Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

The effect of ziprasidone on body weight and energy expenditure in female rats

Subin Park[a,1], Min-Seon Kim[b,*,1], Churl Namkoong[b], Min-Hyeon Park[c], Jin Pyo Hong[a,*]

[a] Department of Psychiatry, Asan Medical Center, Ulsan University College of Medicine, Seoul, South Korea
[b] Department of Internal Medicine, Asan Medical Center, Ulsan University College of Medicine, Seoul, South Korea
[c] Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 15 July 2011
Accepted 19 October 2011

ABSTRACT

Ziprasidone, a novel antipsychotic agent with a unique receptor-binding profile, has been reported to have lower propensity for weight gain compared with other atypical antipsychotics. Here, we examined the effects of ziprasidone on resting energy expenditure, physical activity, thermogenesis, food intake, and weight gain in female Sprague-Dawley rats. Ziprasidone (20 mg/kg) or vehicle was administered once daily for 7 weeks; and body weight, food intake, resting energy expenditure, locomotor activity, colonic temperature on cold exposure, and abdominal fat were measured. Compared with control animals, ziprasidone-treated rats gained significantly less weight ($P = .031$), had a lower level of physical activity ($P = .016$), showed a higher resting energy expenditure ($P < .001$), and displayed a greater capacity for thermogenesis when subjected to cold ($P < .001$). In addition, ziprasidone-treated rats had a lower level of abdominal fat than did controls, although the difference was not significant. Ziprasidone had no effect on food intake. Our results indicate that, in female Sprague-Dawley rats, a 7-week treatment regimen of ziprasidone induces a significant decrease in weight gain by increasing resting energy expenditure without decreasing food intake and even with a lower level of physical activity. Further studies are needed to elucidate the precise mechanism of lower propensity of weight gain of ziprasidone.

1. Introduction

Weight gain is a commonly observed adverse effect associated with antipsychotic drug therapy in patients with a variety of psychotic disorders [1-4]. Although most conventional antipsychotics cause modest increases in weight [4-7], the atypical antipsychotics, including clozapine, risperidone, olanzapine, and quetiapine, are associated with more marked weight gain [3-6,8,9]. Such gain in weight is a common cause of poor adherence to antipsychotic therapy and a potential contributor to comorbidity, including glucose intolerance [10], diabetes mellitus [11], and sleep apnea [12].

In contrast to other atypical antipsychotic agents, ziprasidone, a novel antipsychotic agent with a unique receptor-

Author contributions: MSK and JPH designed the study. MSK and CN participated in data collection. CN and SP analyzed the data. SP prepared the first draft of the report. JPH and MSK supervised the statistical analysis. SP, JPH, and MHP interpreted the results. SP wrote the final report with input from all the authors. SP and JPH revised the manuscript. All authors had full access to all the data in the study and approved the version to be published.

* *Corresponding author*. Department of Psychiatry, Asan Medical Center, Songpa-gu, Seoul 138-736, South Korea. Tel.: +82 2 3010 3421; fax: +82 2 485 8381.
E-mail address: jphong@amc.seoul.kr (J.P. Hong).

[1] These authors contributed equally to this work.

0026-0495/$ – see front matter.
doi:10.1016/j.metabol.2011.10.011

binding profile such as highest 5-HT_{2A}/D2 receptor affinity ratio, 5-HT_{1A} agonism, and unique blockade of serotonin and norepinephrine transporters, has been reported to cause minimal weight gain [2,13-15] or even weight loss [16-18]. The drug also has significant advantages in terms of metabolic effects compared with other atypical antipsychotics [14,19,20].

Despite the well-documented propensity of antipsychotics to cause weight change, the underlying mechanism has yet to be elucidated. To date, all of increased appetite, sedation, and hyperprolactinemia have been suggested to be relevant [21]. Mechanistically, the weight gain associated with olanzapine and clozapine use has been attributed to the high affinities of the drugs for the 5-HT_{2C} serotonin and H1 histamine receptors, where they act as an antagonist [22-25]. Both serotonin and histamine are involved in regulation of food intake and can affect the levels of motor activity and energy expenditure [26,27].

A number of preclinical studies have provided insights into the mechanism underlying antipsychotic-induced weight gain. Many studies have demonstrated increases in body weight and food intake in female, but not male, rats treated with atypical antipsychotics [28-35]. Fell and colleagues [36-38] described a significant weight gain in female rats treated subchronically with haloperidol, risperidone, or olanzapine, but not ziprasidone. The cited authors also reported that only olanzapine significantly increased food intake and that locomotor activity was significantly reduced in all treatment groups including those receiving olanzapine, risperidone, and ziprasidone [39]. A recent study found that long-term olanzapine treatment of male rats induced body weight gain and acute drug injection caused hyperphagia, but treatment with ziprasidone induced neither weight gain nor hyperphagia [40]. Another recent study found that rats treated with haloperidol and ziprasidone showed a significantly decreased weight gain and decreased food consumption compared with control animals [41].

Body weight is determined by the balance between food intake and energy expenditure. As mentioned above, previous studies on antipsychotic-induced weight gain have focused mainly on the effects of such agents on food intake [21,28,30-42]; and only a few preclinical studies have investigated the effects of antipsychotic agents on locomotor activity [39,43], thermogenesis [34,43], and resting energy expenditure [44-46]. In addition, there is no study investigating the effect of ziprasidone on thermogenesis and resting energy expenditure.

The aim of the present study was to evaluate the effects of ziprasidone on resting energy expenditure, thermogenesis, physical activity, food intake, and weight gain in female Sprague-Dawley rats. Based on previous reports [36,39,40], we postulated that ziprasidone would be associated with a low propensity for weight gain because the drug might increase resting energy expenditure without a decrease in food intake or an increase in physical activity.

2. Methods

2.1. Animals and experimental design

Eight-week-old female Sprague-Dawley rats weighing 200 to 250 g were obtained from Orient Bio (Seoul, Korea) and maintained in a temperature- (21°C ± 2°C) and humidity (50%)-controlled room with a 12-hour/12-hour light/dark cycle (light on at 7:00 AM), with free access to standard rat chow and water. All animal procedures were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of the Asan Institute for Life Sciences.

Animals were randomly divided into 2 groups (n = 10 per group). Rats receiving ziprasidone (Pfizer, New York, NY) were given the drug (20 mg/kg) dissolved in 2 mL of distilled water by oral gavage. Control animals received the same volume of distilled water. The two groups did not differ in mean body weight (249.5 ± 12.9 g for rats receiving ziprasidone and 239.5 ± 13.5 g for control rats, $t = 1.7$, $P = .106$) before treatment. Ziprasidone or vehicle was administered chronically for 9 weeks via single daily doses given at 10:00 AM following measurement of food and water intake and body weight. All animals were housed under the same conditions for a period of 2 weeks before drug treatment. We chose the daily drug dose of 20 mg/kg by reference to the data of von Wilmsdorff et al [41], which used a dose of 20 mg/kg in their 18-week study examining the metabolic effect of the drug. This dose in the rats corresponds to human equivalent dose of 3 mg/kg [47,48]. It is somewhat higher than other previous studies using 10 to 12 mg/kg of ziprasidone [34,49]. However, a recent study showed an inverse relationship between ziprasidone dose and body weight gain and food intake in preliminary work using 10, 20 and 25 mg/kg [41]; and we thus used a dose of 20 mg/kg to maximize the protective effect against weight gain in the present work.

2.2. Body weight and food intake measurements

Body weight was measured weekly, and food intake were assessed daily between 8:00 AM and 9:00 AM. Body weight was measured to only 7 weeks of drug administration because various experiments including indirect calorimetry, exposure to cold, and computed tomography (CT) to score abdominal fat levels, performed after 7 weeks of treatment, were expected to stress the animals and thus affect body weight gain. Body weight change was calculated from the day before drug treatment commenced, and biweekly changes are shown. Food intake was recorded daily for each rat to an accuracy of 0.01 g; and the mean food consumption in weeks 2, 4, 6, and 7 was calculated.

2.3. Energy expenditure measurement

Energy expenditure was measured over 1 hour by indirect calorimetry (Columbus Instruments, Columbus, OH) after 7 weeks of ziprasidone or vehicle treatment. Animals were placed in a metabolic chamber after 6 hours of fasting and allowed to acclimatize to the chamber for at least 30 minutes before measurements were made. Sampling and analysis of chamber gas were performed every 10 second for 10 minutes, and the data were averaged. Energy expenditure was calculated according to the following formula: expenditure = $(3.815 + 1.232 \times VO_2/VCO_2) \times VO_2$.

2.4. Thermogenesis

After about 9 weeks of ziprasidone or vehicle treatment, animals were placed in a refrigerator maintained at 4°C to test

the thermogenic effect of the drug. Colon temperature was measured immediately and at 30 min, 1 hour, 1.5 hours, and 2 hours after cold exposure using a colonic thermometer (model 52; Harvard Apparatus, Holliston, MA).

2.5. *Locomotor activity*

The effect of ziprasidone on physical activity, as assessed by movement distance, was also evaluated. The behavioral test was performed between 2:00 PM and 6:00 PM in animals treated with ziprasidone or vehicle for 7.5 weeks. Rats were individually housed and allowed to acclimatize for 1 hour in individual transfer cages in the behavioral testing room. Locomotor activity was evaluated using an Activity Monitor (MED Associates, St Albans, VM) composed of an open-field chamber (43.2 × 43.2 × 30.5 cm) containing 16 × 16 photocells for measurement of horizontal movements. Locomotor activity was measured as the total distance traveled over 60 minutes.

2.6. *Quantitation of abdominal fat*

To evaluate abdominal adiposity, CT (GE Medical Systems, Milwaukee, WS) was performed on 3 representative rats of each group; and median weight gain values were determined in week 8 of treatment. Rats were placed in the prone recumbent position, and CT imaging was performed on the abdominal region using transverse slices (3 mm in thickness; 21-mm centers). A computer-based image analysis system was used to make detailed comparisons of both visceral and subcutaneous adipose tissue depots.

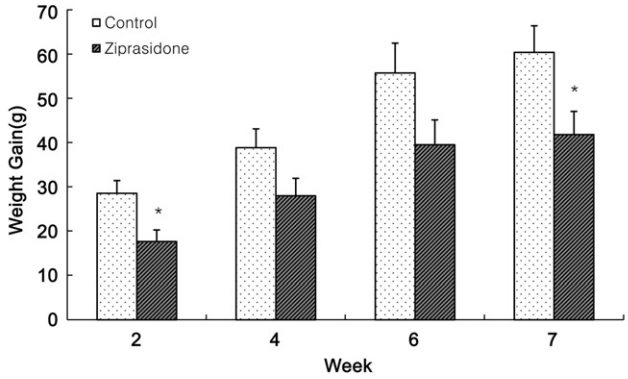
2.7. *Statistical analysis*

Independent t tests were used to compare weight gain, food consumption, resting energy expenditure, body temperature after cold exposure, movement distance, and abdominal adiposity between female rats treated daily for 7 weeks with drug or vehicle. All statistical analyses were performed using SPSS (v 12.0), with statistical significance defined at an α level < .05.

3. Results

3.1. *Effect of ziprasidone on weight gain*

Fig. 1 shows the effect of ziprasidone (20 mg/kg) on weight gain over 7 weeks. Weight gain was significantly lower in ziprasidone-treated rats than in controls in both weeks 2 and 7 (t = –2.80, P = .012, statistical power = 0.800 and t = –2.34, P = .031, statistical power = 0.374, respectively). Although the difference was not significant, the ziprasidone-treated animals showed a lower level of weight gain than did controls in weeks 4 and 6. By week 7, body weight in the vehicle-treated group had increased by an average of 60.4 ± 19.0 g from the day before treatment, whereas the body weight of the ziprasidone-treated animals had increased by an average of 41.8 ± 16.5 g, that is, 69% of the value of controls.



	Body weight (g), Mean (SD)				
	Week 0	Week 2	Week 4	Week 6	Week 7
Control	249.5 (12.9)	267.11 (16.3)	277.48 (17.3)	289.01 (22.2)	291.32 (22.9)
Ziprasidone	239.5 (13.5)	267.97 (16.8)	278.31 (22.3)	295.17 (29.3)	299.86 (26.8)

Fig. 1 – Effect of ziprasidone (20mg/kg) on body weight gain in female rats treated daily for 7 weeks with drug or vehicle given by oral gavage. Weight gain are shown as means ± SEMs; n = 10 per group. *P < .05.

3.2. *Effect of ziprasidone on food intake*

Food intake in the vehicle- and ziprasidone-treated groups was constant over the entire 7 weeks of the study (Fig. 2). This suggests that the drug suppresses weight gain without inhibiting food intake.

3.3. *Effect of ziprasidone on energy expenditure*

Resting energy expenditure measured normalized by weight was significantly higher in ziprasidone-treated rats than in controls in week 7 (62.5 ± 11.5 vs 32.3 ± 14.8 kcal/[d kg], t = –5.13, P < .001, statistical power = 0.999) (Fig. 3A). To exclude the effect of group difference in body weight, we also calculated absolute resting energy expenditure (unnormalized by weight), which was still significantly higher in ziprasidone-treated rats than in controls (18.2 ± 3.5 vs 9.6 ± 4.3 kcal/d, t = 4.85, P < .001, statistical power = 0.998) (Fig. 3B).

3.4. *Effect of ziprasidone on thermogenesis*

Ziprasidone treatment resulted in a significant increase in colonic temperature 60, 90, and 120 minutes after exposure to cold (t = 2.50, P = .021, statistical power = 0.713; t = 5.47, P < .001, statistical power = 1.000; and t = 5.07, P < .001, statistical power = 0.999, respectively) compared with that of control animals (Fig. 4). This suggested that ziprasidone was thermogenic.

3.5. *Effect of ziprasidone on movement*

Ziprasidone significantly decreased movement distance at week 7.5 compared with that of control animals (3590.4 ± 572.7 vs 1880.3 ± 294.7 cm, t = 2.66, P = .016, statistical

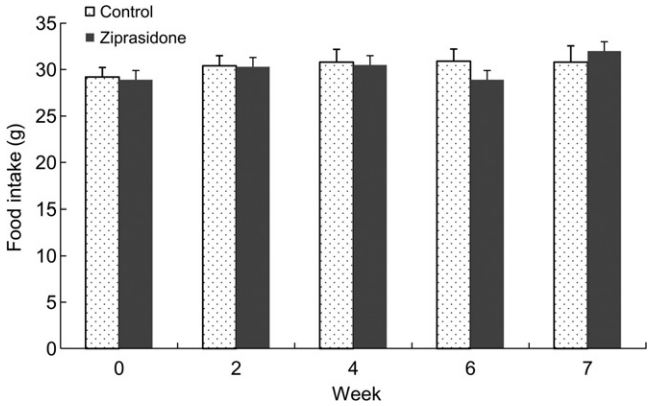


Fig. 2 – Effect of ziprasidone (20 mg/kg) on food intake by female rats treated daily for 7 weeks with drug or vehicle given by oral gavage. Data are shown as means ± SEMs; n = 10 per group.

power = 1.000) (Fig. 5). This suggests that ziprasidone suppresses weight gain even though the level of physical activity is decreased.

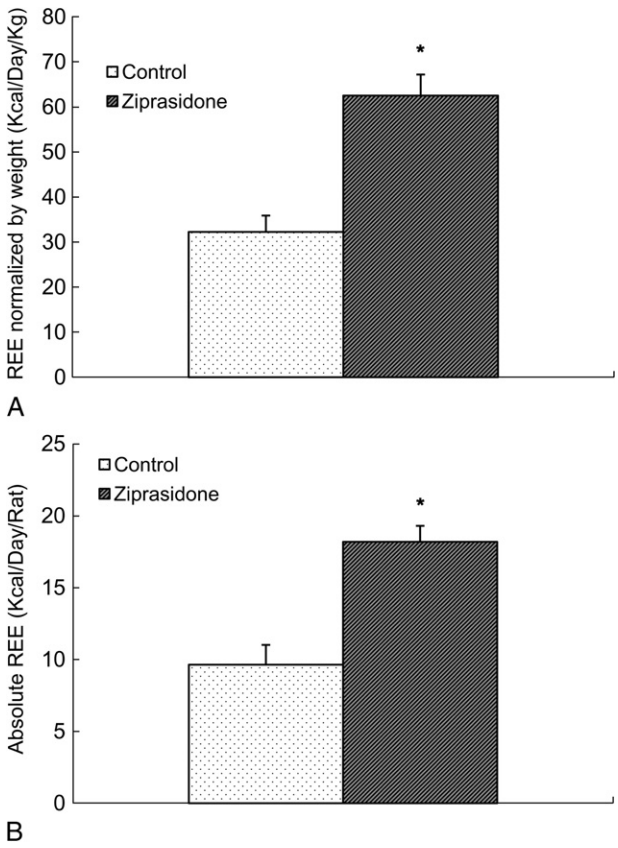


Fig. 3 – Effect of ziprasidone (20 mg/kg) on resting energy expenditure normalized by weight (kilocalories per day per kilogram) (A) and absolute resting energy expenditure (kilocalories per day per rat) (B) in female rats treated daily for 7 weeks with drug or vehicle given by oral gavage. Data are shown as means ± SEMs; n = 10 per group. *P < .05. REE indicates resting energy expenditure.

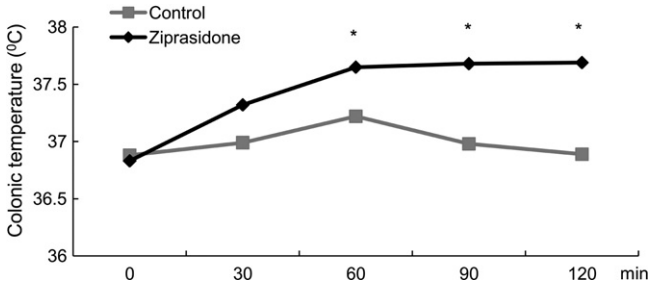


Fig. 4 – Effect of ziprasidone (20 mg/kg) on movement distance over 60 minutes in female rats treated daily for 7 weeks with drug or vehicle given by oral gavage. Data are shown as means ± SEMs; n = 10 per group. *P < .05.

3.6. *Effect of ziprasidone on abdominal adiposity*

Abdominal CT scans of rats treated with vehicle or ziprasidone (10 mg/kg) showed that drug-treated animals had a lower level of abdominal fat than did controls, although the difference was not significant (Fig. 6A, B). Both the subcutaneous and intraabdominal fat levels of ziprasidone-treated rats were 12% less than those of controls (Fig. 6C).

4. Discussion

To the best of our knowledge, this is the first study to investigate the effect of ziprasidone on resting energy expenditure and thermogenesis, as well as food intake and body weight, in female Sprague-Dawley rats. In the present work, we found that, compared with control animals, ziprasidone-treated rats gained significantly less weight, consumed the same amount of food, had a lower level of physical activity, showed a higher resting energy expenditure, and displayed a greater capacity for thermogenesis when subjected to cold.

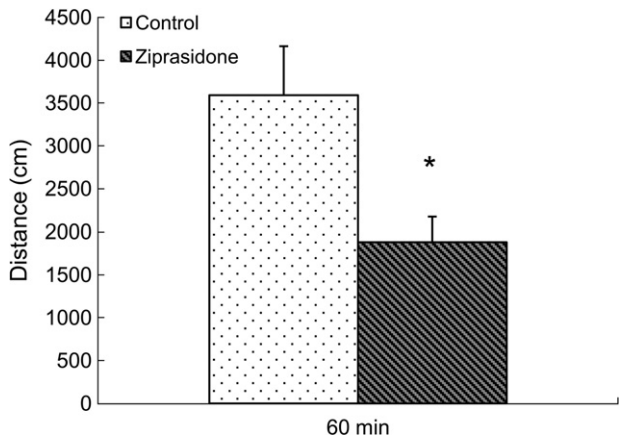


Fig. 5 – Effect of ziprasidone (20 mg/kg) on colonic temperature of female rats after exposure to cold. The animals were treated daily for 9 weeks with drug or vehicle given by oral gavage. Data are shown as means ± SEMs; n = 10 per group. *P < .05.

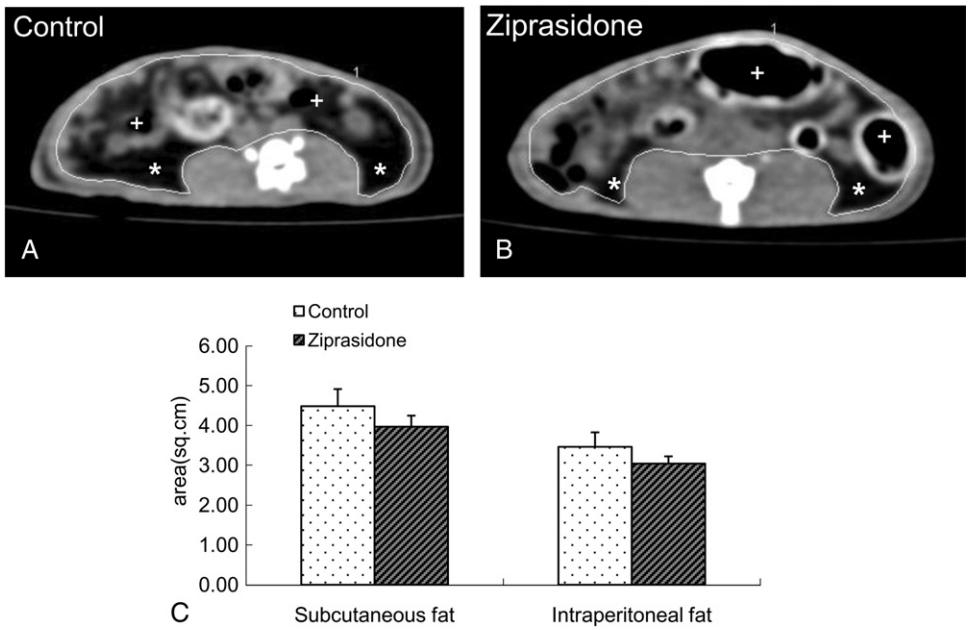


Fig. 6 – Computer tomographic scans of abdominal fat in rats treated daily for 8 weeks with vehicle (A) or ziprasidone (20mg/kg) (B), and the effect of ziprasidone on abdominal adiposity. Data are shown as means ± SEMs; n = 3 per group. *: intraperitoneal fat, +: bowel gas.

Previous studies found that ziprasidone induced somewhat less weight gain than did other atypical antipsychotics such as olanzapine and risperidone. However, compared with vehicle, the difference in weight gain was not significant [34,36,39,40,49,50]. In the present study, ziprasidone-treated rats showed less weight gain then did control animals. The high dose of ziprasidone used in the present study (20 mg/kg) compared with those of previous reports (2.5-12 mg/kg) may explain the difference; a previous report [41] that used the same dose of ziprasidone as used in the present study also found that weight gain decreased significantly in drug-treated animals. This previous preliminary dosing trial [41] showed an inverse relationship between ziprasidone dose and weight gain when the drug was administered over 2 weeks.

In the present study, compared with control animals, use of ziprasidone significantly decreased physical activity, consistent with results of previous clinical trials that showed a lower level of physical activity (a sedative effect) in patients treated with ziprasidone, although this was less marked than what was observed when clozapine or quetiapine was prescribed [51-53].

Consistent with the results of previous studies [33,34,36,39,40], ziprasidone had no significant effect on food intake. The lack of a hyperphagic drug action partially explains the weight-neutral effect of the drug compared with other atypical antipsychotics that do have such effects (olanzapine is an example) [34,39,42]. However, this does not explain the fact that weight gain in the drug-treated group was less than that in control animals. In addition, when the decrease in physical activity (which would result in a positive energy balance if food intake does not change) is considered, ziprasidone should induce more weight gain than that seen in controls; however, the reverse was the case.

We suggest that an increase in resting energy expenditure may be an intrinsic pharmacological mechanism preventing weight gain when ziprasidone is taken. This may be explained by the fact that the drug has low affinities for the histamine H1 receptors, acts as a partial agonist of the 5-HT_{1A} receptor, and inhibits the reuptake of serotonin and norepinephrine [24,25]. No effects, increased energy expenditure, and decreased energy expenditure following long-term olanzapine treatment have been described in both rats [44-46] and human subjects [54-57]. No clinical study has analyzed the effect of ziprasidone on resting energy expenditure, and further work in humans is needed.

Thermogenesis induced by cold may be an important aspect of ziprasidone action. Increased food intake, shivering, and oxidation of brown adipose tissue can cause an increase in body temperature owing to thermogenic effects [58,59]. Body temperature regulation may also involve the hypothalamic neuropeptide orexin, which has been shown to be important in regulation of food intake and locomotor activity [60]. The mechanism of thermogenesis caused by ziprasidone is unclear, but may be associated with an increase in resting energy expenditure and lipolysis.

A previous study found that haloperidol (1 mg/kg) and olanzapine (1 mg/kg) induced significant increases in adiposity, whereas ziprasidone (10 mg/kg) caused only moderate fat accumulation, compared with controls [34]. However, in the present work, ziprasidone-treated rats showed somewhat lower levels of abdominal fat than did controls, although the difference was not significant. We suggest that the higher dose (20 mg/kg) of ziprasidone used in the present study resulted in accumulation of less fat than that found in the cited work; this notion is indirectly supported by the inverse relationship between drug dose and weight gain noted in the

previous preliminary study [41]. However, selection bias is possible in the present work because we chose only 3 representative rats (that showed median weight gain values) from each group for abdominal adiposity measurement.

In conclusion, our results indicate that, in female Sprague-Dawley rats, a 7-week treatment regimen of ziprasidone induces a significant decrease in weight gain by increasing resting energy expenditure without decreasing food intake and even with a lower level of physical activity. However, owing to the small number of animals used and the fact that only one drug dose was used based on the previous studies without preliminary dose test, our results should be considered preliminary in nature. Another limitation includes that we measured resting energy expenditure and thermogenesis only after treatment, and 1 hour might be short to measure resting energy expenditure. Dose/response studies are needed, and further work with the measurement of metabolic parameters and organ tissue mass would be useful to elucidate the precise mechanism of lower propensity of weight gain of ziprasidone.

Funding

This study was supported by grants from the National Research Foundation of Korea, funded by the Korean government (grant no. 2009-0079566).

Conflict of Interest

There is no conflict of interest with any of the authors.

REFERENCES

[1] Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001;62(Suppl 7): 22-31.
[2] Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.
[3] Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. J Am Acad Child Adolesc Psychiatry 2002;41:337-43.
[4] Tollefson GD, Beasley Jr CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457-65.
[5] Atmaca M, Kuloglu M, Tezcan E, et al. Weight gain, serum leptin and triglyceride levels in patients with schizophrenia on antipsychotic treatment with quetiapine, olanzapine and haloperidol. Schizophr Res 2003;60:99-100.
[6] Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J Clin Psychiatry 2001;62:231-8.
[7] Klett CJ, Caffey Jr EM. Weight changes during treatment with phenothiazine derivatives. J Neuropsychiatr 1960;2:102-8.
[8] Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 1999;156:702-9.
[9] Tran PV, Tollefson GD, Sanger TM, et al. Olanzapine versus haloperidol in the treatment of schizoaffective disorder. Acute and long-term therapy. Br J Psychiatry 1999;174:15-22.
[10] Hedenmalm K, Hagg S, Stahl M, et al. Glucose intolerance with atypical antipsychotics. Drug Saf 2002;25:1107-16.
[11] Hagg S, Joelsson L, Mjorndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59: 294-9.
[12] Wirshing DA, Pierre JM, Wirshing WC. Sleep apnea associated with antipsychotic-induced obesity. J Clin Psychiatry 2002;63: 369-70.
[13] Arato M, O'Connor R, Meltzer HY. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. Int Clin Psychopharmacol 2002;17:207-15.
[14] Kingsbury SJ, Fayek M, Trufasiu D, et al. The apparent effects of ziprasidone on plasma lipids and glucose. J Clin Psychiatry 2001;62:347-9.
[15] Ratner Y, Gibel A, Yorkov V, et al. Effectiveness, safety, and tolerability of ziprasidone for treating schizophrenia patients undergoing usual care: a 12-month, open-label, flexible-dose, naturalistic observational trial. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1401-9.
[16] Kudla D, Lambert M, Domin S, et al. Effectiveness, tolerability, and safety of ziprasidone in patients with schizophrenia or schizoaffective disorder: results of a multi-centre observational trial. Eur Psychiatry 2007;22:195-202.
[17] Daniel DG. Tolerability of ziprasidone: an expanding perspective. J Clin Psychiatry 2003;64(Suppl 19):40-9.
[18] Manschreck TC, Boshes RA. The CATIE schizophrenia trial: results, impact, controversy. Harv Rev Psychiatry 2007;15: 245-58.
[19] Kim SW, Shin IS, Kim JM, et al. Effectiveness of switching from aripiprazole to ziprasidone in patients with schizophrenia. Clin Neuropharmacol 2010;33:121-5.
[20] Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2009:CD006627.
[21] Baptista T, Zarate J, Joober R, et al. Drug induced weight gain, an impediment to successful pharmacotherapy: focus on antipsychotics. Curr Drug Targets 2004;5:279-99.
[22] Goudie AJ, Halford JC, Dovey TM, et al. H(1)-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003;28:2209 [author reply 10-11].
[23] Schmidt AW, Lebel LA, Howard Jr HR, et al. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425:197-201.
[24] Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003;28:519-26.
[25] Reynolds GP. Receptor mechanisms in the treatment of schizophrenia. J Psychopharmacol 2004;18:340-5.
[26] Nonogaki K, Abdallah L, Goulding EH, et al. Hyperactivity and reduced energy cost of physical activity in serotonin 5-HT(2C) receptor mutant mice. Diabetes 2003;52:315-20.
[27] Vickers SP, Clifton PG, Dourish CT, et al. Reduced satiating effect of d-fenfluramine in serotonin 5-HT(2C) receptor mutant mice. Psychopharmacology (Berl) 1999;143:309-14.
[28] Arjona AA, Zhang SX, Adamson B, et al. An animal model of antipsychotic-induced weight gain. Behav Brain Res 2004;152: 121-7.
[29] Baptista T, Araujo de Baptista E, Ying Kin NM, et al. Comparative effects of the antipsychotics sulpiride or risperidone in rats. I: bodyweight, food intake, body

composition, hormones and glucose tolerance. Brain Res 2002;957:144-51.
[30] Cooper GD, Pickavance LC, Wilding JP, et al. Effects of olanzapine in male rats: enhanced adiposity in the absence of hyperphagia, weight gain or metabolic abnormalities. J Psychopharmacol 2007;21:405-13.
[31] Goudie AJ, Smith JA, Halford JC. Characterization of olanzapine-induced weight gain in rats. J Psychopharmacol 2002;16: 291-6.
[32] Kirk SL, Neill JC, Jones DN, et al. Ziprasidone suppresses olanzapine-induced increases in ingestive behaviour in the rat. Eur J Pharmacol 2004;505:253-4.
[33] Minet-Ringuet J, Even PC, Guesdon B, et al. Effects of chronic neuroleptic treatments on nutrient selection, body weight, and body composition in the male rat under dietary self-selection. Behav Brain Res 2005;163:204-11.
[34] Minet-Ringuet J, Even PC, Goubern M, et al. Long term treatment with olanzapine mixed with the food in male rats induces body fat deposition with no increase in body weight and no thermogenic alteration. Appetite 2006;46: 254-62.
[35] Thornton-Jones Z, Neill JC, Reynolds GP. The atypical antipsychotic olanzapine enhances ingestive behaviour in the rat: a preliminary study. J Psychopharmacol 2002;16:35-7.
[36] Fell MJ, Gibson R, McDermott E, et al. Investigation into the effects of the novel antipsychotic ziprasidone on weight gain and reproductive function in female rats. Behav Brain Res 2005;160:338-43.
[37] Fell MJ, Neill JC, Marshall KM. Effects of the classical antipsychotic haloperidol and atypical antipsychotic risperidone on weight gain, the oestrous cycle and uterine weight in female rats. Eur Neuropsychopharmacol 2004;14: 385-92.
[38] Fell MJ, Marshall KM, Williams J, et al. Effects of the atypical antipsychotic olanzapine on reproductive function and weight gain in female rats. J Psychopharmacol 2004;18:149-55.
[39] Fell MJ, Anjum N, Dickinson K, et al. The distinct effects of subchronic antipsychotic drug treatment on macronutrient selection, body weight, adiposity, and metabolism in female rats. Psychopharmacology (Berl) 2007;194:221-31.
[40] Shobo M, Yamada H, Mihara T, et al. Two models for weight gain and hyperphagia as side effects of atypical antipsychotics in male rats: validation with olanzapine and ziprasidone. Behav Brain Res 2011;216:561-8.
[41] von Wilmsdorff M, Bouvier ML, Henning U, et al. The impact of antipsychotic drugs on food intake and body weight and on leptin levels in blood and hypothalamic ob-r leptin receptor expression in wistar rats. Clinics (Sao Paulo) 2010;65:885-94.
[42] Snigdha S, Thumbi C, Reynolds GP, et al. Ziprasidone and aripiprazole attenuate olanzapine-induced hyperphagia in rats. J Psychopharmacol 2008;22:567-71.
[43] Cope MB, Li X, Jumbo-Lucioni P, et al. Risperidone alters food intake, core body temperature, and locomotor activity in mice. Physiol Behav 2009;96:457-63.
[44] Coccurello R, Brina D, Caprioli A, et al. 30 days of continuous olanzapine infusion determines energy imbalance, glucose intolerance, insulin resistance, and dyslipidemia in mice. J Clin Psychopharmacol 2009;29:576-83.
[45] Coccurello R, Caprioli A, Ghirardi O, et al. Chronic administration of olanzapine induces metabolic and food intake alterations: a mouse model of the atypical antipsychotic-associated adverse effects. Psychopharmacology (Berl) 2006;186:561-71.
[46] Liebig M, Gossel M, Pratt J, et al. Profiling of energy metabolism in olanzapine-induced weight gain in rats and its prevention by the CB1-antagonist AVE1625. Obesity (Silver Spring) 2010;18:1952-8.
[47] Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. FASEB J 2008;22:659-61.
[48] Research CfDEa. Estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers. Rockville (MD): U.S. Food and Drug Administration; 2002.
[49] Pillai A, Parikh V, Terry Jr AV, et al. Long-term antipsychotic treatments and crossover studies in rats: differential effects of typical and atypical agents on the expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. J Psychiatr Res 2007;41:372-86.
[50] Abdul-Monim Z, Reynolds GP, Neill JC. The atypical antipsychotic ziprasidone, but not haloperidol, improves phencyclidine-induced cognitive deficits in a reversal learning task in the rat. J Psychopharmacol 2003;17:57-65.
[51] Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics : differential risk and clinical implications. CNS Drugs 2007;21:911-36.
[52] Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia. Clin Ther 2002;24:21-37.
[53] Greenberg WM, Citrome L. Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials. CNS Drug Rev 2007;13:137-77.
[54] Gothelf D, Falk B, Singer P, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. Am J Psychiatry 2002;159:1055-7.
[55] Graham KA, Perkins DO, Edwards LJ, et al. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. Am J Psychiatry 2005;162:118-23.
[56] Fountaine RJ, Taylor AE, Mancuso JP, et al. Increased food intake and energy expenditure following administration of olanzapine to healthy men. Obesity (Silver Spring) 2010;18: 1646-51.
[57] Virkkunen M, Wahlbeck K, Rissanen A, et al. Decrease of energy expenditure causes weight increase in olanzapine treatment—a case study. Pharmacopsychiatry 2002;35:124-6.
[58] Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. Nature 2000;404:652-60.
[59] Nedergaard J, Golozoubova V, Matthias A, et al. UCP1: the only protein able to mediate adaptive non-shivering thermogenesis and metabolic inefficiency. Biochim Biophys Acta 2001;1504:82-106.
[60] Thorpe AJ, Kotz CM. Orexin A in the nucleus accumbens stimulates feeding and locomotor activity. Brain Res 2005;1050:156-62.