally observed during administration of typical APs, but not with the atypical agents with the exception of RIS [49].

Experimental studies in animals may provide insight into the mechanisms by which the APs impair bodyweight (BW) and metabolism regulation. However, the only published animal model of AP-induced obesity involves sub-chronic or chronic administration of sulpiride (SUL) in rats [3–5,13,12,11,10,28,9,38,39]. The validity of this model for human research may be questioned for several reasons. First, sulpiride is a specific blocker of dopamine D₂–D₃ receptors [50], whereas the atypical APs in current clinical practice interact with norepinephrine, histamine and serotonin receptors as well [42]. Second, sulpiride only induces significant BWG in female rats and prepuberal males [3,4,9,39,46]. However, AP-induced obesity and metabolic dysregulation are observed in both men and women [2,20,21,32]. And third, hyperinsulinemia and hyperglycemia which are usually detected in obese people [22] are not observed in female rats with SUL-induced obesity [10,28] but are unexpectedly observed in male rats that did not gain weight during SUL treatment [9].

It is thus necessary to explore the effects of other APs in rats in order to develop an animal model with better resemblance to human obesity and metabolic dysregulation induced by APs. Since clozapine does not induce BWG in rats and olanzapine is not commercially available for experimental research, we selected risperidone (RIS), which is an AP widely used in the treatment of schizophrenia and other mental disorders and on average displays a moderate propensity to induce obesity in humans [1,47,51]. In fact, case reports have been published of massive BWG during RIS administration [2]. Contrarily to SUL, RIS interacts with several neurotransmitter receptors involved in BW and food intake (FI) regulation [2,42]. The affinity (potency) of RIS for specific receptors is as follows: 5-HT₃ pred >α₁ >D₂ >5-HT₁D >H₁ >α₂ >5-HT₂C >5-HT₁A >muscarnic [42].

In the present studies, we wanted to investigate the gender and drug-specific effects on BW, FI and some metabolic regulators after chronic AP treatment. We report here two experiments. In the first experiment, three doses of RIS were tested in male or female adult rats. Significant BWG was only observed in females. Hence, in the second experiment we compared the effects in female rats of RIS and SUL on BWG, FI, glucose tolerance, some hormones involved in BW regulation and body composition. The comparative effects of these two agents on food efficiency, differential macronutrient intake and brain neuropeptides will be reported in an accompanying paper.

2. Materials and methods

Adult Wistar rats (Charles River, Canada) weighing 220–250 g (females) and 280–300 g (males) were housed 2 per cage (first experiment) or individually (second experiment) in a 12–12 h light/dark cycle, with lights on or off at 8:00 and 20:00 h respectively. BW and FI were monitored for 6 days before starting the experiments and they did not differ between the different groups (data not shown). Room temperature was kept at 20 centigrade. Animals were fed ad libitum with a 20% fat diet (product # 95169, Harlan Tekland, Madison, Wisconsin). Food was placed in spillage-proof feeders. Pharmacological treatments, BW and FI assessment (to the nearest 0.1 g) were conducted at 12:00 h. All experimental procedures were approved by the McGill University Committee for Animal care.

2.1. Drug treatment

Racemic SUL and RIS (Sigma, St. Louis, MO) were dissolved in 0.1 N HCl and tartaric acid respectively, and pH was adjusted to 7.0. Drugs were administered subcutaneously in a volume of 0.1 cc/100 g.

2.2. Blood sampling and oral glucose tolerance test

General anesthesia was achieved by intramuscular administration of a solution made of Ketamine HCl (50 mg/ml), Xylazine HCl (5 mg/kg) and Acepromazine (1 mg/kg). The total volume was 1 ml/kg of BW. A catheter (26G, Abbott Labs) was placed in the tail dorsal artery and was filled with heparinized (2 U/ml) physiological saline at 12:00. The oral glucose tolerance test (glucose, 1 g/kg per gavage) was conducted in a counterbalanced order 36 h after surgery. Blood samples (0.1 cc) were removed before and after the glucose administration (at 0, 30, 60, 90 and 120 min; total 0.6 cc of blood) while the animal was gently placed in a plastic rodent restrainer. The catheter was immediately withdrawn at the end of the glucose tolerance test, and 2 days later the rats were decapitated after 6 hours of fasting. Trunk blood was collected for hormonal determination. For this purpose all animals were decapitated in a counterbalanced sequence between 17:00 and 19:00 h. In order to minimize the effects of stress on hormone levels, less than 1 minute elapsed between handling the animals and decapitation. Bodies were processed for body composition analysis (see below).
2.3. Experiment 1: Effects of risperidone on BW and FI in female or male rats

For each gender, 32 animals were randomly assigned to 4 groups of 8 subjects each, which received one of the following treatments: vehicle (0.1 cc/kg), RIS 0.125, 0.25 or 0.5 mg/kg for 16 days. These doses of RIS are known to induce little impairment in motor behavior in rats [43]. Measurement of BWG and FI was conducted as stated above. Since no additional studies were carried out in males, an oral glucose tolerance test was conducted in the rats treated with VEH and RIS 0.5 mg/kg at day 14. Serum glucose and insulin levels were assessed in all blood samples. Leptin, corticosterone and prolactin levels were measured in blood samples collected immediately after decapitation of the animals at the end of the experiment.

2.4. Experiment 2: Comparison between the effects of risperidone and sulpiride on BW, FI, glucose tolerance, vaginal cycle, hormones and glucose tolerance in female rats

Twenty-nine female rats were divided into 3 groups that received one of the following treatments for 12 days: 0.9% NaCl, 0.1 cc/kg (n=9), RIS 0.5 mg/kg (n=11) or SUL 20 mg/kg (n=9). This SUL dose has been shown to induce the maximal BWG after prolonged treatment [3].

The intra-arterial catheter was placed on day 9 after onset of drug treatment, and was withdrawn when the glucose test was completed. On day 10 the animals were fasted for 6 hours and then the oral glucose tolerance test was conducted as described in the blood sampling section. Insulin and glucose were assessed in all blood samples. Leptin, corticosterone, prolactin, progesterone and estradiol concentrations were assessed in the basal samples obtained by decapitation on day 12.

2.5. Glucose and hormone quantification

Circulating glucose levels (mg dl\(^{-1}\)) were measured by the glucose oxidase/peroxidase method from Sigma-Aldrich, St. Louis, MO, USA. Hormones were assessed by specific radioimmunoassay with commercial kits from Linco, MO, USA, for leptin (ng ml\(^{-1}\)) and insulin (ng ml\(^{-1}\)); from ICN Costa Mesa, CA, USA for 17β-estradiol (pg ml\(^{-1}\)), progesterone (ng ml\(^{-1}\)), and corticosterone (μg dl\(^{-1}\)); and from ALPCO Windham, NH, USA for prolactin (ng ml\(^{-1}\)). The inter- and intra-assay variation was below 10% in all assays.

2.6. Vaginal cycle assessment

The stage of the oestrous cycle was assessed by daily vaginal smears during the last 4 days of treatment. Pretreatment evaluation was not conducted. Each sample was classified in any of the following histological categories: proestrus, estrus or diestrus. At the end of the 4-day period each animal was defined as having normal or abnormal vaginal cycle.

2.7. Body composition assessment

The detailed procedure is described elsewhere [41]. Briefly, carcasses were collected and processed to determine their contents in energy, fat and protein. They were autoclaved at 125 kPa for 15 min to soften hard tissues and homogenized in a volume of water corresponding to twice their weight. The homogenized carcasses were freeze-dried pending the determination of their energy and nitrogen contents. Carcass energy content was determined by adiabatic bomb calorimetry and carcass nitrogen was determined in 250–300 mg samples of dehydrated carcasses using the Kjeldahl procedure. Carcass protein content was computed by multiplying the carcass content by 6.25. The energy as protein was subtracted from total carcass energy in order to determine energy as non-protein matter. As carbohydrate represents a negligible part of carcass total energy, energy from non-protein matter was assumed to be essentially that of fat. Twenty-nine female rats were divided into 3 groups that received one of the following treatments for 12 days: 0.9% NaCl, 0.1 cc/kg (n=9), RIS 0.5 mg/kg (n=11) or SUL 20 mg/kg (n=9). This SUL dose has been shown to induce the maximal BWG after prolonged treatment [3].

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2.8. Statistical analysis

Analysis was conducted with the SPSS program, version 10.0 for Windows. BWG and FI data were analyzed with a two-way analysis of variance (ANOVA) and pair-wise analysis as a post-hoc test. Cumulative FI (all food intake during the experimental period), the areas under the curves for glucose (AUGC) and insulin (AUIC), hormones and body composition were analyzed with a one-way ANOVA followed by the Tukey test (for 3 group comparisons). A two-tailed t test for independent samples was conducted for 2 group comparisons. Bivariate correlation and linear regression were conducted; when BWG was included, it was considered as the dependent variable. The data on the vaginal cycle was analyzed with the chi-squared test with the Yate’s correction. Results were considered significant when \(P<0.05\).

3. Results

3.1. Bodyweight and food intake

Risperidone significantly increased BWG and FI in female rats at the 3 doses under evaluation (\(P=0.001\), see
Fig. 1. Effects of risperidone on BWG and FI in female rats. (A) BWG was significantly increased by RIS: treatment×time interaction: \( f(45, 512)=1.4, P=0.035 \). There were not significant differences between the 3 doses of RIS. Arrows signal the period in which significant differences were observed by pair-wise comparisons (*) \( P<0.05 \). (B) FI was significantly increased by RIS, particularly by the dose of 0.5 mg/kg: treatment×time interaction: \( f(45, 256)=1.74, P=0.006 \); (*) (pair-wise comparisons) \( P<0.05 \). Analysis of the cumulative FI (g) reached marginal statistical significance: VEH: 540±15; RIS 0.125: 605±26; RIS 0.25: 588±28; RIS 0.5: 635±22; \( f(3, 15)=2.96, P=0.075 \).

Fig. 1). There were no significant differences between the 3 doses. In relation to FI, even though significant differences were observed at some time-points with dose of 0.5 mg/kg, the cumulative FI only reached marginal significance (\( P=0.075 \), see Fig. 1).

By contrast, in males, BWG and FI were not affected for all 3 doses used (\( P=0.9 \), Fig. 2). A small increase in FI was observed in RIS-treated animals, particularly with the intermediate dose (0.25 mg/kg), but it was only a trend (\( P=0.14 \), Fig. 2).

When RIS was compared with SUL in females, it was observed that both APs significantly enhanced BWG (\( P=0.0001 \)) and FI (\( P=0.028 \)), the effect on BW being more robust after SUL treatment (Fig. 3). The BWG was completely accounted for in increased lipid content (Table 1). In comparison to the VEH group, the gain in fat and energy were significantly higher after SUL but not after RIS administration.

3.2. Glucose tolerance and hormones

Male rats treated with RIS (0.5 mg/kg) displayed significantly higher prolactin (\( P=0.0001 \)) and corticosterone (\( P=0.002 \)) levels than the VEH group. No differences between the 2 groups were observed in leptin levels, AUG and AUI (Table 2).

In female rats, the AUGC was significantly lower in the SUL treated group compared to the groups treated with VEH or RIS (\( P=0.006 \)). However, no significant differences between the treatment groups were observed in the AUIC (Table 3). Serum leptin levels were significantly higher after SUL than after VEH or RIS treatments (\( P=0.009 \), Table 3). No significant correlation was observed between BWG and the AUGC in any group. In the RIS group BWG and the AUIC correlated significantly: \( r=0.692, P=0.018 \). Leptin and BWG significantly correlated only in the SUL group: \( r=0.742, P=0.022 \).

Prolactin and corticosterone levels were similarly increased by SUL or RIS (\( P=0.0001 \) and 0.005 respectively). Estradiol levels were significantly higher in the RIS group (\( P=0.002 \)), whereas progesterone levels were similar in all treatment groups (Table 3). No significant correlation was observed between BWG and these hormones in the VEH and SUL groups. In the RIS group a significant correlation was observed between BWG and estradiol levels: \( r=0.73, P=0.01 \); in the SUL group, this correlation only reached marginal statistical significance: \( r=0.361, P=0.063 \).

3.3. Vaginal cycle

Eight out of 9 VEH-treated rats displayed normal
4. Discussion

4.1. Effects of RIS in male rats

As in previous studies with SUL [17,14,39,46], RIS did not significantly affect BWG or FI in male rats and did not induce any significant change in leptin or insulin levels and glucose tolerance.

As expected, hyperprolactinemia was observed in RIS-treated rats. Serum corticosterone levels were also significantly higher after RIS administration and it may be related to hyperprolactinemia [43] and/or increased appetite. In agreement with the lack of effects on BW, RIS did not induce any significant change in leptin levels and on glucose tolerance and insulin levels.

We have previously shown that SUL significantly decreased glucose tolerance in male rats, even though it did not affect BWG [11]. Thus, with respect glucose regulation, SUL effects in male rats appear to be stronger than those observed after RIS administration. This agrees with the clinical finding that RIS induces little effects on glucose metabolism in humans [35].

Since a small trend for RIS to increase FI was observed, it is possible that BWG in males could be observed by using other experimental protocols. For example, intraperitoneal administration of haloperidol did not affect BWG in males [3], while administered using slow release pumps it did increase BWG in male rats [40]. In addition to the route of administration, other RIS dose, different types of diets or rodent strains should be tested before definitively concluding that this agent is devoid of effect.

4.2. Effects of RIS or SUL in female rats

Both, SUL or RIS significantly increased BW and FI. However, BWG was significantly higher after SUL than after RIS administration (P=0.001) in spite of similar effects on FI (P=0.38). This suggests enhanced food

![Fig. 3. Comparative effects of risperidone and sulphuride on BWG and FI in female rats.](image)

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total energy (kJ)</th>
<th>Initial energy (kJ)</th>
<th>Gain in energy (kJ)</th>
<th>Protein content (g)</th>
<th>Lipid content (g)</th>
<th>Protein gain (g)</th>
<th>Lipid gain (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>3390±165</td>
<td>1963±20</td>
<td>1426±156</td>
<td>53.7±1.1</td>
<td>54.3±4.1</td>
<td>4.2±0.8</td>
<td>33.8±4.1</td>
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<td>N=10</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sulphuride</td>
<td>3891±145 (a)</td>
<td>1961±22</td>
<td>1931±133</td>
<td>54.2±0.6</td>
<td>66.7±3.6</td>
<td>4.7±0.4</td>
<td>46.4±3.5</td>
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<tr>
<td>N=9</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>3184±131</td>
<td>1963±39</td>
<td>1186±105</td>
<td>53.8±1.1</td>
<td>48.1±2</td>
<td>4.3±0.6</td>
<td>27.6±2.7</td>
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<tr>
<td>N=9</td>
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</tbody>
</table>

(kJ)=kilojoules
(a) f (2,29)=6.5, P=0.005; SUL vs. VEH, P=0.004; RIS vs. VEH, P=0.4; SUL vs. RIS, P=0.059.
(b) f=8.14, P=0.002; SUL vs. VEH, P=0.001; RIS vs. VEH, P=0.4; SUL vs. RIS, P=0.03.
(c) f=6.9, P=0.004; SUL vs. VEH, P=0.003; RIS vs. VEH, P=0.4; SUL vs. RIS=0.053.
(d) f=7.57, P=0.002; SUL vs. VEH, P=0.002; IRIS vs. VEH, P=0.4; SUL vs. RIS, P=0.042.
efficiency in the SUL group, as discussed elsewhere (manuscript in preparation).

Interestingly, the magnitude of SUL-induced BWG in this study was higher than previously observed in earlier studies with this agent. This finding may be related to the fact that in the present study we used subcutaneous instead of intraperitoneal administration of SUL. The subcutaneous route allows a more sustained drug delivery and may be reflected in a more robust effect on BW and FI. SUL treatment in female rats.

The SUL- or RIS-induced BWG was completely accounted for by a proportional increase in lipid content, as it treated rats. However, BWG significantly correlated with be reflected in a more robust effect on BW and FI. SUL treatment in female rats.

The expected increase in leptin levels was only observed in SUL-treated rats. This finding suggests that a modest impairment in carbohydrate regulation observed in humans with primary obesity and during atypical AP-administration. For example, the magnitude of hyperinsulinemia and insulin resistance positively correlates with the body mass index in primary obesity [25]. In addition, BWG and serum glucose levels correlated positively with BW during olanzapine administration in subjects with schizophrenia [24]. By contrast, the metabolic profile in SUL-treated females appears to suggest an increase in insulin sensitivity (low glucose levels and normal insulin levels). The differential effects of RIS and SUL on glucose levels are probably related to the multiple effects of RIS on monoamine systems, some of them like serotonin being actively involved in carbohydrate metabolism regulation [33].

The assessment of the reproductive hormones was of particular interest since it has been proposed that a decreased estradiol synthesis related to hyperprolactinemia

Table 2

<table>
<thead>
<tr>
<th></th>
<th>AUGC</th>
<th>AUIC</th>
<th>Prolactin</th>
<th>Corticosterone</th>
<th>Leptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (n=8)</td>
<td>178±4</td>
<td>4.2±3.1</td>
<td>30.3±5.2</td>
<td>19.4±1.8</td>
<td>2.3±0.2</td>
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<tr>
<td>Risperidone (n=8)</td>
<td>188±8</td>
<td>4.0±0.5</td>
<td>82.3±4.4 (a)</td>
<td>28.4±1.5 (b)</td>
<td>2.4±0.2</td>
</tr>
</tbody>
</table>

Values represent mean±S.E.M. AUGC=area under the glucose curve; AUIC=area under the insulin curve; (a) t (14)=7.5, P=0.0001; (b) t (14)=3.8, P=0.002.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>AUG</th>
<th>AUIC</th>
<th>Prolactin</th>
<th>Corticosterone</th>
<th>Leptin</th>
<th>PRG</th>
<th>EST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone N=10</td>
<td>224±6</td>
<td>3.5±0.5</td>
<td>188±10</td>
<td>27.4±0.8</td>
<td>4.2±0.3</td>
<td>45.4±14.2</td>
<td>147±16 (c)</td>
</tr>
<tr>
<td>Sulpiride N=9</td>
<td>195±7 (a)</td>
<td>5.2±0.8</td>
<td>203±11</td>
<td>26.0±0.7</td>
<td>7.5±12.0 (d)</td>
<td>51.1±12.1</td>
<td>92±10</td>
</tr>
<tr>
<td>Vehicle N=9</td>
<td>225±8</td>
<td>3.6±1.6</td>
<td>38±11 (b)</td>
<td>21.8±1.7 (c)</td>
<td>3.9±0.8</td>
<td>38.9±0.8</td>
<td>79±9</td>
</tr>
</tbody>
</table>

AUG=area under the glucose curve; AUIC=area under the insulin curve; CORT=corticosterone; PRG=progesterone; EST=estradiol.
(a) f (2,28)=6.3, P=0.006; sulpiride (SUL) vs. vehicle (VEH), P=0.012; SUL vs. risperidone (RIS), P=0.013.
(b) f=68, P=0.0001; RIS vs. VEH, P=0.0001; SUL vs. RIS, P=0.0001.
(c) f=6.4, P=0.005; RIS vs. VEH, P=0.005; SUL vs. VEH, P=0.051.
(d) f=5.7, P=0.009; SUL vs. VE, P=0.015; SUL vs. RIS, P=0.02.
(e) f=8.3, P=0.002. RIS vs. VEH, P=0.003; RIS vs. SUL, P=0.013.
may mediate the effects of some APs on BW and FI [39]. The present results do not support that contention because estradiol levels did not differ between the SUL and VEH groups. In fact, estradiol levels were significantly elevated in the RIS group, and correlated significantly with BWG (P=0.0.1).

High serum progesterone levels are associated with BWG in hyperprolactinemic female rats [37]. Therefore, high progesterone levels were expected in the SUL- or RIS groups, because prolactin stimulates progesterone production by the corpus luteum. This hypothesis was not confirmed either. Collectively, these results show that, in spite of a disruption in the vaginal cycle, RIS or SUL administration in female rats did not simulate the effects of typical APs in women, who instead showed hypogonadism and hypoprogesteronemia [14,8,6].

As expected, a highly significant hyperprolactinemia was observed in both SUL- and RIS-treated rats. Prolactin promotes BWG and adiposity by acting directly in the brain [45] and perhaps by decreasing ovarian estradiol synthesis [7]. However, prolactin alone does not explain the stronger effect of SUL on BWG, since hormone levels were similar in the SUL and RIS groups.

Corticosterone displays potent effects on general FI, specific macronutrient intake, glucose and lipid metabolism [27,44]. This hormone was significantly elevated by the same magnitude after SUL or RIS administration. Since one remarkable effect of corticosterone is the impairment of insulin sensitivity [44], further studies must clarify how SUL-treated female rats appear to display normal or increased insulin sensitivity.

5. Conclusions and future studies

Similar to previous findings with SUL [3,4,9,39,46], RIS induced significant BWG only in female rats. However, a small, non-significant effect on FI was observed in males, which may be amplified with other experimental protocols. The lack of effects of chronic AP administration on BW and FI in male rats is particularly interesting, since acute FI stimulation has been reported [48,29]. The mechanisms involved in this relevant sex-dependent effect require further clarification.

In female rats, SUL induced a stronger BWG than RIS. Such difference was reflected in the serum leptin levels and body composition. An important difference between the two agents was that SUL-treated rats consistently display lower glucose levels than VEH-treated controls. Whereas insulin levels did not differ between the RIS and VEH groups, BWG significantly correlated with the AUIC in the former group. In this sense, RIS treatment better simulates AP-induced BWG in humans.

The animal model using RIS, particularly its lack of effects in male rats, may be refined using alternative ways of drug administration and perhaps high-carbohydrate diet (instead of or in addition to high-fat diet as used here). This last option is worthwhile testing since a significant hyperphagia after acute administration of RIS, clozapine or olanzapine was produced by using a carbohydrate-rich-diet in mice, a species in which AP-induced BWG is particularly difficult to model [23].

Preliminary reports are contradictory regarding whether olanzapine stimulates BWG in both genders in rats [29,30]. A recent study showed that repeated olanzapine administration promotes BWG in female rats, but FI, carbohydrate metabolism and hormones were not evaluated [19]. Interestingly, results obtained with acute protocols for FI assessment in rats suggest that olanzapine inhibits satiety mechanisms [48]. This last study and our results on glucose metabolism and gonadal steroids indirectly suggest that RIS induces BWG in rats mainly through appetite stimulation.

Dyslipidemia is a clinically relevant side effect of some atypical APs in psychiatric patients [34]. An important limitation of studies on the effects of APs in rats is the conspicuous resistance of these animals to develop atherosclerosis. Their blood lipid profile also differs significantly from humans, since rats display low LDL- and high HDL-cholesterol blood levels [11,26]. Therefore, future experimental studies on the impact of APs on lipid metabolism might consider the use of more suitable species such as rabbits or genetically modified mice [36].

Acknowledgements

This study was supported by the CDCH-T, grant M-718-01-03-B (Los Andes University, Mérida, Venezuela), by a Pfizer (Canada) fellowship to Trino Baptista and NARSAD Young Investigator Awards to Serge Beaulieu and Rhida Joober.

References


