# Olanzapine and sibutramine have opposing effects on the motivation for palatable food

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**Both olanzapine and sibutramine target serotonergic and noradrenergic neurotransmission and influence body weight, but in opposite ways. The second-generation antipsychotic olanzapine, an antagonist at serotonergic and noradrenergic receptors, frequently induces weight gain as a side-effect, whereas sibutramine, a noradrenaline/serotonin reuptake inhibitor, is known as a weight-reducing agent. To investigate whether altered motivation for palatable food influences the effect of these drugs on body weight, we determined their effects on responding for sucrose pellets under a progressive ratio schedule of reinforcement in rats. We found that a low dose of olanzapine selectively increased responding to sucrose, without affecting free-feeding intake of sucrose. In contrast, sibutramine dose-dependently reduced responding to sucrose and similarly reduced free-feeding intake. Furthermore, coadministration of a dose of sibutramine that failed to affect responding to sucrose when administered alone prevented the increase in motivation by the effective dose of olanzapine. These data show that increased motivation for palatable food is likely to be a significant contributor to olanzapine-induced weight gain. Moreover, the ability of sibutramine to reduce this motivation for palatable food may play an important role in the efficacy of sibutramine as an add-on treatment to counteract olanzapine-induced weight gain. *Behavioural Pharmacology* 00:000–000 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Weight alterations are frequently observed with psychoactive drugs that target the serotonin (5-HT) and noradrenaline (NA) system (Malone, 2005). Olanzapine and sibutramine are two examples that show opposite effects on body weight.

Olanzapine is a second-generation antipsychotic drug, that is an antagonist at 5-HT and alpha-adrenergic receptors, as well as at several other receptors (Bymaster *et al.*, 1999). It is considered to be one of the most effective drugs on the market today for the treatment of schizophrenia and bipolar disorder (Scherk *et al.*, 2007; Smith *et al.*, 2007; Leucht *et al.*, 2009a, 2009b). Unfortunately, similar to other second-generation antipsychotics, the significant weight gain that frequently occurs as a side-effect is a major cause for concern (Parsons *et al.*, 2009). The exact mechanisms underlying olanzapine-induced weight gain remain unclear, but clinical reports suggest that altered eating behavior is a major component. Patients using second-generation antipsychotics frequently report an increase in appetite (Basson *et al.*, 2001; Costa e Silva *et al.*, 2001; Eder *et al.*, 2001; Kluge *et al.*, 2007) and seem more susceptible to hunger (Blouin *et al.*, 2008). Furthermore, it has been suggested that second-generation antipsychotics may induce craving for palatable foods and sugary drinks (Bromel *et al.*, 1998; Kluge *et al.*, 2007), with similar effects observed in certain animal studies (Cilia *et al.*, 2001; Zhang *et al.*, 2005b; Galistu *et al.*, 2011). Increased desire for high-calorie foods can have a marked impact on total caloric intake of patients and could therefore be an important contributing factor to antipsychotic-induced weight gain, although appropriate clinical studies are lacking to confirm this.

Sibutramine inhibits the reuptake of 5-HT, NA and, at higher doses, also of dopamine. Although it was originally designed as an antidepressant, it has mainly been used as a weight-loss drug (Luque and Rey, 2002). It is one of the drugs that has been successfully used as add-on treatment to counteract antipsychotic-induced weight gain in clinical trials (Henderson *et al.*, 2005; McElroy *et al.*, 2007). The

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mechanisms responsible for the attenuation of antipsychotic-induced weight gain by sibutramine are not entirely clear. However, a recent meta-analysis indicated that, in studies investigating the effects of mitigating agents on olanzapine-induced weight gain, predictors of weight loss were reductions in appetite, hunger, and craving for carbohydrates (Stauffer *et al.*, 2009). Indeed, sibutramine has been shown to reduce hunger and food intake in both humans and rodent models. However, to our knowledge it has not been investigated whether sibutramine also affects motivation for palatable food, independent of its effects on hunger or satiety (Jackson *et al.*, 1997; Grignaschi *et al.*, 1999; Chapelot *et al.*, 2000; Halford *et al.*, 2010).

On the basis of these clinical findings, we hypothesized that olanzapine increases the motivation for palatable food, whereas sibutramine reduces it. Second, we hypothesized that, when both drugs are coadministered, sibutramine attenuates the effect of olanzapine and that this mechanism plays a role in the efficacy of this drug to reduce olanzapine-induced weight gain. Moreover, as sibutramine acts as a reuptake inhibitor for NA and 5-HT, an interaction effect would suggest that NA and/or 5-HT receptors are involved in the effects of olanzapine on the motivation for palatable food.

To test these hypotheses, we first determined the effects of sibutramine and olanzapine on the motivation for palatable food in a rat model, using a progressive ratio (PR) schedule of reinforcement (Hodos, 1961; Richardson and Roberts, 1996; La Fleur *et al.*, 2007). Next, we examined the effect of combined administration of olanzapine and sibutramine. To further characterize the effects observed under the PR schedule, we also determined the effects of olanzapine and sibutramine in a 'free-feeding' paradigm in which rats no longer needed to work to obtain their food reward, but had free access to sucrose pellets for a limited time each day. Although the effects of antipsychotics on body weight appear more pronounced in female than in male rats (Boyda *et al.*, 2010), we preferred to use male rats, because feeding behavior in female rats is subject to larger variability because of their estrous cycle (Ter Haar, 1972; Blaustein and Wade, 1976).

## Methods

### Subjects

Male Wistar rats, weighing 275–300 g, were purchased from Charles River Laboratories (Crl-Wu, Sulzfeld, Germany). They were individually housed in a temperature and humidity-controlled room ($21 \pm 2^{\circ}$C) under a reversed 12 h/12 h light/dark cycle (lights on at 19 : 00 h). In their home cage, rats had free access to water and standard laboratory chow [CRM(E), Special Diet Services, Witham, Essex, UK] throughout the experiment to ensure that responding for palatable food was not affected by food restriction. Each experiment was performed in the dark phase, when rats are normally active and eat the most. All experimental procedures were approved by the Committee for Animal Experimentation of Utrecht University and were conducted in agreement with Dutch laws (Wet op de Dierproeven, 1996) and European regulations (Guideline 86/609/EEC).

### Training

#### *Operant conditioning*

To assess effects on the motivation to work for palatable food, rats were trained to lever-press for sucrose pellets under a PR schedule of reinforcement. We used 12 operant conditioning chambers designed for rats ($30.5 \times 24.2 \times 21.0$ cm; Med Associates, Georgia, Vermont, USA). Each chamber had a metal grid floor and was equipped with two retractable levers with white cue lights above them and a food pellet dispenser that could deliver 45 mg pellets (Noyes precision sucrose pellets, formula F, Research Diets, New Brunswick, New Jersey, USA) to a food tray. All chambers were contained in sound-attenuated and ventilated cabinets and were illuminated during sessions by a white house light. Data collection and processing was controlled by MED-PC software (Med Associates, Med Associates, Georgia, Vermont, USA).

Five days after arrival, training of rats was initiated with a shaping procedure, followed by seven sessions under a fixed ratio 1 schedule, with two sessions per day and allowing at least 3 h between sessions. During shaping, rats were placed in the operant cage for 60 min. Every minute the cue light above the active lever was switched on and a sucrose pellet was delivered. During fixed ratio sessions, each press on the active lever resulted in the delivery of one sucrose pellet, illumination of the cue light, and retraction of both levers. Twenty seconds after delivery of the pellet, the cue light was switched off and the levers were reinserted into the chamber. Responding on the inactive lever was recorded, but had no programmed consequences. Sessions lasted 30 min or until rats earned 60 rewards. Next, rats were switched to a PR schedule with one session a day. Under a PR schedule, the cost of a reward is progressively increased over successive trials to determine the amount of work the rat is willing to perform to acquire it. The response requirement for each reward increased as follows (Roberts and Bennett, 1993; Richardson and Roberts, 1996): response = formula $(5 \times e^{0.2 \times \text{reward number}})$-5, resulting in the following series: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 603, 737, etc. Each session ended when the rat failed to earn a reward within 60 min. The number of rewards earned at the end of the session was termed 'breakpoint', which can be interpreted as a measure of the motivational value of the reward. Responding was considered stable when the number of earned sucrose pellets did not differ more than 20% for three sessions. Most rats stabilized within five to 10 sessions; therefore, we proceeded with injections after 2 weeks of training. At this point, the ratio of inactive to active lever presses was $\sim$1.6% on average ($\sim$4.5 lever presses per session), indicating that rats had learned to respond specifically on the active lever.

#### *Free feeding*

This paradigm was used to test the effects of drug administration on intake of freely available sucrose. Rats were placed in test cages for 60 min each day. These cages were identical to the home cage but contained only bedding and a hopper filled with sucrose pellets (identical to those used for operant conditioning). Food hoppers were weighed before and after each session to quantify sucrose intake. After 2 weeks of training, we proceeded with drug administration.

#### *Experiment 1: effects on operant responding for sucrose pellets*

For this experiment, a total of 36 rats were trained in operant cages to respond for sucrose pellets under a PR schedule of reinforcement. The experiment was performed in two runs: the first group of 12 rats received olanzapine injections only, the second group of 24 rats also received sibutramine injections. Rats were given an intraperitoneal (i.p.) injection of saline 30 min before training on two separate days to habituate them to i.p. injections. Next, all rats ($n = 36$) received three injections of olanzapine (0.1, 0.3, and 1 mg/kg) and a saline injection (according to a Latin square design), serving as their own control (experiment 1A).

After determining the dose–response curve for olanzapine, the 24 rats of the second experimental run received injections of sibutramine (0.1, 0.3, and 1 mg/kg) and saline according to a Latin square design (experiment 1B).

On the basis of the results of experiment 1A and 1B, we chose to test the effect of combined administration of the effective dose of olanzapine, which significantly increased breakpoint (0.1 mg/kg), and the subeffective dose of sibutramine, that is, the highest dose that did not affect breakpoint (0.3 mg/kg). Therefore, the same rats ($n = 24$) received an injection of olanzapine followed by sibutramine and, as a control, saline followed by saline (experiment 1C).

#### *Experiment 2: effects on operant responding for fat-enriched pellets*

To investigate whether the effect of olanzapine might be more pronounced on operant responding for fatty palatable food, an additional pilot experiment was performed in which we determined the dose–response curve for olanzapine using a method identical to that of experiment 1A but using 12 rats that had to lever-press for fat-enriched pellets (13.7% fat; Omni Treat tab, Richmond Indiana, USA) instead of sucrose pellets.

#### *Experiment 3: effects on free-feeding intake of sucrose pellets*

For this experiment, 24 naïve rats were trained in the free-feeding paradigm. Rats received a saline injection (i.p.) 30 min before access to the sucrose pellets on two separate days to habituate animals to the i.p. injection procedure. Next, each rat received injections of olanzapine (0.03, 0.1, and 0.3 mg/kg) and a saline injection according to a Latin square design (experiment 3A). Finally, each rat received injections of sibutramine (0.1, 0.3, and 1 mg/kg) and saline according to a Latin square design (experiment 3B).

### Drugs

Olanzapine (Chempacific Corp., Baltimore, Maryland, USA) was dissolved in a minimum quantity of 1 mol/l hydrochloric acid and diluted with saline, after which pH was set to ~5.5 with 1 mol/l NaOH. The obtained stock solution of 3 mg/ml was aliquoted and stored at −20°C. On injection days, aliquots were defrosted and diluted to the required concentrations. The highest dose of olanzapine (1 mg/kg) was chosen on the basis of a pilot experiment that revealed a marked reduction in operant responding at a dose of 3 mg/kg, most likely because of sedation. All injections of olanzapine were administered i.p. 1 h before testing, with a minimum of 3 days between injections.

Sibutramine hydrochloride (Tocris Bioscience, Bristol, England, UK) was dissolved in slightly warmed saline to obtain a solution of 1 mg/ml (calculated as base), which was further diluted with saline as necessary. Because we were interested in determining the effects of sibutramine that were independent of its effects on hunger and satiety, the highest dose was chosen on the basis of previous experiments in our laboratory that revealed significant effects on total food intake only at doses of 3 mg/kg or higher. All injections of sibutramine were administered 30 min before testing (i.p.) with a maximum of one injection per week. All injection volumes were 1 ml/kg, and a washout period of at least 1 week was included after each dose–response curve experiment.

### Data analysis

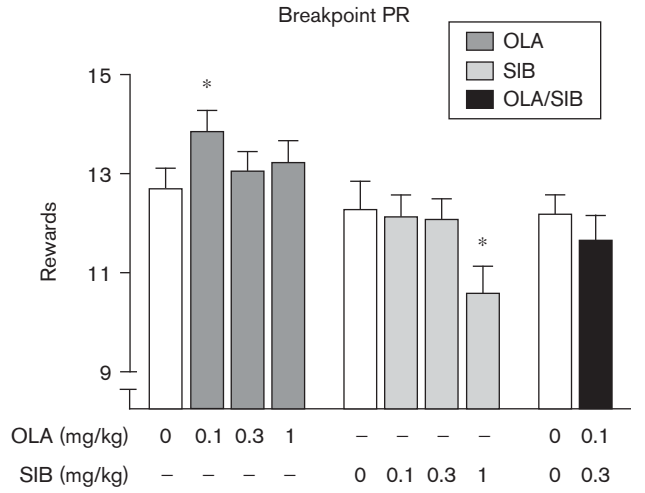
All data are presented as mean values ± SEM. Effects on PR performance (breakpoint) are presented as the number of rewards obtained in the session after each injection. Effects on free-feeding intake are presented as change in sucrose intake compared with control injection. Statistical analysis was performed using SPSS software (version 15.0 for Windows, SPSS Inc., Chicago, Illinois, USA). Because the data were not normally distributed, nonparametric tests were used. Data from each experiment were first analyzed by Friedman's analysis of variance. Where appropriate, this was followed by a two-tailed Wilcoxon signed rank test between each treatment condition versus the control condition. Findings were considered as statistically significant if $P$ value was less than 0.05.

## Results

### Experiment 1

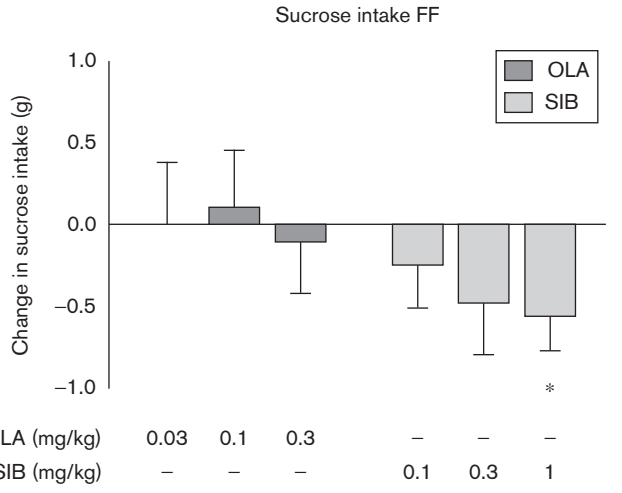
Olanzapine significantly affected breakpoint (the number of rewards obtained) in experiment 1A [Fig. 1; $\chi^2(3) = 9.9$, $P = 0.018$]. Post-hoc tests revealed that this was due to the effect of the lowest dose of 0.1 mg/kg, which caused a significant increase in breakpoint to work for sucrose

**Fig. 1**




Effects of administration of olanzapine (OLA) and sibutramine (SIB), alone or in combination, on operant responding for sucrose pellets under a progressive ratio schedule of reinforcement in experiment 1. Data are expressed as mean (±SEM) number of rewards earned at the end of the test sessions. *$P$ less than 0.05 versus saline injection.

**Fig. 2**




Effects of olanzapine (OLA) and sibutramine (SIB) on free feeding of sucrose pellets in experiment 3. Data are expressed as change in sucrose intake compared with control injection (mean ± SEM). *$P$=0.015.

pellets ($Z = -2.90$, $P = 0.002$). At higher doses, this effect was no longer significant (Fig. 1). In both of the experimental runs the largest increase in breakpoint was observed at the lowest dose of olanzapine administered; thus, we could not exclude effects occurring at even lower doses. However, after completing the first dose–response experiment (1A), we additionally tested the dose of 0.03 mg/kg of olanzapine against saline injection ($n = 24$); this dose had no effect on breakpoint for sucrose pellets (data not shown), indicating that the 0.1 mg/kg dose was indeed the dose resulting in the maximal effect on operant responding.

In experiment 1B sibutramine decreased responding for sucrose pellets [Fig. 1; $\chi^2(3) = 12.1$, $P = 0.006$], but this effect was only significant at a dose of 1 mg/kg ($Z = -2.53$, $P = 0.01$; Fig. 1). Responding on the inactive lever presses was not significantly affected by either sibutramine or olanzapine (data not shown).

When olanzapine (0.1 mg/kg) was followed by administration of the subeffective dose of sibutramine (0.3 mg/kg) in experiment 1C, it no longer affected breakpoint compared with control injections ($Z = -1.30$, $P = 0.21$; Fig. 1).

### Experiment 2

In this pilot experiment, in which rats lever-pressed for fat-enriched pellets instead of sucrose pellets, the dose–response curve of olanzapine exhibited an inverted-U shape, with a maximum effect observed at the 0.1 mg/kg dose (average increase of 1.1 rewards ± 0.8). Although the effect failed to reach significance because of the limited number of animals [$\chi^2(3) = 4.24$, $P = 0.2$], the shape of the dose–response curve of olanzapine was remarkably similar to that observed for sucrose pellets in experiment 1A (data not shown). Because the effect on operant responding for fat-enriched pellets in this pilot experiment was also of comparable magnitude, only sucrose pellets were used for the rest of the study.

### Experiment 3

In experiment 3A, free-feeding intake of sucrose pellets after saline injection was 4.0 ± 0.4 g. Administration of olanzapine failed to show any significant effects (Fig. 2). In experiment 3B, sucrose intake after saline injection was 5.3 ± 0.4 g. Sibutramine dose-dependently reduced the intake of sucrose pellets [$\chi^2(3) = 12.3$, $P < 0.01$]. As in experiment 1B, this effect was only significant for the 1 mg/kg dose ($Z = -2.51$, $P = 0.03$). Because olanzapine failed to show any effect in this paradigm we did not investigate the effects of combined administration.

## Discussion

In this study, we investigated the effects of the second-generation antipsychotic drug olanzapine and the weight-loss drug sibutramine on the motivation to work for palatable food in male rats. We found that olanzapine increased operant responding for sucrose pellets under a PR schedule of reinforcement, whereas sibutramine dose-dependently reduced operant responding, indicating an opposite effect of these two drugs on the motivation to work for palatable food. With combined administration, the effect of olanzapine on operant responding was counteracted by a dose of sibutramine that failed to affect motivation significantly when administered alone, which suggests that both drugs affect motivation for palatable food through interacting mechanisms.

It has been shown previously that rats increase their motivation to work for food when they are food restricted, if the palatability of the food is increased, and after administration of certain drugs such as opioids (Hodos, 1961; Solinas and Goldberg, 2005). In these cases, intake of food is also increased under conditions in which animals are not required to perform any demanding tasks to obtain it (Kelley *et al.*, 2002; Barbano *et al.*, 2009). In contrast, certain pharmacological manipulations selectively affect the motivation to perform a demanding task to earn a food reward, without any effects on the intake of freely available food – for example, dopamine depletion in the nucleus accumbens (Salamone and Correa, 2002). Thus, drug effects on motivation for food and on free-feeding intake can occur through overlapping but distinct neural and behavioral mechanisms. We previously found that olanzapine increases chow intake only after acute administration of doses of 0.3 mg/kg or higher (E.M. van der Zwaal, S.E. La Fleur, R.A.H. Adan *et al.*, unpublished data). In the present study, however, a lower dose of 0.1 mg/kg increased motivation for sucrose. Moreover, we failed to observe an effect on free-feeding intake of sucrose. Taken together, this implies that olanzapine, at low doses, selectively affects the motivation to work for palatable food.

The lack of effect on free-feeding intake of sucrose argues against an effect of olanzapine on the perceived palatability of the sucrose pellets. This is in line with our previous finding that olanzapine did not affect the intake of a sucrose solution when rats were offered a diet choice in their home cage (van der Zwaal *et al.*, 2010). It is also consistent with two clinical studies that failed to observe any difference in food choice in patients treated with second-generation antipsychotics (Gothelf *et al.*, 2002; Henderson *et al.*, 2006). Therefore, olanzapine-treated patients may not have increased preference for palatable foods; yet, when they do experience a desire for these foods, they are more likely to perceive it as 'craving' and willing to put in more effort to fulfill their desire. The subsequent increase in (high calorie) food intake may be one of the pathways through which olanzapine induces weight gain, although it appears that additional mechanisms also play a role (Cooper *et al.*, 2007; van der Zwaal *et al.*, 2010).

Contrary to olanzapine, sibutramine caused a decrease in breakpoint when rats responded for sucrose under a PR schedule, indicating a reduction in motivation for sucrose. However, under free-feeding conditions, sibutramine also significantly reduced intake of sucrose pellets, which suggests that the effect of sibutramine on motivation may have been secondary to effects on perceived palatability or satiation. Previous studies in rats indicate that sibutramine does not affect regular food intake at doses lower than 2 mg/kg (Jackson *et al.*, 1997; Grignaschi *et al.*, 1999); yet, in the present study we already observed an effect on sucrose intake at a dose of 1 mg/kg. Similarly, a number of other studies that offered food that was more palatable than standard laboratory chow also reported reductions in food intake after administering doses of sibutramine that were lower than 2 mg/kg (Cifani *et al.*, 2009; Tallett *et al.*, 2009; Pratt and Connolly 2010; Higgs *et al.*, 2011). Taken together, these findings suggest that sibutramine affects palatable feeding at doses that are lower than those that affect regular food intake. Additional studies would be necessary to confirm whether sibutramine may affect the perceived palatability of food independently of effects on satiety – for example, observation of hedonic reactions (Berridge and Kringelbach, 2008).

After combined administration, a low dose of sibutramine (0.3 mg/kg), which failed to affect operant responding or free-feeding intake of sucrose when administered alone, was able to prevent the increase in breakpoint observed after olanzapine administration (0.1 mg/kg). Although it is not possible to fully exclude effects of treatment history on the data of the present study, the lack of effect of olanzapine on breakpoint when combined with administration of a subeffective dose of sibutramine suggests that antagonism of olanzapine at NA and/or 5-HT receptors (Bymaster *et al.*, 1999) may be involved in its effect on motivation for sucrose. Similar to sibutramine, the 5-HT releaser fenfluramine and the 5-HT reuptake inhibitor fluoxetine have been shown to reduce operant responding for palatable food in sated animals (Evenden and Ko, 2007; Sanders *et al.*, 2007), and there are studies suggesting that the 5-$HT_{2C}$ receptor plays a role in this effect (Ward *et al.*, 2008; Higgs *et al.*, 2011). Similarly, the NA reuptake inhibitor thionisoxetine reduces free-feeding intake of palatable food (Rowland *et al.*, 2000), although, to our knowledge, the role of specific NA receptor subtypes in the motivation for palatable food has not been investigated. Investigation of transporter occupancy after administration of sibutramine to rats previously showed that, at a dose of 1 mg/kg, occupancy of NA transporters was ~35%, whereas that of 5-HT transporters was only 3% (Thomas *et al.*, 2009). Thus, NA receptors are more likely than 5-HT receptors to be involved in the effects of olanzapine and sibutramine on food motivation observed in the present study (Bymaster *et al.*, 1996).

Considering the inverted-U shape of the olanzapine dose–response curve, it is relevant to ask whether the attenuation of the effect of the effective dose of olanzapine by sibutramine in this study could be due to potentiation of this dose by sibutramine (e.g. by increasing plasma levels or enhancing the sedative effects of olanzapine). However, previous data from our laboratory showed that sibutramine did not enhance the effect of olanzapine on observed locomotor activity (S.K. Janhunen, S.E. La Fleur, R.A.H. Adan, unpublished). Furthermore, therapeutic doses of sibutramine failed to alter the pharmacokinetic properties of therapeutic doses of olanzapine in a 10-day study in humans (*www.rxabbott.com/pdf/meridia.pdf*), making a pharmacokinetic

interaction less likely, especially at the low doses used in the present study. Nevertheless, further studies are necessary to confirm whether NA and/or 5-HT receptors play a role in the effect of olanzapine on food motivation.

Although olanzapine administration caused a significant increase in responding for sucrose, this effect was only significant at the dose of 0.1 mg/kg. Doses that were both higher and lower than 0.1 mg/kg failed to increase breakpoint significantly, whereas we observed a marked decrease in breakpoint when a dose of 3 mg/kg was administered (data not shown). A similar pattern was observed in the pilot experiment using fat-enriched pellets instead of sucrose pellets and also in a study using marmosets that reported an increase in operant responding (PR schedule) for banana milkshake at a dose of 0.05 mg/kg olanzapine, but not at higher or lower doses (Cilia *et al.*, 2001). Therefore, the dose–response curve of olanzapine in this paradigm appears to have an 'inverted-U' shape. A similar curve has also been described previously for the effects of olanzapine on food intake (Cooper *et al.*, 2005), as well as for the effect of clozapine (a second-generation antipsychotic closely related to olanzapine) on the motivation for milkshake and sucrose (Cilia *et al.*, 2001; Zhang *et al.*, 2005b; Galistu *et al.*, 2011).

In previous experiments, we observed reduced locomotor activity for more than 2 h after acute administration of doses of olanzapine of 0.3 mg/kg or higher (E.M. van der Zwaal, S.E. La Fleur, R.A.H. Adan, unpublished data), most likely because of sedative side-effects for which rats appear very sensitive (Ahnaou *et al.*, 2003). We therefore believe that at higher doses the ability to make the number of required responses within the available time may be compromised because of sedation. This possibility has been previously suggested by researchers who administered olanzapine to female rats responding for a sucrose reinforcer (Zhang *et al.*, 2005a). Although they failed to observe an increase in breakpoint at doses varying from 0.25 to 1 mg/kg, their mathematical model used to analyze lever-pressing speed indicated that administration of olanzapine enhanced the efficacy of the reinforcer, and that it also reduced motor capacity, which limited the effects on breakpoint (for details on this mathematical model see Zhang *et al.*, 2005a). Therefore, in the paradigm used in the present study, a dose of 0.1 mg/kg olanzapine appears high enough to increase motivation for palatable food but low enough to prevent confounding of this effect by sedation.

In summary, this study shows that olanzapine and sibutramine have opposing effects on the motivation of rats to work for palatable food. Moreover, a low dose of sibutramine was able to counteract the effect of olanzapine, suggesting involvement of NA and/or 5-HT receptors in this effect. As alterations in motivation to work for palatable food may significantly influence total caloric intake, this mechanism is likely to contribute to the weight gain induced by olanzapine and to the weight-reducing effects of sibutramine.

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### Conflicts of interest

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