Distinct endocrine effects of chronic haloperidol or risperidone administration in male rats

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Abstract
Antipsychotic drugs have been used effectively for the treatment of schizophrenia symptoms, but they are often associated with metabolic side effects such as weight gain and endocrine disruptions. To investigate the possible mechanisms of antipsychotic-induced metabolic effects, we studied the impact of chronic administration of a typical antipsychotic drug (haloperidol) and an atypical antipsychotic (risperidone) to male rats on food intake, body weight, adiposity, and the circulating concentrations of hormones and metabolites that can influence energy homeostasis. Chronic (28 days) haloperidol administration had no effect on food intake, weight gain or adiposity in male rats, whereas risperidone treatment resulted in a transient reduction in food intake and significantly reduced body weight gain compared to vehicle-treated control rats. Whereas neither antipsychotic had any effect on serum lipid profiles, glucose tolerance or the circulating concentrations of hormones controlled by the hypothalamo-pituitary-thyroid (free T4), adrenal (corticosterone), somatotropic (IGF-1), or gonadotropic axes (testosterone), haloperidol increased circulating insulin levels and risperidone increased serum glucagon levels. This finding suggests that haloperidol or risperidone induce distinct metabolic effects. Since metabolic disorders such as obesity and type 2 diabetes mellitus represent serious health issues, understanding antipsychotic-induced endocrine and metabolic effects may ultimately allow better control of these side effects.

1. Introduction
Schizophrenia is a debilitating neuropsychiatric illness characterized by multidimensional phenotype with a profound disruption in cognition and emotion, along with negative (i.e. apathy, lack of emotion, poor or non-existent social functioning) and positive (i.e. hallucinations, delusions) symptoms. It affects approximately 1% of the population worldwide. The underlying aetiology of schizophrenia is still largely unknown, but it is likely to be a complex interplay between genetic predisposition and environmental effects (e.g. early developmental stressors).

Antipsychotic drugs have been used for the treatment of schizophrenia since the 1950s. They can be categorized as either conventional (typical), such as chlorpromazine and haloperidol, or novel (atypical), such as clozapine, olanzapine, quetiapine, aripiprazole and risperidone, which were introduced after 1990. Typical drugs are efficient in reducing symptoms of psychosis but not particularly useful against negative symptoms or cognitive deficits. Atypical antipsychotic drugs have gained popularity over typical antipsychotics due to their efficacy in controlling not only psychotic (positive) but also negative symptoms. In addition, atypical antipsychotics induce fewer side effects such as extrapyramidal symptoms (EPS) including akathisia, dystonia and tardive dyskinesia. EPS are caused by the dopaminergic antagonism of antipsychotics (Green et al., 2000). Moreover, atypical antipsychotic drugs have been increasingly used for the clinical management of other conditions such as mania, bipolar disorder, dementia, and severe anxiety (Hellewell, 2006 and Nemeroff, 2005). However, one serious disadvantage of atypical antipsychotic drugs is an increased propensity of excessive weight gain and diabetes mellitus associated with their use (Conley and Kelly, 2005, Green et al., 2000 and Henderson, 2001), although the degree of weight gain induced by the different atypical agents may range significantly. For
example, the atypical antipsychotics clozapine and olanzapine have been reported to induce substantial weight gain of approximately 4 kg over ten weeks period while others like sertindole and risperidone had more modest effects with mean weight gain of 2.92 kg and 2.10 kg respectively after ten weeks of treatment (Allison et al., 1999). With regard to other metabolic side-effects, while both the typical antipsychotic haloperidol and the atypical drug risperidone have been linked with the development of diabetes mellitus, controversy exists over the risk of diabetes associated with their use (Feldman et al., 2004 and Miller et al., 2005).

Antipsychotic-induced metabolic side effects such as weight gain and endocrine disruptions have important clinical implications as they significantly increase morbidity and mortality, reduce quality of life, interfere with medication compliance and increase the chance of psychotic relapse (Allison et al., 2003, Russell and Mackell, 2001 and Weiden et al., 2004). The mechanisms responsible for these antipsychotic-induced side effects are poorly understood. Since excess body weight is linked to insulin resistance and progression to type 2-diabetes, it has been suggested that antipsychotics induce diabetes via increases in body weight and adiposity (Baptista et al., 2002a and Kato and Goodnick, 2001). However, obesity is not the only mechanism by which antipsychotics engender diabetes, since cases of newly diagnosed diabetes have been observed in lean people taking antipsychotics in the absence of weight gain, and withdrawal of certain antipsychotic drugs can normalize diabetes even before drug-induced effects on body weight are reversed (Clark and Burge, 2003 and Liberty et al., 2004). In addition, population studies in people taking antipsychotic drugs have shown the incidence of diabetes mellitus to be unrelated to the degree of weight gain (Farwell et al., 2004). To further complicate understanding of the links between antipsychotic use, weight gain and diabetes in human studies, many people under treatment with antipsychotics have schizophrenia, and schizophrenia per se is associated with diabetes mellitus (Feldman et al., 2004 and Liberty et al., 2004).

Therefore in order to elucidate the possible mechanisms of antipsychotic-induced metabolic effects, we investigated the impact of chronic administration of a typical antipsychotic drug (haloperidol) and an atypical antipsychotic (risperidone) on food intake, body weight, adiposity, and circulating hormone and metabolite levels in male rats. We have chosen haloperidol and risperidone as both are commonly used antipsychotics that produce low to moderate increases in body weight and are associated with diabetes mellitus risk in humans (Allison et al., 1999, Feldman et al., 2004, Liberty et al., 2004 and Miller et al., 2005). Both drugs act on multiple neurotransmitter receptors, although each drug can be characterized by a unique receptor binding profile (Goldstein, 2000). Haloperidol acts primarily on dopamine D2 receptors with lower activity at D1, D3, D4, 5-HT2A and α1 adrenergic receptors (Goldstein, 2000 and Miyamoto et al., 2005). On the other hand, as with many atypical antipsychotics, risperidone possesses high serotonin (5-HT2A) receptor antagonism combined with relatively milder D2 receptor antagonism, compared to either its activity on 5-HT2A receptors or haloperidol's activity on D2 receptors (Goldstein, 2000, Megens et al., 1994 and Miyamoto et al., 2005). Current literature on the effects of haloperidol and risperidone on body weight gain and food intake vary, which is mostly likely due to the widely different drug treatment designs (dose and duration of drug treatment, mode of administration, diet composition, species and gender of experimental subjects). Haloperidol has been reported to increase body weight in female rats with or without increase in food intake (Fell et al., 2004, Fell et al., 2005 and Pouzet et al., 2003). Chronic risperidone treatment lead to increases in both body weight gain and food intake in female rats (Baptista et al., 2002b and Pouzet et al., 2003). A similar effect on body weight gain was observed in risperidone-treated female mice but without any accompanying increase in food intake (Cope et al., 2005). In contrast to the commonly observed body weight gain in female rodents, haloperidol or risperidone did not induce body weight gain in male rats (Baptista et al., 2002b and Pouzet et al., 2003). However, the antipsychotic-induced effect on body weight is dose-sensitive, as another study reported body weight gain in male rats at low but not high doses of risperidone (Ota et al., 2002) and another study showed that female rats receiving a low dose of haloperidol (0.04 mg/kg/day) did not gain weight (Arjona et al., 2004). The mechanisms behind the antipsychotic induced weight gain in female but not male rodents were poorly understood but has been attributed to a selective interaction between the antipsychotics and female hormones (Baptista et al., 1997 and Baptista et al., 1998).

The observation that male rats do not gain excessive weight following chronic
treatment with haloperidol or risperidone provides a model to study the direct effect of these drugs on endocrine function and metabolic parameters independent of antipsychotic-induced weight gain. By understanding the primary hormonal and metabolic effects of different antipsychotic drugs we could gain insight into the etiology of antipsychotic-induced weight gain and diabetes and therefore design better strategies to combat these serious side effects.

2. Methods

2.1. Animals and experimental design
Male adult Sprague–Dawley rats (9–10 weeks of age, 357 ± 75 g at transfer; University of Adelaide Laboratory Animal Services, Adelaide, Australia) were kept under standard laboratory conditions of controlled temperature (22 °C) and illumination (12-h light cycle, lights on at 07:00 h). After transfer, rats were allowed to habituate to the new holding facility for seven days. Test animals were allocated to three experimental groups (n = 12 rats/group) which received one of the following infusions for 28 days: “vehicle”: osmotic minipump implants (Model 2ML4: Alzet, Palo Alto, CA, USA) loaded with vehicle (acetic acid solution adjusted to pH 5.0 ± 0.3); “haloperidol”: osmotic minipump implants loaded with haloperidol (0.4 mg/kg/day); “risperidone”: osmotic minipump implants loaded with risperidone (2.13 mg/kg/day). In this study, we used doses of haloperidol or risperidone that achieve 80% or greater D2 receptor occupancy, therefore producing extrapyramidal symptoms that prove drug release and action. Since risperidone achieves D2 receptor occupancy less readily than haloperidol, it was administered in proportionally higher doses (2.13 mg/kg/day) relative to haloperidol (0.4 mg/kg/day) (Kapur and Remington, 2001, Kapur and Seeman, 2001, Kapur et al., 2003 and Wadenberg et al., 2001). This dosing regimen also takes into consideration the reported 4–6 times shorter half-life of antipsychotic drugs in rodents than humans and highlights the advantage of using minipumps in the present study for continuous drug administration to achieve receptor occupancies comparable to clinical use in humans (Kapur et al., 2003). Rats were group-housed (three rats of same treatment group per cage) and were fed a normal chow diet ad libitum (6% calories from fat, 21% calories from protein, 71% calories from carbohydrate, 2.6 kilocalories/g, Gordon’s Speciality Stock Feeds, Yanderra, NSW, Australia). All research and animal care procedures were approved by the Garvan Institute/St Vincent’s Hospital Animal Experimentation Ethics Committee and were in agreement with the Australian Code of Practice for the Care and Use of Animals for Scientific Purpose. All efforts were made to minimise animal suffering and reduce the number of animals used.

2.2. Osmotic pump implantation and chronic drug administration
Under halothane anaesthesia, minipumps were implanted subcutaneously on the upper back of rats. In brief, the upper back was shaved and a 1.5 cm long incision was made in the skin. The minipump was inserted under the skin into a subcutaneous pocket formed with forceps, which was then sewn shut with non-absorbable suture (3-0 Ethicon Prolene: Johnson & Johnson, New Brunswick, USA). The wound was treated with 5 mg/ml solution of bupivicaine (0.01 ml/100 g) before animals were returned to their home cage for recovery.

2.3. Body weight and food intake measurement
Body weight and food intake were measured daily for the first week following surgery. Subsequently, body weight was recorded twice per week on days 9, 13, 16, 20, 23 and 27 post-surgery, and 24-h food intake was measured at day 2 to 7, day 14 and day 21 post-surgery. Final body weight was obtained prior to cull on day 28.

2.4. Glucose tolerance tests
After 11–14 days of treatment, animals were fasted overnight and given an intraperitoneal injection of glucose (1 g/kg) using a 50% glucose solution (Astra Zeneca, North Ryde, Australia). Blood samples (10 µL) were collected from the tail vein of conscious unrestrained rats at 0, 15, 30, 45, 60, 75, 90 and 120 min following glucose injection, and blood glucose levels were measured using an AccuCheck™ blood glucose meter (Roche Diagnostics, Mannheim, Germany).
2.5. Tissue collection
Twenty-eight days following minipump implantation, food was removed from cages at 08:00 h and rats were culled 3–6 h later by decapitation under halothane anaesthesia for collection of trunk blood. Right inguinal, right retroperitoneal, mesenteric and right epididymal white adipose tissue (WAT) depots, brown adipose tissue (BAT), pancreas, liver, right testis and right seminal vesicle were dissected out and weighed. Adipose tissue depots were weighed as an index of adiposity in the different groups of animals. The pancreas and liver were weighed because changes in the weight of these tissues can indicate changes in the regulation of energy homeostasis (e.g. altered hepatic glycogen or lipid storage significantly affect liver weight). Testis and seminal vesicle were weighed as an index of activity of the hypothalamo-pituitary-gonadotropic axis, which not only significantly affects the weight of these tissues (Pierroz et al., 1996) but also affects body composition (Mudali and Dobs, 2004).

2.6. Serum analysis
Serum hormone and metabolite levels were determined with commercial assay kits from Roche Diagnostics (triglyceride), Linco Research (St Louis, MO) (glucagon, insulin), ICN Biomedicals (Costa Mesa, CA) (corticosterone, free T4, testosterone), Wako Pure Chemical Industries (Japan) (free fatty acid) and Bioclone Australia (Sydney, Australia) (insulin-like growth factor 1, IGF-1). Basal serum glucose levels were determined with a glucose oxidase kit (Trace Scientific, Melbourne Australia).

2.7. Statistical analysis
All data are expressed as means ± SE (standard error of the mean). Differences among groups of rats were assessed by ANOVA or repeated measure ANOVA followed by Fisher's PLSD post-hoc comparisons if appropriate (StatView version 4.51, Abacus Concepts, Berkeley, CA). Statistical significance was defined as P < 0.05.

3. Results

3.1. Effect of haloperidol or risperidone on body weight and food intake
Initial body weights were not significantly different among the three experimental groups (vehicle, 375.6 ± 7.9 g; haloperidol, 374.9 ± 5.1 g; risperidone, 362.3 ± 8.8 g; F(2,31) = 1.031, p = 0.369). Repeated measures ANOVA revealed a significant difference in growth rate among groups (Fig. 1A, F(2,24) = 3.018, p < 0.0001), which was attributed to the slower growth rate in the risperidone treated group compared to the vehicle treated control and haloperidol treated rats (Fisher's PLSD, p < 0.0001 for both comparisons). This was illustrated by the marked difference in total body weight gain at the end of 28 days of infusion, with risperidone-treated rats gaining significantly less weight than both the vehicle-treated control group and the haloperidol-treated group (Fig. 1B, F(2,33) = 10.211, p = 0.0004; Fisher's PLSD, p < 0.001, risperidone vs. vehicle or p < 0.01 risperidone vs. haloperidol). No difference was observed between the haloperidol- and vehicle-treated control groups (Fisher's PLSD, p = 0.433).

An acute reduction in food intake relative to vehicle-infused animals was observed in risperidone-treated rats at day 2 (F(2,9) = 10.373, p < 0.01), day 4 (F(2,9) = 5.692, p < 0.05), day 6 (F(2,9) = 4.668, p < 0.05) and one week following minipump implantation (Fig. 1C, F(2,9) = 4.84, p < 0.05). This reduction was not observed at two or three weeks post-surgery (Fig. 1C, F(2,6) = 3.846, p = 0.084 and F(2,9) = 2.09, p = 0.180, respectively). Food intake was not significantly affected by haloperidol treatment (Fig. 1C). Repeated measures ANOVA did not reveal significant differences in food consumption over time between different drug treatment groups (F(2,14) = 1.25, p = 0.278).

3.2. Effect of haloperidol or risperidone on glucose tolerance
There was no difference among the three groups of rats with respect to fasting blood glucose levels or blood glucose levels measured at any time point during the glucose tolerance test (Fig. 2A, repeated measures ANOVA, F(2,14) = 1.133, p = 0.320), except for 90 min following glucose challenge when risperidone treated rats had slightly lower blood glucose than the other two groups (risperidone, 4.467 mM vs. vehicle or haloperidol, 4.775 mM, ANOVA, F(2,33) = 3.615, p < 0.05; Fisher's PLSD, p < 0.05). For area under the glycemic response
curves, neither antipsychotic treatment group was different to the vehicle-treated control group although there was a slight but significant difference between the two antipsychotic treatment groups, with higher glucose levels in the haloperidol group than in the risperidone group (Fig. 2B, $F(2,33) = 3.314, p < 0.05$; Fisher's PLSD, $p < 0.05$).

3.3. Effect of haloperidol or risperidone on body tissue composition
Absolute weights of the different white adipose tissue (WAT) deposits, brown adipose tissue (BAT) and organs were similar among groups except for a significant reduction in mesenteric
WAT \( F(2,33) = 3.296, p < 0.05; \) Fisher’s PLSD, \( p < 0.05 \) vs. haloperidol), pancreas \( F(2,33) = 7.051, p < 0.01; \) Fisher’s PLSD, \( p < 0.01 \) vs. vehicle or haloperidol) and liver \( F(2,33) = 4.614, p < 0.05; \) Fisher’s PLSD, \( p < 0.01 \) vs. vehicle) weights in the risperidone-treated group (Table 1). However, these differences were proportionate to the low body weight gain observed in risperidone-treated rats, since tissue weights relative to body weight were similar across groups, except for a higher relative testis weight \( F(2,33) = 4.775, p < 0.05; \) Fisher’s PLSD, \( p < 0.01 \) vs. haloperidol) observed for the risperidone-treated group (Table 1).

### 3.4. Hormonal and metabolic changes

Although serum glucagon levels were increased in both treatment groups, only risperidone-treated rats showed statistically significant change where glucagon increased four-fold compared to vehicle-treated controls (Table 2, \( F(2,16) = 4.791, p < 0.05; \) Fisher’s PLSD, \( p < 0.01, \) risperidone vs. vehicle). Circulating insulin levels were also varied, with haloperidol—but not risperidone-treated rats exhibiting significantly higher serum insulin levels than those of the vehicle-treated control group (Table 2, \( F(2,33) = 3.486, p < 0.05; \) Fisher’s PLSD, \( p < 0.05, \) haloperidol vs. vehicle). Neither haloperidol nor risperidone treatment affected serum concentrations of any of the other hormones or metabolites measured (Table 2).

### 4. Discussion

This study examined the effects of chronic subcutaneous infusion of supratherapeutic doses of a typical (haloperidol) and an atypical (risperidone) antipsychotic drugs on endocrine
functions and metabolic profile in male Sprague–Dawley rats. Release and action of antipsychotic agents was confirmed by the observation of extrapyramidal symptoms such as a catalepsy-like phenotype and vacuous chewing movements as a model for tremor or tardive dyskinesia in humans, as published elsewhere (Karl et al., 2006). Chronic (28 days) haloperidol administration had no effect on food intake, weight gain or adiposity in male rats whereas risperidone treatment resulted in a transient reduction in food intake and significantly reduced body weight gain compared to vehicle-treated control rats. Whereas neither antipsychotic had any effect on serum lipid profiles, serum glucose concentrations, glucose tolerance, or the circulating concentrations of hormones controlled by the hypothalamic-pituitary-thyroid (free T4), -adrenal (corticosterone), -somatotropic (IGF-1), or -gonadotropic axes (testosterone), the two antipsychotics had distinct effects on endocrine activities, with haloperidol increasing circulating insulin levels and risperidone increasing serum glucagon levels.

Although clinical use of haloperidol has been associated with modest weight gain in humans, we showed that increased body weight gain and hyperphagia are not immediate early effects of this drug in male rats. In keeping with this, body weight was not affected when haloperidol was administered orally to male rats for three or six weeks (Minet-Ringuet et al., 2005 and Pouzet et al., 2003), and was even suppressed under the longer treatment period of 80 weeks (Yoshida et al., 1995). The early stages of obesity, indicated by an increase in percent body fat, have been observed even in the absence of increases in body weight or food intake (Kushi et al., 1998, Pedrazzini et al., 1998 and Sainsbury et al., 1997). This is due to preferential channelling of fuels from lean tissues such as muscle and bone towards white

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<tr>
<th></th>
<th>Vehicle</th>
<th>Haloperidol</th>
<th>Risperidone</th>
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<tbody>
<tr>
<td>Glucagon (pM)</td>
<td>13.58 ± 2.50</td>
<td>23.25 ± 8.46</td>
<td>53.81 ± 11.66**</td>
</tr>
<tr>
<td>Insulin (pM)</td>
<td>135.37 ± 16.34</td>
<td>210.13 ± 26.78</td>
<td>165.18 ± 15.34</td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>8.82 ± 0.44</td>
<td>8.57 ± 0.39</td>
<td>8.28 ± 0.33</td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>83.82 ± 7.63</td>
<td>91.00 ± 8.71</td>
<td>100.58 ± 15.02</td>
</tr>
<tr>
<td>FFA (mEq/L)</td>
<td>0.28 ± 0.04</td>
<td>0.31 ± 0.04</td>
<td>0.26 ± 0.03</td>
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<tr>
<td>Free T4 (pM)</td>
<td>24.60 ± 0.77</td>
<td>27.37 ± 0.93</td>
<td>25.21 ± 0.84</td>
</tr>
<tr>
<td>Corticosterone (ng/mL)</td>
<td>160.23 ± 18.42</td>
<td>159.93 ± 19.61</td>
<td>161.20 ± 29.48</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>792.79 ± 31.65</td>
<td>820.60 ± 42.46</td>
<td>716.83 ± 42.16</td>
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<tr>
<td>Testosterone (nM)</td>
<td>4.87 ± 0.78</td>
<td>4.03 ± 0.57</td>
<td>3.54 ± 0.78</td>
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*p < 0.05, **p < 0.01 compared to vehicle treated group. #p < 0.05, ##p < 0.01 compared to haloperidol treated group.
in adipose tissue under the influence of hormonal changes such as increased serum levels of insulin (Cusin et al., 1990), corticosterone (Guillaume-Gentil et al., 1993) and growth hormone (Ho et al., 1996) and reduced serum levels of thyroid hormones (Kyle et al., 1966), IGF-1 (Shaw et al., 2003), and testosterone (Mudali and Dobs, 2004). However, our data show that not only does chronic haloperidol administration to male rats have no effect on body weight or food intake, it also has no effect on adiposity or the serum levels of many of the hormones that modulate body composition.

Basal circulating levels of insulin were significantly elevated by 1.5 fold in male rats after 28 days of haloperidol administration compared to vehicle-infused control rats. Others have reported a slight or non-significant increase in serum insulin levels following chronic haloperidol administration to male rats (Manzanares et al., 1988 and Minet-Ringuet et al., 2005). This increase in circulating insulin has been suggested as one of the reasons preventing body weight gain in male rats treated with haloperidol (Baptista et al., 2002c), which follows Eckel's proposal that insulin resistance may be an adaptive response for weight maintenance (Eckel, 1992). While hyperinsulinemia, insulin resistance and dyslipidemia are often detected in people treated with antipsychotics (Clark and Burge, 2003 and Sacchetti et al., 2005), it is unclear whether these conditions are direct drug effects or are related to weight gain since many of these subjects have gained significant weight through the course of antipsychotic drug treatment. There were very few studies examining the effect of haloperidol treatment on insulin level in humans (Brambilla et al., 1975 and Brambilla et al., 1976). While these human studies failed to show an impact of haloperidol on circulating insulin levels by 30 days of haloperidol treatment, interpretation of the data was limited due to the diabetes and hyperinsulinemia already present in these schizophrenia patients. Therefore, it was not possible from these studies to determine the direct effect of haloperidol on insulin secretion. Our results were unaffected by the potential diabetogenic effect of schizophrenia per se and demonstrate that hyperinsulinemia is a direct effect of haloperidol and not a secondary effect due to increased adiposity or weight gain.

Intriguingly, previous in vitro studies showed that haloperidol affects neither basal nor glucose-stimulated insulin secretion in pancreatic cells (Best et al., 2005 and Melkersson, 2004). However, haloperidol caused marked depolarisation of the membrane potential of rat pancreatic β cells in the presence of both low and high concentrations of glucose, and decreased cell input conductance, both of which could alter insulin secretion. Moreover, haloperidol was found to block the ATP-sensitive potassium (KATP) channels in rodent pancreatic β cells via interaction with the Kir6.2 subunit of the channel (Yang et al., 2004). In pancreatic β cells, closure of the KATP channels leads to membrane depolarisation, opening of voltage-gated calcium channels and a rise in intracellular calcium that triggers insulin secretion (for review, see Kanno et al., 2002). The reduction in channel open probability and prolonged closed time of KATP channels caused by haloperidol could be a potential mechanism by which this drug induces hyperinsulinemia. Interestingly, a recent report identified a mutation in the Kir6.2 subunit that lead to greatly reduced intrinsic open probability in congenital hyperinsulinism (Lin et al., 2006). Further studies are needed to resolve the discrepancy between the in vitro and in vivo data, which may in part due to a difference in acute and chronic drug administration and the doses of drug used.

Another mechanism by which haloperidol induced hyperinsulinemia may be linked to its antagonistic action on dopamine D2 receptors. Indeed, chronic administration of sulpiride, a dopamine D2–D3 receptor antagonist, leads to elevated circulating insulin and glucose levels in rats during a glucose tolerance test (Baptista et al., 2002c). In addition, dopamine D2-like receptors are expressed in both rat and human pancreatic β cells and mediate inhibition of glucose-stimulated but not basal insulin secretion (Rubin et al., 2005). However, it is interesting to note that the risperidone-treated rats did not increase basal serum insulin significantly despite high occupancy of D2 receptors at the dose used.

It is possible that haloperidol-induced hyperinsulinemia is a primary etiological factor in the development of dyslipidemia, increased adiposity, weight gain, insulin resistance, glucose intolerance, and eventual progression to diabetes mellitus (indicated by fasting hyperglycemia) in people under treatment with this typical antipsychotic drug. Excess insulin in animals and man has been shown to induce insulin resistance and fat accumulation (Cusin et al., 1990 and Marangou et al., 1986). Experimental reduction of insulinemia in hyperinsulinemic, obese, insulin resistant animal models of type 2-diabetes (leptin-deficient ob/ob mice and fa/fa rats) significantly reduced body weight, hepatic and adipose tissue lipogenesis, circulating triglyceride levels, and improved insulin sensitivity (Assimacopoulos-
Jeannet and Jeanrenaud, 1976 and Standridge et al., 2000). Although we saw no evidence of progression to glucose intolerance, fasting hyperglycemia, dyslipidemia or increased adiposity in the rats chronically treated with haloperidol in this study, it would be interesting to see if longer-term treatment eventually engenders these hallmark characteristics of diabetes mellitus.

The atypical antipsychotic risperidone has been associated with weight gain and diabetes mellitus in clinical use. However, our current findings would argue against obesity or diabetes being early or direct effects of risperidone, since adiposity, glucose tolerance, serum lipid profiles, and the circulating concentrations of many of the hormones that regulate body composition were unaltered in male rats chronically treated with risperidone. On the contrary, we observed a significant reduction in body weight gain and early stage food intake in risperidone-treated male rats compared to vehicle-infused controls. This is in keeping with another study showing that 0.5 mg/kg/day risperidone reduced body weight gain in male rats, albeit lower doses (0.005 to 0.05 mg/kg/day) had the opposite effect (Ota et al., 2002). In another study, male rats treated subcutaneously with 0.125 to 0.5 mg/kg/day risperidone for 16 days showed no change in food intake or body weight gain compared to control animals (Baptista et al., 2002b). Taken together, our data suggest that chronic risperidone treatment in rats at the current dose does not induce changes in food intake or hormonal/metabolic changes that could predispose to the development of obesity or diabetes mellitus. The metabolic side effects reported in people under treatment with risperidone could therefore be due to species-specific effects of this drug, confounding variables, or perhaps dose differences.

Unlike haloperidol, which significantly increased serum insulin levels, we observed no significant effect of risperidone on circulating insulin concentrations in rats. In contrast, risperidone but not haloperidol induced a marked and significant increase in serum concentrations of glucagon. From the current study it is not clear if this change is secondary to other effects of risperidone (such as weight loss), or whether the increased serum glucagon levels are a direct effect of risperidone on the glucagon-producing alpha cells of the islets of Langerhans.

In summary, this study has demonstrated distinct endocrine disturbances in male rats treated with the typical antipsychotic drug haloperidol or the atypical antipsychotic risperidone. Chronic administration of haloperidol for four weeks lead to an increase in basal serum insulin levels in the absence of increases in food intake, adiposity or body weight, whereas risperidone treatment resulted in reduced food intake, reduced body weight, and elevated serum glucagon levels. Our findings suggest that if haloperidol or risperidone induced metabolic side effects, these side effects would be due to different mechanisms. Since hyperinsulinemia may be involved in the development of increased adiposity, weight gain, glucose intolerance, type 2 diabetes mellitus and dyslipidemia in predisposed individuals, understanding the effects of antipsychotic-induced hyperinsulinemia may allow better control of these side-effects, particularly in patients with a family history of diabetes or obesity or a higher predisposition towards these disorders.

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