

Effects of Atypical Antipsychotic Drugs on Intralipid Intake and Cocaine-Induced Hyperactivity in Rats

Abegale W Hartfield¹, Nicholas A Moore² and Peter G Clifton^{*,1}

¹Department of Psychology, University of Sussex, Brighton, UK; ²Eli Lilly & Co, Erl Wood Manor, Windlesham, UK

Clozapine and olanzapine have been shown to acutely stimulate consumption of a fat emulsion (Intralipid) by male Lister hooded rats. We initially investigated the extent of any sex difference in Intralipid hyperphagia associated with olanzapine treatment. We then examined the degree of Intralipid hyperphagia produced by a range of atypical antipsychotic drugs having different associations with human weight gain, and also determined their effects on cocaine-stimulated locomotor activity as a measure of functional dopamine antagonism *in vivo*. Olanzapine (0.1–1 mg/kg) stimulated Intralipid intake to an equal extent in male and female rats. Quetiapine (10 mg/kg) also stimulated Intralipid intake whereas ziprasidone (0.3–10 mg/kg) or risperidone (0.03–0.3 mg/kg) did not have this effect. All of the compounds, except quetiapine, reduced cocaine-stimulated locomotor activity but the relationship to the degree of Intralipid hyperphagia was variable. Since there was a positive relationship between Intralipid hyperphagia and the reported extent of human body weight gain, we conclude that Intralipid hyperphagia may have predictive value for this drug-associated side effect and is not related to the dopamine antagonist properties of these agents.

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INTRODUCTION

In humans, treatment with some atypical antipsychotic drugs is associated with weight-gain (Hemphill *et al*, 1975; Claus *et al*, 1992; Beasley *et al*, 1996; Kraus *et al*, 1999). Allison *et al* (1999) performed a meta-analysis of published data suggesting that clozapine and olanzapine are associated with the greatest weight-gain, followed by quetiapine and risperidone; while haloperidol treatment produces only modest weight gain and ziprasidone appears to be weight neutral in most patients. Similar conclusions have been reached in reviews by Taylor and McAskil (2000) and Wetterling (2001); specifically that the rank order for weight-gain liability in humans is, highest first: clozapine and olanzapine, quetiapine, risperidone, haloperidol, and ziprasidone.

The mechanism(s) responsible for weight gain associated with atypical antipsychotic compounds remain unknown. Selective dopamine D₂ receptor antagonists, such as risperidone and haloperidol, may induce persistent elevation of plasma prolactin levels. Secondary endocrine

consequences of hyperprolactinaemia may dispose towards elevated body weight (Baptista, 2002). Some clinical drug trials have recorded the incidence of increased appetite as an adverse drug effect. For example, clozapine was reported to increase desire to eat in up to 75% of patients, and to result in binge eating in some patients (Bromel *et al*, 1998). In a systematic study of the phenomenon in humans, the daily calorie intake, diet composition (carbohydrate/protein/fat), resting energy expenditure, and physical activity were measured in adolescent male patients with schizophrenia taking either olanzapine or haloperidol (Gothelf *et al*, 2002). The olanzapine-treated patients gained weight and showed an increase in daily calorie intake by an average of 589 kcal, an increase of nearly 28% over baseline (Gothelf *et al*, 2002). Diet composition (carbohydrate/protein/fat), resting energy expenditure, and daily physical activity in these patients did not change during olanzapine treatment (Gothelf *et al*, 2002).

Antipsychotic drugs may also increase food intake in rodents under some circumstances. In a series of studies, Baptista and co-workers have reported that chronic sulpiride treatment increases food intake and body weight in female, but not male, rats (Parada *et al*, 1989) and risperidone produces a similar sex-linked weight gain (Baptista *et al*, 2002). Kaur and Kulkarni (2002) tested the antipsychotic compounds chlorpromazine, haloperidol, clozapine, olanzapine, risperidone, and sulpiride in female mice and found that food intake was increased over a time period ranging from 30 min to 2–5 h. Previously, we have

*Correspondence: Dr PG Clifton, Department of Psychology, University of Sussex, John Maynard Smith Building, Brighton, BN1 9QG, UK, Tel: +44 1273 678396, Fax: +44 1273 678611.

E-mail: pete@sussex.ac.uk

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reported that male rats significantly increased their consumption of a fat emulsion (10% Intralipid) during a 30-min test session following acute treatment with the atypical antipsychotic compounds clozapine or olanzapine (Hartfield *et al*, 2003a). There is conflicting evidence concerning gender differences in antipsychotic-associated weight gain in humans. For example, Basson *et al* (2001) found a greater weight gain in olanzapine treated males whereas Tollefson *et al* (1997) observed no gender differences during olanzapine treatment.

Here, we measured Intralipid intake in both male and female rats following olanzapine treatment in order to determine the extent of any sex difference in Intralipid hyperphagia. We then measured Intralipid intake following administration of three atypical antipsychotic drugs (quetiapine, risperidone, or ziprasidone) with lower reported associations with human body weight gain. Finally, each of these agents was examined for its ability to attenuate cocaine-induced locomotor activity. Attenuation of cocaine-induced locomotor activity is widely used as a model to study *in vivo* dopamine function (Ogren *et al*, 1984) and as a screening test for new antipsychotic drugs (Arnt, 1995; Moore, 1999). Atypical antipsychotic drugs have broad pharmacological profiles and differ in the extent of dopaminergic blockade relative to their effects at other neurotransmitter receptors (Bymaster *et al*, 1996; Schotte *et al*, 1996). Here, the degree of *in vivo* dopamine receptor blockade was examined by assessing the degree of attenuation of cocaine-induced locomotor activity produced using the same dose range, route, and timing of administration as used in the Intralipid drinking experiments. High levels of dopamine blockade are likely to induce motor side effects that disrupt ingestive behavior.

MATERIALS AND METHODS

Subjects

In the Intralipid intake experiments, four separate groups of Lister hooded rats (Harlan, UK) were used. The olanzapine experiment used a younger group of nine male and nine female rats in order to minimize sex differences in body size. The males weighed between 220 and 260 g and the females between 180 and 200 g at the beginning of the drug treatment phase of the experiment. Three groups of 12 male rats were used to test quetiapine (weighing between 280 and 310 g), risperidone (weighing between 270 and 310 g), or ziprasidone (weighing between 270 and 300 g). The rats were housed in groups of three in large solid-bottomed polyethylene cages (RB2, North Kent Plastics, UK). The rats were moved to drinking cages (slightly modified RB3 cages, North Kent Plastics, UK) each day for a 30-min testing session and then placed back in their group cages. Food and water were only removed for the duration of the drinking test.

In the cocaine-induced locomotor activity experiments, four groups of forty male Lister hooded rats (Harlan, UK) were used with weights of 240–260 g for the olanzapine group; 235–255 g for the quetiapine group; 150–190 g for the risperidone group and 150–170 g for the ziprasidone group. All rats were housed in groups of four or five prior to testing. Rats were weighed and moved to the activity cages

immediately before the start of the test session. Food and water were not available during testing.

Drugs

Olanzapine, quetiapine (Seroquel), and ziprasidone were all dissolved in a vehicle of 165 μ l of 10% lactic acid that was then brought up to volume with distilled water, sonicated if necessary and then neutralized with 1 M NaOH to obtain a final pH of at least 6.0. Risperidone was dissolved in a vehicle made by placing five drops of 10% lactic acid in distilled water and then the solution was sonicated briefly. Cocaine was dissolved in distilled water.

In the Intralipid intake experiments, each antipsychotic drug, or its vehicle was administered 30 min prior to testing. Doses used were: olanzapine (0, 0.1, 0.3, 1.0 mg/kg/i.p.); quetiapine (0, 0.3, 1.0, 3.0, 10 mg/kg/i.p.); risperidone (0, 0.03, 0.1, 0.3 mg/kg/i.p.); and ziprasidone (0, 0.1, 0.3, 1.0 mg/kg/i.p.). Dose ranges were chosen to be either below or at the low end of the dose range at which each compound produces *in vivo* dopamine antagonism.

In the cocaine-induced locomotor activity experiments, each antipsychotic drug or its vehicle was administered immediately prior to the rat being placed in the activity cage. Doses used for each antipsychotic drug were: olanzapine (0.1, 0.3, 1.0 and 3.0 mg/kg/i.p.); quetiapine (1.0, 3.0, 10.0 and 30.0 mg/kg/i.p.); risperidone (0.1, 0.3, 1.0 and 3.0 mg/kg/i.p.); and ziprasidone (0.3, 1.0, 3.0 and 10.0 mg/kg/i.p.). Cocaine (40 mg/kg/i.p.) was administered to all animals 30 min later.

Intralipid Intake Experiments

The rats were moved to drinking cages (modified RB3 cages, North Kent Plastics, UK) each day for a 30-min testing session and then placed back in their group cages. Animals were habituated to daily presentation of a 10% Intralipid (Fresenius Kabi Ltd, Warrington, UK) emulsion in the drinking cages for 14 days prior to starting the experiment. Intralipid is supplied in a 20% commercial preparation (2 kcal/ml) and to obtain a 10% Intralipid emulsion (1.0 kcal/ml) the refrigerated supply of 20% preparation was diluted each day with fresh tap water. Intralipid consists of purified soybean oil, purified egg phospholipids, and glycerol forming a stable emulsion that makes it useful in drinking studies.

Each animal acted as its own control and received each drug dose (total of three drug administrations) or vehicle in an ascending Latin square counterbalanced design with treatments separated by a minimum of 48 h. Animals in the quetiapine group were treated with an extra dose after a break of several weeks. The quetiapine-treated animals were habituated again, in the same way to daily presentation of 10% Intralipid in the drinking cages. Each animal then received quetiapine 10 mg/kg or its vehicle in a counterbalanced design with treatments separated by a minimum of 48 h.

The rats were moved to the drinking cages immediately prior to the 30-min test session each day. The drinking cages and procedure are similar to that already described (Lee and Clifton, 1992; Hartfield *et al*, 2003a) in that the test cages are standard solid-bottomed cages having a stainless-

steel drinking spout attached to one side wall. Intralipid emulsion was delivered from a reservoir to the spout by a peristaltic pump via polythene tubing. A microprocessor system controlled pump activation by detecting licks of the spout and switching the pump on for 0.5 s. Number of licks and number of pump activations were both noted independently by the recording software to a resolution of 10 ms. The pumps delivered 1.40 g of emulsion per minute (or 11.7 mg per 0.5 s pump activation) thus allowing pump activation to be used as a measure of consumption. The delivery rate is just under the maximal rate at which rats can drink from a spout. Rats were placed into the drinking cages in quick succession, facing away from the spouts and drinking sessions start in all cages simultaneously by remote control as the experimenter left the cubicle.

Behavioural activity was measured using a cage-rack photobeam activity system (PAS; San Diego Instruments, San Diego, CA) that consisted of twenty perspex cages ($355 \times 235 \times 190 \text{ mm}^3$) placed inside a photobeam frame. Locomotor activity was recorded from the time rats were placed into the activity cages, immediately after administration of the relevant antipsychotic drug. After 30 min rats were dosed with cocaine and replaced into the same activity cage. After 2 h, activity recording finished and the rats were removed. Each cage had four horizontal photobeams 1.5 cm above the cage floor and each time a beam was broken, an automatic counter mechanism was triggered. PAS monitored activity throughout the test session and provided total activity counts every 10 min and also a distinction between fine movements (repeated breaking of the same photobeam caused by grooming or stereotype) and ambulations (breaking of consecutive beams). Testing took part in the light part of the photoperiod. No food or water was available during the activity experiments and rats were not habituated to the activity cages prior to testing, as this would have extinguished exploratory behavior of the novel environment.

A between-subjects design was employed and each animal was allocated at random to receive one dose of antipsychotic or its vehicle. There were a total of eight animals per antipsychotic dose treatment group. In all, 20 rats were tested at one time, and two groups of 20 were run on each test day.

Analysis

In the Intralipid intake experiments, two-way (drug \times gender) analyses of variance (ANOVA) with repeated measures on drug conditions, followed by planned paired *t*-tests (Bonferroni correction), were used to compare olanzapine treatments to vehicle treatment with respect to total Intralipid intake. One-way analyses of variance (ANOVA) with repeated measures on drug conditions followed by *post hoc* Dunnett's *t*-tests were used to compare treatment means to vehicle with respect to total Intralipid intake following quetiapine, risperidone, or ziprasidone treatments.

In the cocaine-induced locomotor activity experiments, one-way ANOVAs were used to analyze total activity counts following cocaine administration for each treatment.

To determine the relationship between clinically-observed weight gain and Intralipid consumption, we took data from

Allison *et al* (1999) and Wetterling (2001) for human weight gain. For the analysis from the data of Allison *et al* (1999), we used their preferred estimate of weight gain over 10 weeks, although the estimate for quetiapine depended on a study with shorter duration (see Table 4, footnote a,). The minimal effective dose for Intralipid hyperphagia was taken from the present data or from Hartfield *et al* (2003a). Agents that did not enhance intake were assigned a value of 0 and we then calculated a Pearson correlation coefficient.

RESULTS

Olanzapine

Olanzapine increased Intralipid intake in both male and female rats ($F(3,48) = 13.96$, $p < 0.001$; Figure 1a) but there was no gender difference ($F(1,16) = 3.75$, ns) and no interaction (drug \times gender) ($F(3,48) = 0.33$, ns). Male rats demonstrated increases of 16% (ns) at 0.1 mg/kg, 32% ($p < 0.05$) at 0.3 mg/kg, and 51% ($p < 0.01$) at 1.0 mg/kg of olanzapine. Female rats displayed very similar elevations of 27% (ns) at 0.1 mg/kg, 40% ($p < 0.01$) at 0.3 mg/kg, and 51% at 1.0 mg/kg of olanzapine ($p < 0.01$).

Total cocaine-induced locomotor activity counts were reduced during olanzapine treatment ($F(4,35) = 5.57$, $p = 0.001$;

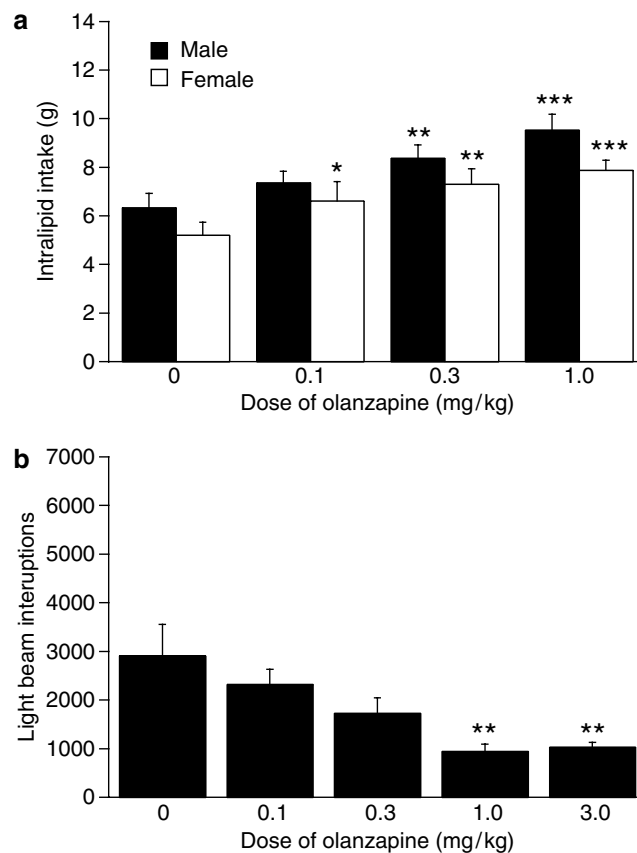


Figure 1 (a) Mean 10% Intralipid intake (in grams) in males and females following administration of olanzapine. (b) The effect of olanzapine treatment on cocaine-induced locomotor activity in males only, shown as total number of light beam interruptions, after cocaine administration. Vertical lines show standard errors. * indicates significant difference ($p < 0.05$) from vehicle. ** indicates significant difference ($p < 0.01$) from vehicle. *** indicates significant difference ($p < 0.001$) from vehicle.

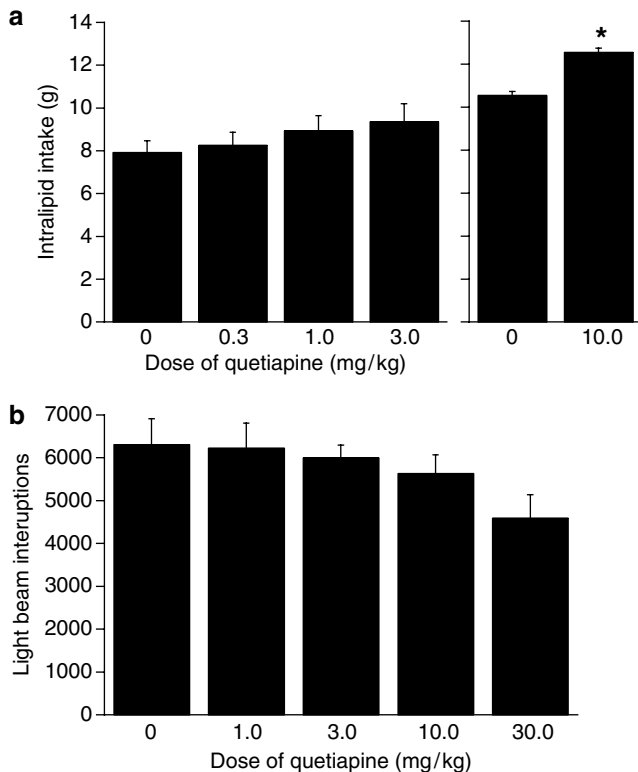


Figure 2 (a) Mean 10% Intralipid intake (in grams) following administration of quetiapine. (b) The effect of quetiapine treatment on cocaine-induced locomotor activity, shown as total number of light beam interruptions, after cocaine administration. Vertical lines show standard errors. * indicates significant difference ($p < 0.05$) from vehicle.

Figure 1b) and this was significant at 1.0 mg/kg ($p < 0.01$) and 3.0 mg/kg ($p < 0.01$).

Quetiapine

Quetiapine increased Intralipid intake in a dose-related manner, 4% at 0.3 mg/kg, 11% at 1.0 mg/kg, and 17% at 3.0 mg/kg. However, in the first dose range tested, this did not quite reach statistical significance ($F(3,32) = 2.72$, $p = 0.061$; Figure 2a). When these animals were retested 3 weeks later, a statistically significant increase in intake of 15% occurred after quetiapine treatment at 10 mg/kg ($F(1,11) = 9.72$, $p = 0.01$; Figure 2a). Total cocaine-induced locomotor activity counts were not significantly reduced by quetiapine at any dose ($F(4,35) = 1.93$, ns; Figure 2b).

Risperidone

Risperidone did not alter Intralipid intake ($F(3,33) = 1.95$, ns; Figure 3a). Total cocaine-induced locomotor activity counts were reduced by risperidone ($F(4,35) = 20.25$, $p < 0.001$; Figure 3b) and this was significant at 0.3 mg/kg ($p < 0.05$) and 1.0 mg/kg ($p < 0.01$) and 3.0 mg/kg ($p < 0.01$).

Ziprasidone

Ziprasidone did not alter Intralipid intake at any dose ($F(3,33) = 0.12$, ns; Figure 4a). Total cocaine-induced

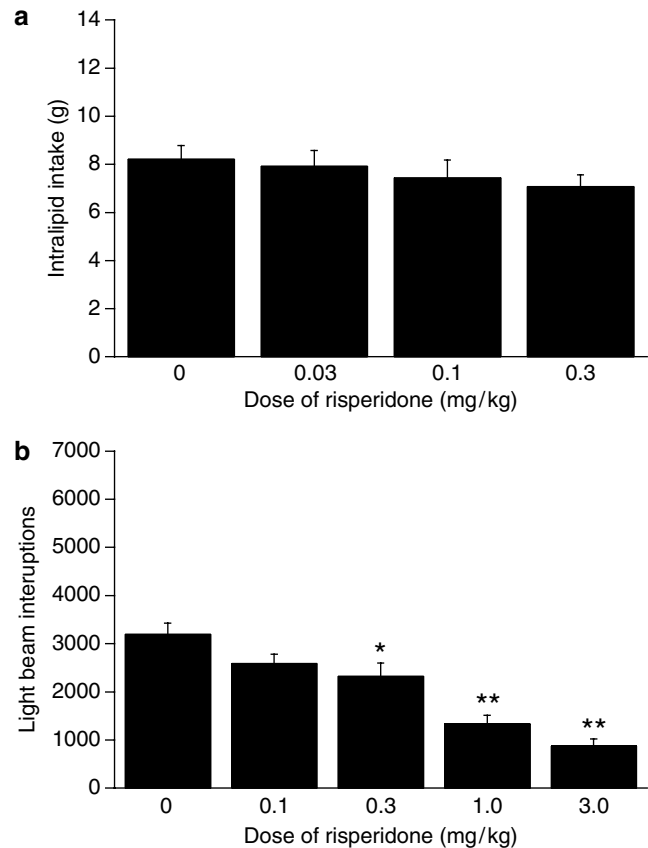


Figure 3 (a) Mean 10% Intralipid intake (in grams) following administration of risperidone. (b) The effect of risperidone treatment on cocaine-induced locomotor activity, shown as total number of light beam interruptions, after cocaine administration. Vertical lines show standard errors. * indicates significant difference ($p < 0.05$) from vehicle. ** indicates significant difference ($p < 0.01$) from vehicle.

locomotor activity counts were reduced by ziprasidone treatment ($F(4,35) = 8.77$, $p < 0.001$; Figure 4b) and this was significant at 3 mg/kg ($p < 0.01$) and 10 mg/kg ($p < 0.01$). (Table 1)

Relationship between Intralipid Intake in Rats and Antipsychotic-associated Weight-gain in Humans.

Intralipid intake (at the highest value obtained) in rats, as reported above for olanzapine, quetiapine, risperidone, and ziprasidone and in Hartfield *et al* (2003a) for clozapine and haloperidol, has a nonsignificant positive correlation ($r = 0.793$, ns; Table 2) with the 10-week human weight-gain liabilities associated with administration of these compounds (Allison *et al*, 1999). There is a significant positive correlation ($r = 0.981$, $p < 0.005$; Table 2) between Intralipid hyperphagia and the amount of weight-gain per month in humans treated with clozapine, olanzapine, quetiapine, risperidone, or ziprasidone (Wetterling, 2001).

DISCUSSION

The data presented here show that olanzapine is equally effective in enhancing the intake of Intralipid in male and female rats over the dose range of 0.1–1.0 mg/kg. In male rats, risperidone or ziprasidone had no significant effect, and a nonsignificant tendency towards reduced Intralipid

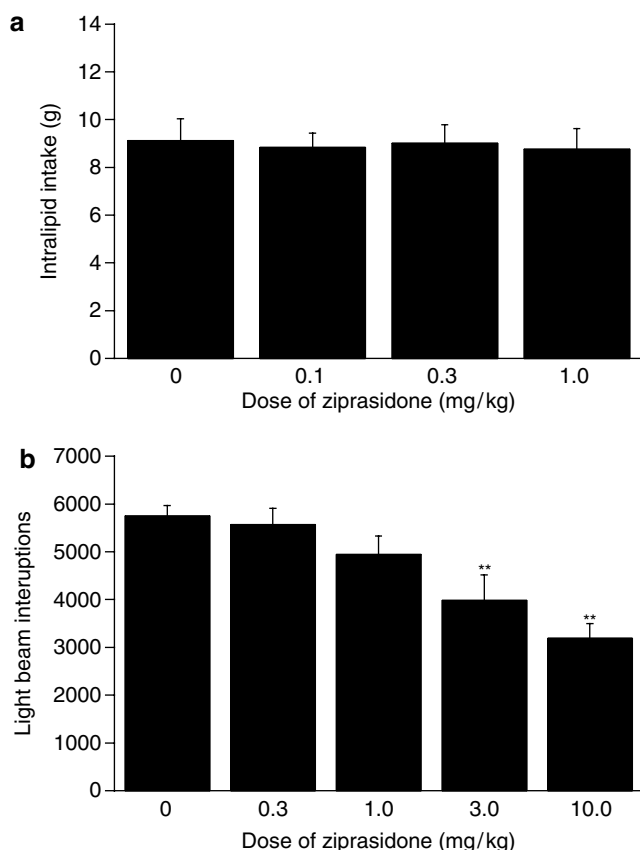


Figure 4 (a) Mean 10% Intralipid intake (in grams) following administration of ziprasidone. (b) The effect of ziprasidone treatment on cocaine-induced locomotor activity, shown as total number of light beam interruptions, after cocaine administration. Vertical lines show standard errors. ** indicates significant difference ($p < 0.01$) from vehicle.

Table 1 The Effect of Various Antipsychotic Agents on Intralipid Drinking and Cocaine Hyperactivity in Lister Hooded Rats

Compound	Intralipid drinking (EDmin)	Suppression of cocaine hyperactivity (EDmin)
Clozapine	0.3	1.0
Haloperidol	NE ^a	0.125
Olanzapine	0.3	1.0
Risperidone	NE	0.3
Quetiapine	10	> 30
Ziprasidone	NE	3.0

^aNE = No stimulatory effect on Intralipid drinking at doses tested.

intake at higher doses, whereas quetiapine produced a significant enhancement of intake at a dose of 10.0 mg/kg. Each drug, with the exception of quetiapine, reduced cocaine-stimulated locomotor activity, although the relationship between the effective doses in the two paradigms was variable.

Olanzapine, clozapine (Allison *et al*, 1999; Wetterling, 2001), quetiapine (Borison *et al*, 1996; Arvanitis and Miller, 1997; Small *et al*, 1997; McIntyre *et al*, 2003) and

Table 2 The Relationship of Effects on Intralipid Drinking and Human Weight Gain

Compound	Stimulation of Intralipid drinking (g)	Weight gain (Allison <i>et al</i> , 1999) (kg)	Weight gain (Wetterling, 2001) (kg)
Clozapine	1.76	4.45	1.70
Haloperidol	0.00	1.08	—
Olanzapine	3.65	4.15	2.30
Risperidone	0.00	2.10	1.00
Quetiapine	1.80	2.18	1.80
Ziprasidone	0.00	0.04	0.80

The relationship of the increase in Intralipid intake (g) in rats following acute drug administration to weight-gain in humans (kg) after 10-weeks of treatment with clozapine, olanzapine, quetiapine, risperidone, ziprasidone or haloperidol (Allison *et al*, 1999) and to weight-gain per month in humans (kg) after treatment with clozapine, olanzapine, quetiapine, risperidone or ziprasidone (Wetterling, 2001).

risperidone (Claus *et al*, 1992; Peuskens, 1995; Emsley, 1999) treatments are associated with weight gain in human males and females. However the weight-gain associated with risperidone treatment is less than that associated with clozapine, olanzapine, or quetiapine (Allison *et al*, 1999; Taylor and McAskill, 2000; Wetterling, 2001). Ziprasidone has a weight-neutral effect in most humans (Keck *et al*, 1998; Daniel *et al*, 1999).

There are several hypotheses concerning the mechanisms responsible for body weight gain associated with antipsychotic drug treatment. Compounds possessing potent D₂ receptor affinity, such as risperidone, may produce persistent and substantial elevations in plasma prolactin (Markianos *et al*, 1999; Esel *et al*, 2001; Turrone *et al*, 2002) that may predispose patients towards increased body weight (Baptista, 2002). In female rats, chronic treatment with several antipsychotic drugs, including sulpiride or haloperidol, is associated with increased body weight (Baptista *et al*, 1987). This effect is not seen in male rats and it is likely that the decreased oestradiol levels in females that result from increased prolactin levels are critical since gonadectomy abolishes the differential effect of sulpiride in male and female rats (Parada *et al*, 1989). However, the Intralipid drinking results reported here demonstrate that the hyperphagic response of male rats to olanzapine is identical to that of female rats, suggesting that a different mechanism is involved. In addition, the increased intake occurs within minutes of drug administration and is therefore unlikely to involve the secondary endocrine effects of raised prolactin levels. In humans, treatment with olanzapine, clozapine, or quetiapine is not associated with persistent or potent hyperprolactinaemia (Markianos *et al*, 1999; Esel *et al*, 2001; Turrone *et al*, 2002) and hence is unlikely to be the mechanism responsible for the association of weight gain with drug treatment.

Preliminary evidence in humans (Gothelf *et al*, 2002) suggests that, at least for olanzapine, stimulation of appetite and a consequent increase in food intake may play an important role in the body weight gain associated with drug treatment. Convergent data from rodent studies support

this hypothesis. Low doses of neuroleptics may enhance acquisition of a food rewarded place preference (Guyon *et al*, 1993). Olanzapine delays the slowing of running speed that occurs in rats performing a simple food-rewarded runway task as they become sated (Thornton-Jones *et al*, 2002). In a similar way olanzapine enhances consumption of Intralipid in a way that suggests delayed onset of satiation (Hartfield *et al*, 2003a). Cyproheptidine can stimulate Intralipid consumption in the same test situation as used here (Hartfield *et al*, 2003b) and is also known to stimulate appetite in humans.

An additional physiological action of some antipsychotic compounds is to induce hyperglycemia. In mice, this effect is pronounced following administration of clozapine or quetiapine, but less marked following risperidone and absent following haloperidol or sulpiride (Dwyer and Donohoe, 2003) administration. It has been suggested that a major part of the effect arises from inhibition of glucose transport into the cell. If this hypothesis is correct, then it is likely to lead to cellular glucoprivation. Other treatments that lead to glucoprivation are known to increase appetite and food intake. For example, 2-deoxyglucose (200 mg) increases blood glucose from 90 to 170 mg% and increases food intake in a short-term test from 1.5 to 5.5 g (Sanders and Ritter, 2000). Clozapine and risperidone produce comparable elevations of blood glucose in the mouse (Dwyer and Donohoe, 2003), but the behavioral consequences have not been evaluated. However, the body weight gain seen in female rats following prolonged sulpiride administration is associated with reduced blood glucose levels (Baptista *et al*, 2002). Thus inhibition of glucose transport could, at most, only account for some examples of weight gain associated with administration of antipsychotic compounds.

In an earlier study, we showed that olanzapine and clozapine, but not haloperidol, stimulate Intralipid consumption in rats (Hartfield *et al*, 2003a). The present data extends this comparison by showing that risperidone and ziprasidone fail to enhance Intralipid consumption whereas quetiapine does stimulate Intralipid intake. It seems unlikely that the failure to observe enhanced intake during treatment with these drugs arose from an inappropriate selection of drug doses. Olanzapine enhanced Intralipid intake at 0.3 and 1 mg/kg (Table 1), and reduced Intralipid intake at 3 mg/kg (Hartfield *et al*, 2003a) while cocaine stimulated locomotor activity was reduced at 1 and 3 mg/kg. Ziprasidone and risperidone were both tested for their effects on Intralipid consumption at dose ranges below those that led to reductions in cocaine-stimulated locomotor activity. Quetiapine failed to attenuate cocaine-stimulated locomotor activity at any dose although Intralipid intake was increased at 10 mg/kg. The effects of these drugs on cocaine-stimulated locomotor activity resemble those reported by Arnt (1995) for amphetamine-stimulated (0.5, 2.0 mg/kg) locomotor activity. In Arnt's study, quetiapine failed to inhibit locomotor activity stimulated by the higher dose of amphetamine, and the overall potency of the remaining compounds was very similar to that reported here. It therefore seems reasonable to conclude that individual features of the pharmacological profile of these drugs has led to the variation in stimulation of Intralipid intake.

The particular pharmacological profile that is required to stimulate Intralipid consumption, or for an association between drug treatment and human body weight gain, remain unclear. In the case of human weight gain, several authors have suggested that 5-HT_{2C} receptor antagonism or histamine H₁ antagonism may play at least a partial role (Baptista, 2002; Kroeze *et al*, 2003). In the case of Intralipid hyperphagia in the rat, it seems that dopamine D₂ receptor antagonism is unlikely to be necessary. Doses of olanzapine, clozapine, and quetiapine that stimulate Intralipid consumption all lie below those that are able to inhibit cocaine-stimulated locomotor activity (Table 1). Such locomotor activity mainly depends on inhibition of striatal dopamine transporters by cocaine and a consequent increase in stimulation of striatal dopamine D₂ receptors. Clozapine, olanzapine, and quetiapine are likely to occupy at least 50% of several other neurotransmitter receptors, as measured by *ex vivo* quantitative autoradiography (Schotte *et al*, 1996) at the doses that stimulate Intralipid consumption. These include 5-HT_{2A}, 5-HT_{2C}, noradrenergic α_1 , and histamine H₁ receptors. Each of these receptors has been implicated in the modulation of ingestive behavior.

5-HT_{2A} receptor activation is not usually associated with a selective reduction in feeding behavior but most studies have used systemic administration of relatively nonselective agents that lead to non-selective disruption of ingestive responses (Simansky and Vaidya, 1990). 5-HT_{2C} receptor stimulation is associated with a reduction in feeding (Clifton, 1994) and 5-HT_{2C} receptor mutant mice develop an obesity syndrome (Tecott *et al*, 1995). Nevertheless, despite extensive studies using a variety of paradigms in both rats (Kennett *et al*, 1997) and mice (Hewitt *et al*, 2002), there is no evidence to suggest that administration of selective 5-HT_{2C} antagonists leads to a stimulation of ingestive behavior. In the rat, stimulation of noradrenergic α_1 receptors within the PVN is associated with reduction of feeding and diurnal changes in noradrenergic α_1 receptor binding have a clearly defined inverse association with diurnal changes in feeding (Morien *et al*, 1999). However, administration of noradrenergic α_1 receptor antagonists, such as prazosin, does not enhance feeding, although more general manipulations of the noradrenaline transporter may have this effect (Wellman, 2000). Finally, the histamine H₁ receptor is also implicated in the control of feeding behavior. Nonselective H₁ antagonists, such as cyproheptidine, enhance feeding behavior in the rat (Hartfield *et al*, 2003b), and H₁ agonists reduce feeding behavior (Morimoto *et al*, 2001). These studies suggest that the hyperphagic action of atypical antipsychotics may depend on their complex pharmacological profile. Such a conclusion would be consistent with the analyses of human data which have concluded that antipsychotic action at a single receptor can only provide a partial explanation for the association with human weight gain (Baptista, 2002; Kroeze *et al*, 2003).

Our data suggests that Intralipid consumption by rats following administration of an atypical antipsychotic may have some utility in predicting human weight gain as a consequence of antipsychotic-associated increases in appetite. Thus, the rank order for facilitation of Intralipid consumption, and for association with human weight gain is identical in our small drug sample. Risperidone and haloperidol represent two departures from accurate predic-

tion since both are associated with some human weight gain, but fail to enhance Intralipid consumption. As discussed above, this probably arises from the fact that weight gain may be enhanced by one of several independent mechanisms, and that these two potent dopamine D₂ receptor antagonists may induce weight gain as a consequence of longer-term endocrine changes, rather than through a stimulation of appetite.

In summary, we have demonstrated that several atypical antipsychotic drugs that are associated with human weight gain following chronic administration also stimulate Intralipid consumption in rats. Several other drugs with limited weight gain liability fail to enhance Intralipid consumption. The neurochemical mechanism for the effect on Intralipid consumption may involve antagonist action at 5-HT_{2C}, noradrenergic α ₁, and/or histamine H₁ receptors. Since treatment of humans with clozapine or olanzapine is also now known to be associated with stimulation of appetite, it seems possible that Intralipid hyperphagia in the rat may have some predictive value in assessing the liability of novel atypical compounds to affect body weight.

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