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## Reducing olanzapine-induced weight gain side-effect by using betahistine: a study in the rat model

Chao Deng

*University of Wollongong, chao@uow.edu.au*

Jiamei Lian

*University of Wollongong, jl841@uowmail.edu.au*

Nagesh Brahmavar Pai

*University of Wollongong, nagesh@uow.edu.au*

Xu-Feng Huang

*University of Wollongong, xhuang@uow.edu.au*

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## Reducing olanzapine-induced weight gain side-effect by using betahistine: a study in the rat model

### Abstract

Olanzapine is effective at treating multiple domains of schizophrenia symptoms. However, it induces serious metabolic side effects. Antipsychotic drug's antagonistic affinity to histamine H1 receptors has been identified as a main contributor for weight gain/obesity side effects. This study therefore investigated whether a combined treatment of betahistine (a H1 receptor agonist and H3 receptor antagonist) could reduce the body weight/obesity induced by olanzapine. Female Sprague Dawley rats were treated orally with olanzapine (1 mg/kg, t.i.d.) and/or betahistine (2.67 mg/kg, t.i.d.), or vehicle for two weeks. Rats treated with olanzapine exhibited significant body weight gain and increased food intake. Co-treatment of olanzapine with betahistine significantly prevented (-45%) weight gain and reduced feeding efficiency compared to sole olanzapine treatment. Betahistine treatment alone had no effect on weight gain and food intake. Olanzapine reduced locomotor activity, but not betahistine. These findings demonstrate that olanzapine-induced body weight gain can partially be reduced by co-treatment with betahistine. Betahistine has H3 receptor antagonistic effects to increase histamine release, which may augment its direct agonistic effects on H1 receptors. These findings have important implications for clinical trials using betahistine to control antipsychotic-induced obesity side effects.

### Keywords

rat, weight, model, induced, effect, gain, betahistine, reducing, study, olanzapine, side

### Disciplines

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**Title:** Reducing olanzapine-induced weight gain side-effect by betahistine: A study in the rat model

**Running title:** Betahistine reduces olanzapine-induced weight gain

**Authors:** Chao Deng<sup>1,2,4\*</sup>, Jiamei Lian<sup>1,2</sup>, Nagesh Pai<sup>2,3</sup>, Xu-Feng Huang<sup>1,2,4</sup>,

1: Centre for Translational Neuroscience, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia

2: Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, 2522 NSW, Australia

3: Graduate School of Medicine, University of Wollongong, NSW 2522, Australia

4: Schizophrenia Research Institute, 384 Victoria Street, Darlinghurst, 2010, NSW, Australia

**\*Corresponding author:**

Dr Chao Deng, Illawarra Health and Medical Research Institute, Wollongong, 2522, NSW, Australia

E-mail: chao@uow.edu.au, Tel: (+61 2) 4221 4934, Fax: (+61 2) 4221 8130

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**Abstract**

Olanzapine is effective at treating multiple domains of schizophrenia symptoms. However, it induces serious metabolic side-effects. Antipsychotic drug's antagonistic affinity to histamine H<sub>1</sub> receptors has been identified as a main contributor for weight gain/obesity side-effects. This study therefore investigated whether a combined treatment of betahistine (a H<sub>1</sub> receptor agonist and H<sub>3</sub> receptor antagonist) could reduce the body weight/obesity induced by olanzapine. Female Sprague Dawley rats were treated orally with olanzapine (1 mg/kg, t.i.d) and/or betahistine (2.67 mg/kg, t.i.d.), or vehicle for two weeks. Rats treated with olanzapine exhibited significant body weight gain and increased food intake. Co-treatment of olanzapine with betahistine significantly prevented (-45%) weight gain and reduced feeding efficiency compared to sole olanzapine treatment. Betahistine treatment alone had no effect on weight gain and food intake. Olanzapine reduced locomotor activity, but not betahistine. These findings demonstrate that olanzapine-induced body weight gain can partially be reduced by co-treatment with betahistine. Betahistine has H<sub>3</sub> receptor antagonistic effects to increase histamine release, which may augment its direct agonistic effects on H<sub>1</sub> receptors. These findings have important implications for clinical trials using betahistine to control antipsychotic-induced obesity side-effects.

**Key words:** Antipsychotic; olanzapine; betahistine; weight gain; food intake; locomotor activity

## **Introduction**

Second generation antipsychotic drugs (SGAs) currently form the first line of treatment for schizophrenia (Leucht et al., 2009; Komossa et al., 2010c), and have also been widely used to control other mental disorders, such as bipolar disorder, dementia, major depression, and Tourette's syndrome (Depping et al., 2010; Komossa et al., 2010a; Komossa et al., 2010b; Zuddas et al., 2011). Among them, olanzapine has proven efficacy to treat schizophrenia with enhanced tolerability compared to older first generation antipsychotics (Lieberman et al., 2005; Balu et al., 2008). Its most serious side-effects, however, are substantial weight gain, increased adiposity and other metabolic disorders including hyperlipidemia, hyperglycemia and type II diabetes mellitus (Nasrallah, 2008; Patel et al., 2009; Komossa et al., 2010c; Correll et al., 2011; Osuntokun et al., 2011). The recent CAFE (Comparison of Atypicals for First-Episode Psychosis) study reported that after 12 weeks of treatment, significant weight gain ( $\geq 7\%$  body weight) occurred in a large number of schizophrenia patients treated with olanzapine (59.8%), compared to risperidone (32.5%) and quetiapine (29.2%). Furthermore, the same investigators found that after 52 weeks of treatment, 80% of olanzapine-treated patients gained  $\geq 7\%$  body weight, compared to 57.6% risperidone and 50% quetiapine-treated patients (Patel et al., 2009). Metabolic dysfunction is a significant issue that needs to be addressed in both scientific and clinical research as it

may lead to further complications such as cardiovascular disease, non-compliance with medication and premature death (by 20-30 years) (Haupt et al., 2005; Stahl et al., 2009).

SGAs have binding affinities for various neurotransmitter receptors, such as dopamine D<sub>2</sub>, serotonin 5HT<sub>2A</sub> and 5HT<sub>2C</sub>, adrenergic  $\alpha_{1-2}$ , muscarinic M<sub>1</sub> and M<sub>3</sub> and histamine H<sub>1</sub> receptors (Nasrallah, 2008). Accumulated evidence revealed that antagonistic properties of H<sub>1</sub>, 5HT<sub>2C</sub> and muscarinic receptors are involved in antipsychotic-induced weight gain/obesity (Kroeze et al., 2003; Matsui-Sakata et al., 2005; Kirk et al., 2009; Reynolds and Kirk, 2010; Weston-Green et al., 2012). In particular, H<sub>1</sub> receptor antagonism has been identified as the main contributor to olanzapine/clozapine-induced body weight gain/obesity side-effects (Matsui-Sakata et al., 2005; Correll, 2008; Lian et al., 2010). A recent study in a rat model showed that short (1 week) and long (12 weeks) term treatment of olanzapine significantly reduced H<sub>1</sub> receptor mRNA expression in the hypothalamic arcuate nucleus (Arc) and ventromedial hypothalamic nucleus (VMH) (Han et al., 2008). It is interesting that H<sub>1</sub> receptor mRNA expression in the Arc showed a significant negative correlation with food intake and fat pad mass (Han et al., 2008). It is reported that olanzapine can directly modulate histaminergic neurotransmission, which is correlated with the regulation of feeding behaviour of rats (Davoodi et al., 2008). Kim and colleagues (2007) found that olanzapine and clozapine activate

hypothalamic AMPK (5' adenosine monophosphate-activated protein kinase) via H<sub>1</sub> receptors to increase food intake and body weight gain (Kim et al., 2007).

The key issue is how to control the antipsychotic-induced body weight gain/obesity side-effect. Since the antagonistic affinity of antipsychotics to H<sub>1</sub> receptors is the major contributor to the weight gain/obesity side-effect, it would be reasonable to combat this side-effect using a H<sub>1</sub> receptor agonist. In addition, the histamine H<sub>3</sub> receptor can act as an histamine autoreceptor and is implicated in the control of food intake via regulation of histamine release (Deng et al., 2010). Therefore, an agent with the properties of both a H<sub>1</sub> receptor agonist and H<sub>3</sub> receptor antagonist would be a good candidate drug to reduce antipsychotic-induced weight gain/obesity. Betahistine is a structural analogue of histamine and has both H<sub>1</sub>-agonistic and H<sub>3</sub>-antagonistic activity in the brain (Fossati et al., 2001; Barak, 2008), therefore has a potential for weight management. Importantly, betahistine has a very high safety profile, having been prescribed to over 130 million patients for the treatment of vestibular disorders since its registration in 1968, with a remarkably low rate (~1:100000) of reported adverse drug reaction (Jeck-Thole and Wagner, 2006). Therefore, we investigated the effects of betahistine on attenuating the body weight gain side-effect induced by olanzapine in a well-established animal model (Huang et al., 2006; Han et al., 2008; Weston-Green et al., 2011).

## **Materials and Methods**

### **Animals and Housing**

Forty-eight female Sprague–Dawley rats (201-225 g) were obtained from the Animal Resources Centre (Perth, WA, Australia). Rats were housed in pairs for 1 week prior to the start of the studies for their adaptation to the new environment, and then housed in individual cages under environmentally controlled conditions (22°C, light cycle from 07:00 to 19:00 and dark cycle from 19:00 to 07:00). They were allowed *ad-libitum* access to water and standard laboratory chow diet (3.9 kcal/g; 10% fat, 74% carbohydrate and 16% protein) throughout the whole experiment. All experimental procedures were approved by the Animal Ethics Committee, University of Wollongong, Australia, and complied with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (2004).

### **Drug Treatment**

Prior to drug treatment, rats were trained to self-administer a sweet cookie dough pellet (0.3 g) without drugs twice per day for one week. Rats were randomly assigned to one of following treatments (n=12/group) for two weeks: (1) olanzapine only (1 mg/kg, t.i.d.; Eli Lilly, USA) treatment, (2) betahistine only (2.67 mg/kg, t.i.d.; Manus Aktteva, India) treatment, (3) combined olanzapine and betahistine (O+B) treatment, or (4) control (vehicle). The pellets with drugs were made prior to administration by mixing droplets



of water with cookie dough powder (containing 30.9% cornstarch, 30.9% sucrose, 6.3% gelatine, 15.5% casein, 6.4% fibre, 8.4% minerals, and 1.6% vitamins) (Deng et al., 2007; Han et al., 2008; Weston-Green et al., 2011). Controls received an equivalent pellet without the drug. Rats were observed during treatment administration to ensure complete consumption of the medication pellet. In the rat, the half-life of olanzapine is 2.5 hours in the plasma and 5.1 hours in the brain, however levels are still high after 8 hours (Aravagiri et al., 1999), comparing to the half-life of 24.2 hours in the plasma and 72 hours in the brain of humans (Tauscher et al., 2002). Therefore, in the present study rats were administered olanzapine three times/day to ensure a consistently high concentrations to better mirror the human scenario of oral administration once per day. Body weight, food intake and water intake of rats were measured once every two days.

### **Open Field Test**

An open field test was performed on day 12 of drug treatment in order to determine whether olanzapine and/or betahistine could influence the locomotor activity of rats. A rat was placed in the centre of a black rectangular arena (60 × 60 cm<sup>2</sup>, 40 cm high) that was exposed to an average lighting of 25 lux. A video camera was used to record the behaviour of the rats for 30 minutes from the top of the arena. The locomotor activity of the rats was analysed using EthoVision Color-Pro software (Noldus Information Technology, Wageningen, the Netherlands) (du Bois et al., 2008; Weston-Green et al.,

2011). The distance moved (cm) and velocity (cm/s) were measured. In 10 rats (one from control, five from olanzapine only and four from O+B groups), behavioural data was not recorded due to video camera failure.

### **Adiposity Measurements**

Following two weeks treatment, all rats were sacrificed by carbon dioxide asphyxiation after 24 hours from the last drug treatment. Post-mortem white adipose tissue (WAT) including perirenal, periovary and inguinal fat, as well as sub-scapular brown adipose tissue (BAT) were dissected and individually weighed (g) (Olds and Olds, 1979).

### **Statistical Analysis**

Statistical analysis was performed using SPSS (Windows version 17.0, SPSS Inc., Chicago). The Kolmogorov-Smirnov test was used to examine the distribution of data from all experiments. Two-way ANOVAs (OLANZAPINE  $\times$  BETAHISTINE) were used to examine behaviour and fat mass data. Three-way repeated ANOVAs (OLANZAPINE  $\times$  BETAHISTINE  $\times$  TIME as repeated measures) were applied to examine accumulated weight gain, food and water intake data. Multiple comparisons were performed using *post-hoc* Dunnett-T tests. Pearson's or Spearman's correlation tests were used to assess the relationships among these measurements. All data were expressed as mean  $\pm$  SEM, and statistical significance was accepted when  $p < 0.05$ .

## **Results**

### **Body Weight Gain**

Three-way repeated ANOVAs (OLANZAPINE × BETAHISTINE × TIME as repeated measures) showed significant main effects of TIME ( $F_{7,308}=145.68$ ,  $p<0.001$ ), and OLANZAPINE factors ( $F_{1,44}=31.89$ ,  $p<0.001$ ), but no effect of the BETAHISTINE factor ( $F_{1,44}=3.17$ ,  $p>0.05$ ) on accumulated body weight gain (Figure 1A). There were significant interactions between the OLANZAPINE factor and TIME ( $F_{7,308}=19.49$ ,  $p<0.001$ ), between the OLANZAPINE and BETAHISTINE factors ( $F_{1,44}=3.96$ ,  $p=0.053$ ), as well as among all three factors ( $F_{7,308}=2.99$ ,  $p<0.01$ ). Post-hoc tests showed that body weight gain during the two weeks period was significantly greater in the olanzapine only group ( $p<0.01$ ) compared to controls from day 4 (Figure 1A). Further analyses revealed that olanzapine treatment significantly increased body weight gain, occurring after four days of treatment with olanzapine and lasting for the entire treatment period (all  $p<0.01$ ). There was a significant increase in total body weight gain following olanzapine treatment compared to control ( $p<0.01$ ) (Table 1). Olanzapine plus betahistine (O+B) co-treatment groups had significantly lower body weight gain than the sole olanzapine group after two weeks treatment ( $p<0.05$ ) (Figure 1A, Table 1). However, no significant difference was demonstrated between the controls and sole

betahistine treated rats (Figure 1A, Table 1). Therefore, co-treatment with betahistine was effective at reducing the body weight gain side-effect induced by olanzapine.

### **Food Intake and Feeding Efficiency**

There were significant main effects of the OLANZAPINE factor ( $F_{1,42}=22.67$ ,  $p<0.001$ ) and TIME ( $F_{6,252}=4106.67$ ,  $p<0.001$ ), as well as significant interactions between TIME and the OLANZAPINE factors ( $F_{6,252}=21.15$ ,  $p<0.001$ ), and between TIME and the BETAHISTINE factors ( $F_{6,252}=2.59$ ,  $p<0.05$ ) (Figure 1B). Post-hoc analysis revealed that the accumulated food intake of rats significantly increased in the olanzapine only group (+15%;  $p<0.01$ ) compared to controls from day 4 (Figure 1B). Further analysis indicated significantly greater accumulated food intake after four days of olanzapine only treatment compared to controls ( $p<0.05$ ). There were significant effects of the OLANZAPINE factor ( $F_{1,42}=25.38$ ,  $p<0.001$ ) and interaction between the OLANZAPINE and BETAHISTINE factors ( $F_{1,42}=8.77$ ,  $p<0.01$ ) on feeding efficiency (accumulated body weight gain/accumulated food intake) (Figure 1C). Compared to the control group, feeding efficiency was significantly increased in the olanzapine treated group ( $p<0.01$ ) and O+B co-treatment group ( $p<0.05$ ), but not the betahistine treatment group ( $p>0.05$ ) (Figure 1C). It is important that, compared to the sole olanzapine treatment group, O+B co-treatment significantly reduced feeding efficiency (-31%;

$p < 0.05$ ). Therefore, co-treatment with betahistine was able to prevent the increasing feeding efficiency caused by olanzapine treatment.

### **Fat Deposits**

There were significant effects of the OLANZAPINE factor on the perirenal ( $F_{1,44}=8.50$ ,  $p < 0.01$ ), periovary ( $F_{1,44}=6.29$ ,  $p < 0.05$ ), inguinal ( $F_{1,44}=17.48$ ,  $p < 0.001$ ) fat mass, and total white fat mass ( $F_{1,44}=13.38$ ,  $p = 0.001$ ), but no difference was found in sub-scapular brown fat mass. Post-hoc analysis revealed a significantly higher inguinal fat mass following sole olanzapine treatment ( $p < 0.05$ ) and O+B co-treatment ( $p < 0.05$ ) compared to control (Table 1). A significant difference in inguinal fat mass was also found between the co-treatment group and betahistine only treated rats ( $p < 0.01$ ). The olanzapine group had more total white fat mass than the control group ( $p = 0.058$ ). However, the O+B co-treatment group showed less periovary fat and intra-abdominal fat than the olanzapine group, but not significant ( $p > 0.05$ , Table 1).

### **Water Intake**

There was a significant main effect of TIME ( $F_{6,264}=1415.89$ ,  $p < 0.001$ ), but not the OLANZAPINE factor ( $F_{1,44}=0.19$ ,  $p > 0.05$ ) and BETAHISTINE factor ( $F_{1,44}=0.56$ ,  $p > 0.05$ ). There was also no interaction between the OLANZAPINE and BETAHISTINE factors ( $F_{1,44}=1.55$ ,  $p > 0.05$ ), or among all three factors ( $F_{6,264}=1415.89$ ,

$p > 0.05$ ) (Figure 1D) (Table 1). Therefore, both olanzapine and betahistine had no effect on water intake.

### **Locomotor Activity**

There was a significant effect of the OLANZAPINE factor on distance moved ( $F_{1,34}=23.28$ ,  $p < 0.001$ ), but no effect of the BETAHISTINE factor ( $F_{1,34}=0.06$ ,  $p > 0.05$ ), and also no significant interaction between the two factors on distance moved ( $F_{1,34}=3.64$ ,  $p > 0.05$ ) (Figure 2). Post-hoc analysis showed a significant decrease in the distance moved in the O+B co-treatment group ( $p < 0.01$ ) and a tendency for a decrease in the olanzapine treatment ( $p = 0.067$ ) compared to the control (Figure 2B). In terms of velocity, a significant effect was found only in the OLANZAPINE factor ( $F_{1,34}=26.03$ ,  $p < 0.001$ ). Compared to the control, the rats with O+B co-treatment ( $p < 0.01$ ) and sole olanzapine treatment ( $p < 0.05$ ) had a significantly lower velocity (Figure 2C). However, there was no significant difference between the O+B and olanzapine treatment in both distance moved and velocity ( $p > 0.05$ ). Betahistine treatment had no effect on both distance moved and velocity ( $p < 0.05$ ).

### **Correlations among body weight, food intake, fat and behavior data**

There were highly significant correlations between total body weight gain and total food intake ( $r = 0.702$ ,  $p < 0.01$ , Figure 3A) and feeding efficiency ( $r = 0.948$ ,  $p < 0.01$ , Figure 3B). Furthermore, total body weight gain was also significantly correlated with intra-

abdominal ( $r=0.319$ ,  $p<0.05$ ) and total fat mass ( $r=0.329$ ,  $p<0.05$ ) (Figure 3C and D). Furthermore, total distance moved was negatively correlated with total body weight gain ( $r=-0.360$ ,  $p<0.05$ ), and total white fat mass ( $r=-0.346$ ,  $p<0.05$ ). Finally, velocity was negatively correlated with total body weight gain ( $r=-0.383$ ,  $p<0.05$ ).

## **Discussion**

This was the first study in an animal model to detect the effect of betahistine on reducing the body weight gain side-effect caused by olanzapine through a combination therapy. A small clinical trial had shown previously that schizophrenia patients co-administered with olanzapine (10 mg/day) and betahistine (48 mg, t.i.d.) for six weeks had no significant weight gain; unfortunately this trial had a very small sample size ( $n=3$ ) and no placebo controls (Poyurovsky et al., 2005). In a well-established olanzapine-induced weight gain/obesity rat model, we showed that a combined treatment of betahistine and olanzapine reduced weight gain by about 45% compared to sole olanzapine treatment, but still had larger body weight gain compared to the placebo control. This finding suggests that betahistine co-treatment can only partially reduce olanzapine-induced weight gain. There was no difference in body and femur length between the groups (Table 1), which indicates that none of the treatments influence animal growth.

## Betahistine reduces olanzapine-induced weight gain

The animal model of olanzapine-induced weight gain has been well established and validated in female rats (Goudie et al., 2002; Fell et al., 2004; Huang et al., 2006; Han et al., 2008; Weston-Green et al., 2011), however it can only be modelled in male rats under certain conditions, ie. feeding with high carbohydrate (54%)-medium fat (31%)-low protein (14%) diets (Minet-Ringuet et al., 2006; Shobo et al., 2010). It is interesting that the sensitivity of female rats to weight gain side-effect over males is also a common observation in the clinic, where female patients have a much higher risk for weight gain side-effects weight gain associated with atypical antipsychotics (Weston-Green et al., 2010). In the present study, the co-treatment group showed a trend for less weight gain after 4 days treatment that became significant from day 10 of treatment. This result is consistent with the time trend of the small human trial in schizophrenia subjects where combined betahistine and olanzapine treatment stopped weight gain after two weeks therapy (Poyurovsky et al., 2005). Similar to the body weight gain data, the food intake and feeding efficiency of the co-treatment group in the present study was higher than the control group, but lower than the olanzapine group. These results suggest that the ability of betahistine to decrease olanzapine-induced body weight gain is at least partially due to reducing food intake, particularly feeding efficiency.

It is interesting that sole betahistine administration showed no effect on body weight and food intake in rats during the two weeks' experiment. Two acute studies have



shown that betahistine is effective at reducing food intake for up to 24 hours in rats and goats (Rossi et al., 1999; Szelag et al., 2001), however there is no report to investigate the long-term effects of betahistine on body weight gain in an animal model. On the other hand, several studies have tested betahistine's anti-obesity effects in humans, but the results were not consistent (Barak, 2008; Barak et al., 2008; Ali et al., 2010). In a randomized, double-blind, placebo-controlled trial in 20 obese subjects, those treated with 16 mg betahistine (b.i.d) for 28 days had reduced fat/protein intake and a 1.1% weight loss, compared to 0.6% weight gain in the placebo group (Barak, 2008). In a following trial for 12 weeks treatment with betahistine (16-48 mg/day) in 281 adults, weight loss was observed in a sub-group of non-Hispanic women  $\leq$  50 years old, although no significant weight loss in over-all comparison with the placebo (Barak et al., 2008). A recent acute study also showed that betahistine did not affect food intake and appetite in obese women after 24 hours treatment (Ali et al., 2010). Possibly, a chronic treatment is important for betahistine to affect food intake, or betahistine may be a more effective treatment under the conditions of antipsychotic ( $H_1$  antagonist)-induced obesity.

In this experiment, the sole olanzapine group had more white fat mass than the control and sole betahistine groups, which was consistent with previous studies (Fell et al., 2004; Cooper et al., 2005; Weston-Green et al., 2011). The co-treatment group showed

a slight decrease in total white fat, which suggests a possible effect of betahistine on white fat. This study showed an effect of olanzapine but not betahistine on reducing activity. Previous studies revealed a similar result of decreased locomotor activity in rats treated with olanzapine and have suggested that olanzapine-induced weight gain/obesity is partially attributable to a decrease in energy expenditure (Arjona et al., 2004; Chintoh et al., 2008; Weston-Green et al., 2011). In fact, treatment of schizophrenia patients with olanzapine can lead to less vigorous physical exercise (Suzanne et al., 2007; Treuer et al., 2009), and affect energy expenditure (Allison et al., 1999), contributing to a high risk of body weight gain/obesity side-effect (Green et al., 2000). Differing to olanzapine, one study found that ziprasidone reduced only locomotor activity but did not induce any weight gain (Fell et al., 2007). An early rat study revealed that betahistine treatment increased the locomotor activity of rats only at very high dose (25 mg/kg, i.p. injection) but not at lower doses (1, 5, 10 mg/kg, i.p. injection) (Alvarez et al., 1993)., Under the condition of our experiment, the results showed that betahistidine could not improve olanzapine-induced hypolocomotor activity in rats.

According to dosage translation between species based on body surface area (Reagan-Shaw et al., 2007), 1 mg/kg olanzapine in rats is equivalent to ~10 mg in humans (60kg body weight), and 2.67 mg/kg betahistine in rats to ~26 mg in humans; both are among

the recommended doses in the clinic. The olanzapine dosage used in this study has a clinically comparable dopamine D<sub>2</sub> receptor occupancy (of approximately 70–80%) (Kapur et al., 2003), and can increase body weight in female rats (Weston-Green et al., 2011). The dosage of betahistine is effective at reducing food intake during acute treatment in rats (Szelag et al., 2001), but the chronic effect is unknown.

Recent evidence indicates that the binding affinities of olanzapine/clozapine to various neurotransmitter receptors such as 5HT<sub>2C</sub> and M<sub>3</sub>, but particularly histamine H<sub>1</sub> receptors, correlate with the weight gain/obesity side-effect (Kroeze et al., 2003; Matsui-Sakata et al., 2005; Kirk et al., 2009; Reynolds and Kirk, 2010; Weston-Green et al., 2012). Although over dozen of drugs (such as metformin, d-fenfluramine, topiramate) have been trialled with some success in partly ameliorating antipsychotic-induced weight gain in both animal models and humans (Maayan et al., 2010), none of them are based on the findings of H<sub>1</sub> receptors as a main contributor of antipsychotic-induced weight gain/obesity. Betahistine is the first drug to target histamine receptors as an anti-obesity approach to antipsychotic-induced weight gain. As a H<sub>1</sub> receptor agonist and H<sub>3</sub> receptor antagonist, betahistine may reduce olanzapine-induced body weight gain/obesity through both the H<sub>1</sub> and H<sub>3</sub> receptors (Figure 4). Under normal conditions, histamine may activate H<sub>1</sub> receptors on hypothalamic neurons, leading to a decrease in food intake. However, olanzapine blocks histamine H<sub>1</sub> receptors on hypothalamic

### Betahistine reduces olanzapine-induced weight gain

neurons causing an increase in food intake (Figure 4A). Since olanzapine has a low affinity to H<sub>3</sub> autoreceptors, it may have little effect on H<sub>3</sub> regulation of histamine release. Under the co-treatment of betahistine and olanzapine (Figure 4B), betahistine (as a H<sub>1</sub> agonist) can directly activate H<sub>1</sub> receptors that may compete and decrease olanzapine's H<sub>1</sub> antagonist effect. Furthermore, as a H<sub>3</sub> receptor antagonist, betahistine increases histamine release by blocking presynaptic H<sub>3</sub> autoreceptors, which may augment its direct agonistic effects on H<sub>1</sub> receptors (Figure 4B). Therefore, betahistine may reduce food intake and weight gain caused by olanzapine treatment through improving H<sub>1</sub> neurotransmission.

In conclusion, this study has shown that co-treatment of betahistine with olanzapine can partially reduce the olanzapine-induced weight gain side-effect through decreased feeding efficiency and food intake. It is worth noting that only a single dose of betahistine was used in this study, therefore further studies are required to test whether co-treatment with higher dosages of betahistine has better outcomes in relation to reducing olanzapine-induced weight gain side-effects. These findings support a recommendation for co-administration of betahistidine and olanzapine in a large-scale clinical trial and an extension of this co-treatment approach to other antipsychotics, such as clozapine and quetiapine to control their weight gain/obesity side-effects.

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**Conflict of interest**

C. Deng and N. Pai have received an honorarium from Eli Lilly Australia for presenting at the Cutting Edge Debate Melbourne (2010). N. Pai has also received an honorarium and grants from Janssen, Astra Zeneca, Bristol Myer, Pfizer, Organon, Lundbeck and Eli Lilly, and Sanofi Aventis. J. Lian and X.-F. Huang have nothing to disclose.

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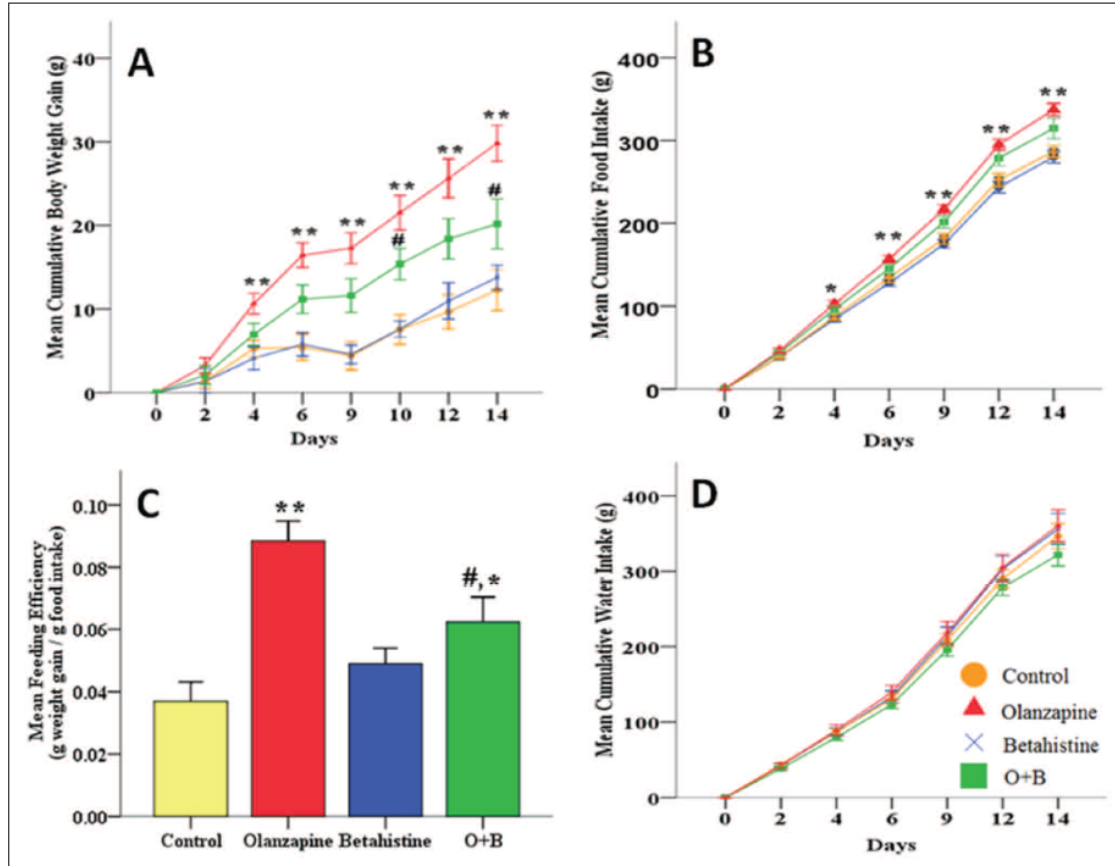
## Betahistine reduces olanzapine-induced weight gain

**Table 1.** Mean body weight, food intake, water intake, fat pad mass (mean±SEM) in female Sprague Dawley rats treated with olanzapine (1 mg/kg, t.i.d.) and/or betahistine (2.67 mg/kg, t.i.d.) or control (vehicle) for 14 days.

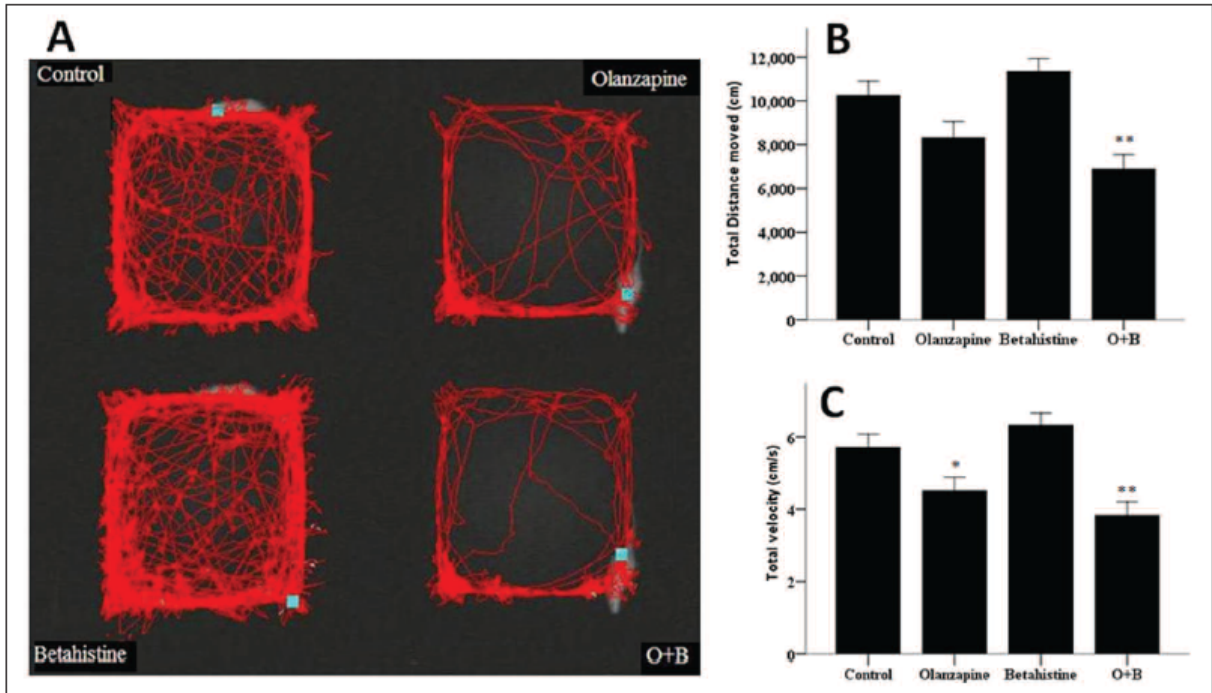
	Control	Olanzapine	Betahistine	O+B
Body weight (g)				
IBW	219.24 ± 3.43	220.80 ± 3.31	217.51 ± 3.52	218.96 ± 3.42
FBW	231.52 ± 4.99	250.63 ± 4.29**	231.28 ± 3.52	239.13 ± 4.72
BWG	12.28 ± 2.46	29.82 ± 2.14**	13.78 ± 1.47	20.17 ± 2.99#
AFI (g)	286.83 ± 7.29	337.17 ± 7.60*	280.15 ± 7.26	314.66 ± 12.30
AWI (mL)	346.66 ± 16.63	360.59 ± 21.21	356.09 ± 20.63	321.87 ± 14.78
Fat pad mass (g)				
Perirenal	2.26 ± 0.22	3.07 ± 0.32	2.11 ± 0.25	2.90 ± 0.30
Periovary	2.95 ± 0.33	3.66 ± 0.39	2.44 ± 0.18	3.23 ± 0.26
Inguinal	2.36 ± 0.17	3.30 ± 0.39*	2.05 ± 0.15	3.35 ± 0.29*
Total intra-abdominal fat	5.22 ± 0.51	6.73 ± 0.67	4.54 ± 0.40	6.14 ± 0.45
Total white fat	7.58 ± 0.61	10.02 ± 1.01	6.60 ± 0.5	9.49 ± 0.70
Brown fat	0.22 ± 0.03	0.24 ± 0.02	0.20 ± 0.02	0.22 ± 0.02
Body length (cm)	19.29 ± 0.23	19.16 ± 0.21	19.28 ± 0.20	19.42 ± 0.21
Femur length (cm)	4.81 ± 0.06	4.84 ± 0.05	4.86 ± 0.05	4.96 ± 0.07

AFI: accumulated food intake; AWI: accumulated water intake; BWG: body weight gain; FBW: final body weight; IBW: initial body weight; O+B: combined olanzapine and betahistine; SEM: standard error of the mean; t.i.d.: three times daily.

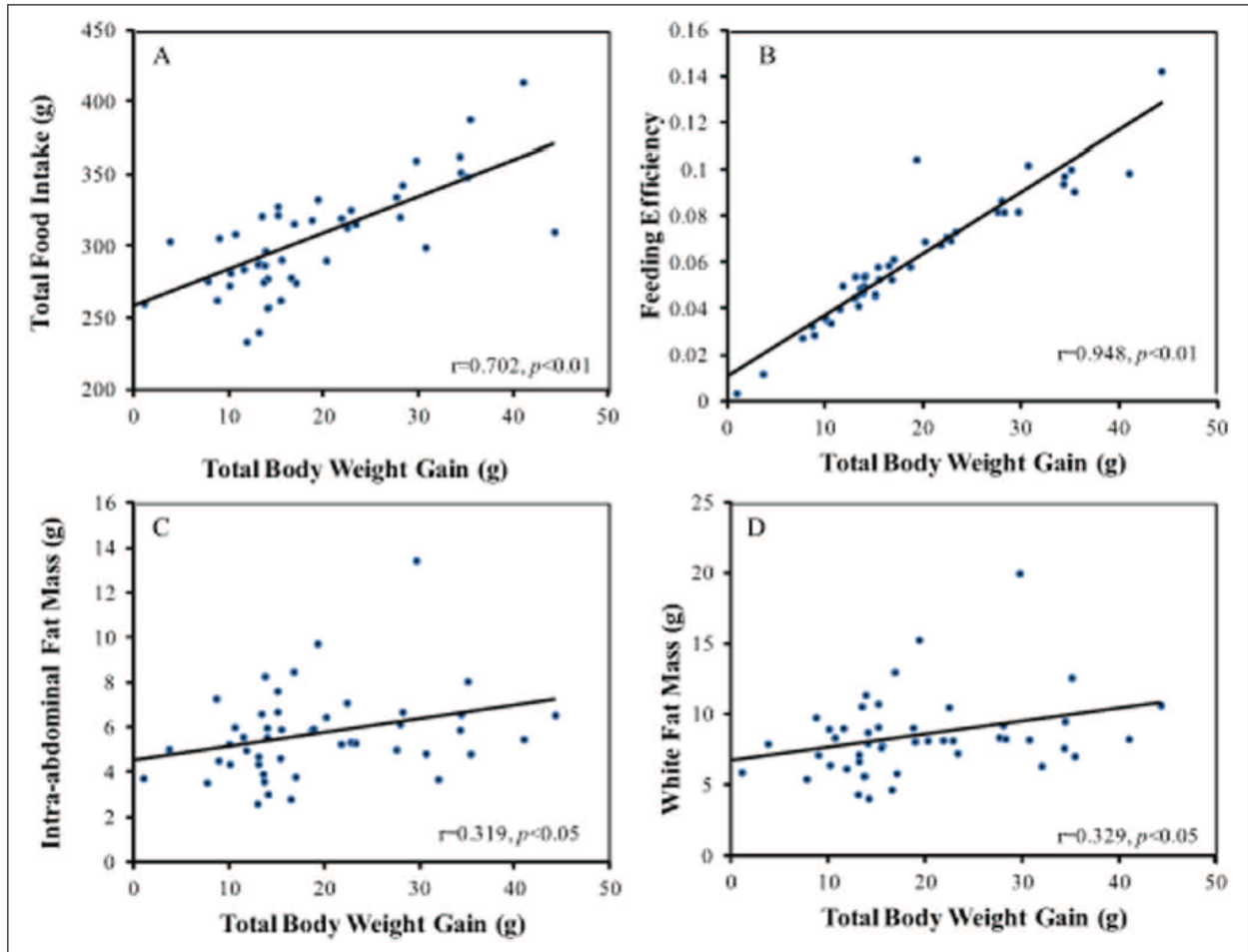
\* $p < 0.05$ , \*\* $p < 0.01$  vs control, # $p < 0.05$  vs olanzapine.



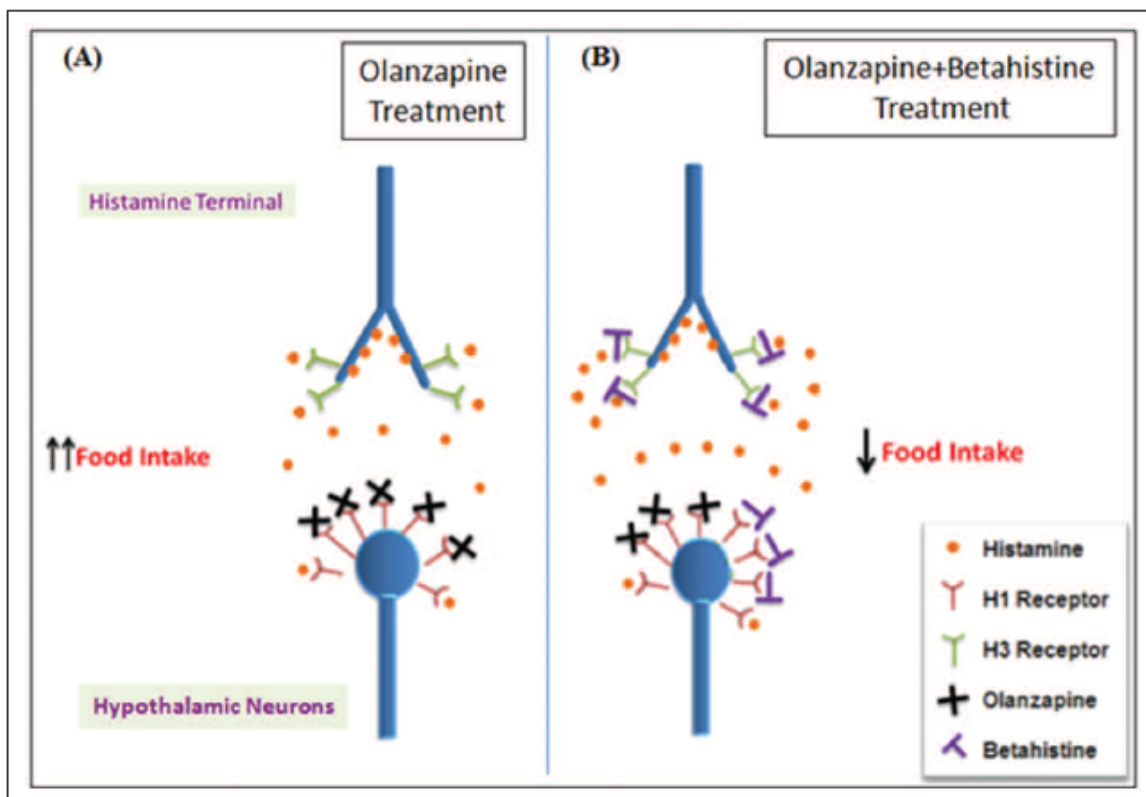
**Figure 1** Cumulative body weight gain (A), food intake (B), feeding efficiency (C) and water intake (D) in female Sprague Dawley rats treated with olanzapine (1 mg/kg, t.i.d.; n=12; ), betahistine (2.67 mg/kg, t.i.d.; n=12), co-treatment (O+B; n=12) or control (vehicle; n=12) for 14 days. (▲ : olanzapine, ×: betahistine, ■: O+B co-treatment, ●: control). \*  $p < 0.05$ , \*\*  $p < 0.01$  vs. control, #  $p < 0.05$  vs. olanzapine.



**Figure 2** (A) Examples of locomotor activity from rats treated with olanzapine (n=7), betahistine (n=12), co-treatment (O+B; n=9) or control (vehicle; n=11). Locomotor activity in the open field test was traced using the Ethovision software. (B) Distance moved and (C) velocity in the open field test. \*  $p < 0.05$ , \*\*  $p < 0.01$  vs. control,



**Figure 3** The correlations between total body weight gain (g) and A: total food intake (g), B: feeding efficiency, C: intra-abdominal fat mass (g), D: white fat mass (g).



**Figure 4** (A) The possible mechanisms of olanzapine-induced weight gain through regulation of food intake by blocking histamine H<sub>1</sub> receptors; (B) The proposed mechanisms of betahistidine co-treatment for reducing olanzapine-induced body weight gain through its antagonistic action on H<sub>3</sub> receptors and agonistic actions on H<sub>1</sub> receptors.