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Plasma nitric oxide and leptin values in patients with olanzapine-induced weight gain

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Abstract

We previously investigated leptin levels in antipsychotic-induced weight gain and found that atypical antipsychotic, especially clozapine and olanzapine-induced weight gain is related to increased levels of leptin. It has been suggested that nitric oxide (NO) is a potential regulator of leptin-induced lipolysis. To explore the pathophysiology of weight gain during atypical antipsychotic treatment, we planned to investigate olanzapine's influence on leptin and NO levels and weight gain. The study comprised 21 patients with schizophrenia who were enrolled in olanzapine monotherapy, and 21 healthy controls. The fasting plasma NO and leptin levels were measured in both patients and controls at baseline. The patients were also evaluated at sixth week according to the Positive and Negative Syndrome Scale (PANSS), body mass index (BMI), weight, serum leptin and NO levels. At baseline, the mean leptin level in the olanzapine group was not different compared to that in controls after BMI or age adjustment. A significant increase in leptin levels by means of olanzapine use was seen ($P < 0.01$). Higher plasma NO levels were observed in patients with schizophrenia compared with the control group at baseline ($P < 0.01$). At the evaluation of week 6, a significant decrease in the mean plasma NO level was found in the olanzapine group ($P < 0.05$). The changes in total PANSS scores were correlated with change in leptin levels ($r = 0.58$, $P < 0.05$), and with the change in weight ($r = 0.54$, $P < 0.05$). In addition, there was a severe significant negative correlation between the changes in leptin levels and NO levels ($r = 0.73$, $P < 0.01$). The results confirmed that leptin and NO might be associated with olanzapine-induced weight gain.

Keywords: Olanzapine; Leptin; Nitric oxide; Weight gain

1. Introduction

One of the reactive oxygen species (ROS), nitric oxide (NO^-) is known to be both an ROS and a neurotransmitter in the central (CNS) and peripheral nervous system. Although NO is described as an atypical neurotransmitter in the nervous system, the implication of secondary messenger seems more appropriate (Schulman, 1997). NO is produced by the family of nitric oxide synthase (NOS) and is known to affect neurodevelopmental process in the CNS (Black et al., 1999). NOS has been demonstrated in rat white adipose tissue (Ribiere et al., 1996), indicating that adipocytes are a potential source of NO production. Recently, evidence for an involvement of NO in both rat and human lipolysis has been reported (Gaudiot et al., 1998; Andersson et al., 1999). Leptin, the ob gene product, provides feedback to the receptors in the central nervous system that control body weight homeostasis (Prolo et al., 1998). It is released from white adipose tissue and some other tissues including brown adipose tissue, the human placenta, and the breast tissue (Himms-Hagen, 1999). A growing number of studies have focused on the leptin levels in psychotropic drug use recently (Melkersson

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et al., 2000; Eder et al., 2001; Atmaca et al., 2002a,b; Fitzgerald et al., 2003; Graham et al., 2005; Hosojima et al., 2005; Smith et al., 2005; Murashita et al., 2005; Eder-Ischia et al., 2005). Leptin administration has reduced food intake and weight, suggesting its role on weight regulation (Halaas et al., 1995; Pelleymounter et al., 1995). The weight gain induced by clozapine and olanzapine has been reported to be associated with an increase in both leptin and triglyceride levels (Osser et al., 1999; Kraus et al., 1999; Atmaca et al., 2002b). However, the mechanism of leptin-induced lipolysis still remains to be completely elucidated. Interestingly, exogenous leptin administration has been shown to induce a dose-dependent release of circulating NO (Frühbeck, 1999). In addition, Frühbeck and Gomez-Ambrosi (2001) suggest that NO is a potential regulator of leptin-induced lipolysis. NO is formed by three isoforms of NOS. Endothelial NOS (eNOS) and neuronal NOS (nNOS) are calcium dependent, while inducible NOS (iNOS) is calcium independent and is synthesized in response to a variety of stimuli (Nathan, 1997). Evidence of NOS has been demonstrated in adipose tissue (Ribiere et al., 1996). Moreover, the involvement of NO in both rat and human lipolysis has been emphasized (Frühbeck and Gomez-Ambrosi, 2001). Stimulation of iNOS in skeletal muscle and white adipose tissue has been proposed as an association between obesity and insulin resistance (Kapur et al., 2000; Perreault and Marette, 2001). Another possibility explaining the reduced adiposity in iNOS−/− mice is related to an elevated lipolytic activity. This is supported by the observation that blockade of NO production with an inhibitor of NOS rises the lipolysis in humans, indicating an inhibitory effect of NO on lipolysis (Andersson et al., 1999).We have previously investigated leptin levels in antipsychotic-induced weight gain and found that atypical antipsychotic, especially clozapine and olanzapine-induced weight gain is related to increased levels of leptin (Atmaca et al., 2002b). The role of NO on weight was presented above. So, to explore the pathophysiology of weight gain during atypical antipsychotic treatment, we planned to investigate olanzapine's influence on both leptin and NO levels and weight gain.

2. Materials and methods

The sample consisted of 21 patients (14 males and 7 females) who applied to Firat University School of Medicine Department of Psychiatry and were diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. A DSM-IV diagnosis of schizophrenia was established on the basis of independent clinical interviews by one senior psychiatrist. In fact, there were 26 patients free of psychotropic drugs at least for two weeks as the initial sample. But five were not included into the study because of physical reasons (diabetes mellitus in one patient), requirement of additional drug (two patients; chlorpromazine use), and discontinuation because of intolerance ($n = 2$). Control group consisted of 21 age- and sex-matched healthy subjects according to exclusion criteria among the hospital staff who had no history of a psychiatric disorder.

Physical and neurological examination were performed for each of the patients and controls. Liver and kidney function tests were evaluated. Subjects having normal results and without any exclusion criteria were admitted to the study. Exclusion criteria were as follows; alcohol and substance abuse or dependence; having an important medical problem such as Wilson's disease, Down's syndrome, malnutrition, pregnancy, diabetes mellitus, chronic renal failure, cancer, liver cirrhosis and thyroid diseases, treatment with glucocorticoids, anticonvulsants, oral contraceptives, psychotropic drugs and any antioxidant agents such as vitamins (i.e., E and C vitamins), xantin oxidase inhibitors (allopurinol, folic acid), and non-steroidal antiinflammatory drugs; presence of epilepsy and severe neurologic disorder such as Parkinson, Huntington, and Alzheimer diseases; presence of infectious disease and excessive obesity, a previous history of lipid lowering treatment and the presence of any endocrinological state. All participants were carefully assessed to exclude autoimmune, pulmonary, infectious diseases and neoplasms. All patients and controls were free of all medications at least in the previous two weeks. BMI was calculated dividing the weight (in kilograms) by the squared height (in meter) ($\mathrm{BMI} = \mathrm{kg/m^2}$). After the complete description of the study to the subjects, all subjects gave informed written consent which was in accordance with the Declaration of Helsinki and *was approved by the local ethic committee*. All patients received a routine hospital diet. The patients were evaluated at the baseline and sixth week with respect to the Positive and Negative Syndrome Scale (PANSS) (Andreasan, 1983, 1984), BMI, weight, serum leptin and nitrate levels.

Venous blood samples from left forearm vein were collected into 5 ml vacutainer tubes containing potassium EDTA between 7 and 8 a.m. after overnight fasting. Some hematological parameters including hemoglobin, hematocrit, red and white blood cell were measured by using an autoanalyzer (Coulter Max M, Coulter Electronics Ltd., Luton, UK). The data on smoking were obtained from each patient using a questionnaire on one day before blood drawing. Smoking was not permitted after 23.00 h, one day before blood drawing. Firstly, the blood samples were deproteinized. Afterwards, nitric oxide levels were determined by measuring nitrate and nitrite values in Griess reaction. The stable oxidation end products of NO, NO^{2-}, and NO^{3-} can be readily measured in biological fluids and

have been used in vitro and in vivo as indicators of NO production (Evans, 1993). Therefore, plasma nitrite concentration was accepted as an index of NO·. For total nitrite detection, deproteinized plasma was treated with copporized cadmium (Cd) granules to reduce NO^{3-} to NO^{2-}. Nitrite concentrations were quantified by a colorimetric assay based on the Griess reaction (Mahadik et al., 2001). Briefly, a chromophore with a strong absorbance at 545 nm is formed by reaction of nitrite with a mixture of *N*-naphthylethylene diamine and sulphanilamide. A standard curve was established with a set of serial dilutions (10^{-8}–10^{-3} mol/l) of sodium nitrite. Results were expressed as micromoles per liter plasma (μmol/l).

The leptin levels were measured using the DRG Diagnostics kit (DRG Instruments GmbH, Germany) in enzyme-linked immunoassay (ELISA) method.

Statistical analysis was performed using the statistical package for social sciences (SPSS/PC 9.05 version, 1998). In the statistical analysis, Student's *t* test and Pearson's method of correlation were used. Differences were considered significant at $P < 0.05$ for all these tests.

3. Results

No significant difference in age (30.4 ± 7.8 for patients vs. 29.2 ± 6.7 years for controls) was found ($P > 0.05$). With respect to the sex distribution, there were 14 females and 7 males in the olanzapine group, and 12 females and 9 males in controls ($P > 0.05$). As can be seen, there were no significant differences among groups from the point of the mean age, or female/male ratio. At the evaluation of week 6, the mean olanzapine dose was 16.6 ± 5.1 mg/day for the olanzapine group. In addition, there was no difference between patients and controls with regard to the mean duration for smoking, with 9.5 ± 5.3 and 8.3 ± 4.9 years, respectively ($P > 0.05$). Fourteen of the patients and twelve of the controls were smokers. Twelve of fourteen smoker patients had >20 cigarettes per day except for two patients who had between 10 and 20 cigarettes per day. On the other hand, eleven of smoker controls had >20 cigarettes per day.

There was no statistically significant difference between the olanzapine and control groups with respect to the weight at baseline ($P > 0.05$). The mean change in weight for the olanzapine group throughout six weeks was 6.8 ± 3.0 kg ($P < 0.05$).

At baseline, the mean leptin level in the olanzapine group was not different compared to that in controls after BMI or age adjustment ($F = 0.8$, $P > 0.05$ adjusted for BMI; $F = 1.1$, $P > 0.05$ adjusted for age). In the olanzapine group, the mean increase in leptin levels for the study period was 6.1 ± 2.2 mg/dL. Paired *t* test revealed a significant increase in leptin levels by means of olanzapine use ($P < 0.01$).

Higher plasma NO levels were observed in patients with schizophrenia compared with the control group at baseline (36.8 ± 13.2 μM vs. 24.9 ± 11.4 μM in patients and controls, respectively) ($P < 0.01$). NO levels were unaffected by smoking in both patient and control groups. There were also no effects of gender on the NO levels in both groups. At the evaluation of week 6, a significant decrease in the mean plasma NO level was found in the olanzapine group ($P < 0.05$), but not in controls ($P > 0.05$).

No differences were observed in glucose levels between at baseline and week 6 in both patients and controls whereas triglyceride levels were increased in patient group ($P < 0.01$).

The weight, PANSS score, NO and leptin levels, *triglyceride, glucose* and BMI at baseline and week 6 in the groups were presented in Table 1.

The change in leptin levels was correlated with the change in BMI ($r = 0.55$, $P < 0.05$) and with the change in weight ($r = 0.61$, $P < 0.05$) in the patient group. There was a severe significant negative correlation between the

Table 1
The weight, PANSS score, NO and leptin levels, and BMI at baseline and week 6 in the groups

	Patients ($n = 21$)	Controls ($n = 21$)	*P*
Body weight (kg)			
Baseline	62.4 ± 3.9	58.9 ± 3.1	NS
Treatment	69.2 ± 4.5	59.4 ± 3.8	$P < 0.01$
Change	6.8 ± 3.0	0.5 ± 0.4	
P	$P < 0.05$	NS	
PANSS Score			
Baseline	89.9 ± 5.1	–	–
Treatment	78.1 ± 3.8	–	–
P	$P < 0.01$	–	–
NO (μmol/l)			
Baseline	36.8 ± 13.2	24.9 ± 11.4	$P < 0.01$
Treatment	28.2 ± 10.6	25.9 ± 12.6	$P < 0.05$
Change	8.6 ± 5.3	1.0 ± 1.4	
P	$P < 0.05$	NS	
Leptin (mg/dL)			
Baseline	5.9 ± 1.5	5.7 ± 1.3	NS
Treatment	12.0 ± 3.1	6.0 ± 1.7	$P < 0.01$
Change	6.1 ± 2.2	0.3 ± 0.7	
P	$P < 0.01$	NS	
BMI (kg/m^2)			
Baseline	22.7 ± 2.2	22.5 ± 2.9	NS
Treatment	26.5 ± 3.9	23.0 ± 3.3	$P < 0.05$
Change	28.1 ± 1.6	0.3 ± 0.7	NS
P	$P < 0.05$	NS	
Tryglyceride (mg/dL)			
Baseline	162.7 ± 11.4	167.9 ± 19.1	NS
Treatment	190.4 ± 10.9	163.5 ± 16.6	$P < 0.01$
Change	27.7 ± 5.9	4.4 ± 1.3	
P	$P < 0.01$	NS	
Glucose (mg/dL)			
Baseline	103.8 ± 9.7	108.3 ± 11.6	NS
Treatment	105.2 ± 8.4	110.9 ± 15.7	NS
Change	1.4 ± 0.4	4.4 ± 1.3	
P	NS	NS	

changes in leptin levels and NO levels ($r = 0.73$, $P < 0.01$). The changes in total PANSS scores were correlated with change in leptin levels ($r = -0.58$, $P < 0.05$), and with the change in weight ($r = -0.54$, $P < 0.05$).

4. Discussion

Recently numerous studies have shown that leptin and NO which are linked to each other are involved in the control of feeding behavior. From this perspective, it was important to examine the levels of leptin and NO in olanzapine-induced weight gain. Therefore, in the present study, we investigated the effects of ongoing olanzapine treatment on leptin and NO values. We showed that leptin and NO levels were higher in schizophrenic patients compared to age, sex and weight matched controls. To our knowledge, this is the first report evaluating the relationship between leptin and NO together and olanzapine-induced weight gain. The major findings of our study are as follows: (i) Olanzapine use led to a considerable marked increase in weight, leptin levels, as previously found, and NO levels. (ii) The changes in total PANSS scores were correlated with the change in leptin levels, and with the change in weight and NO levels.

The mechanism of antipsychotic-induced weight gain remains incompletely understood. The factors affecting weight gain in patients receiving antipsychotic treatment are probably complex. An important theory is the histamine-1 (H_1) receptor blockade by antipsychotics since H_1 receptors are considered to be involved in the regulation of food intake and moreover, a robust correlation was found between novel antipsychotic affinity for the histamine receptor and antipsychotic-induced weight gain (Richelson, 1996; Wirshing et al., 1999). Apart from this, however, there have been many approaches to account for antipsychotic-related weight gain. Many factors including changes in reproductive hormones (Baptista et al., 2000), gastric misperception of satiety (Coddington and Bruch, 1970) and cortisol elevation (Nash et al., 1988) have been proposed. Furthermore, it has been reported that antagonism on serotonin, dopamine and norepinephrine receptors may be associated with weight gain (Stahl, 1998).

Several studies showed hypothalamus to be a critical target for the satiety effects of leptin (Auwerx and Staels, 1998). It has been reported that leptin has a more potent anorectic effect when administered centrally compared to peripheral administration (Campfield et al., 1995). It is transported via the blood–brain barrier (Stephens et al., 1995), and exhibits its metabolic effects by interacting with specific receptors located in the central nervous system and peripheral tissues (Lee et al., 1996). *After a literature investigating*, we can find numerous references demonstrating the interaction between schizophrenia and plasma NO. No change, decreases and increases have been reported in these studies (Das et al., 1996; Srivastava et al., 2001; Zoroglu et al., 2002; Suzuki et al., 2003; Taneli et al., 2004). In our schizophrenic group, pre-treatment serum NO levels were higher than those of control subjects (36.8 ± 13.2 μM vs. 24.9 ± 11.4 μM, $P < 0.01$), as seen in the investigations of Taneli et al. (2004) and Zoroglu et al. (2002) Post-treatment values were significantly reduced in the our study. Taneli et al. (2004) also found reduced levels after treatment but this did not reach the statistically significance. Further studies with longer therapy periods seem to provide some new clues for novel treatment strategies employing antioxidants and NOS inhibitors in schizophrenia. Recently NO has been demonstrated to play an important role in the regulation of food intake and energy expenditure (Morley and Flood, 1994; Ueta et al., 1995). NO has been shown to be involved in regulating ingestive behavior, and inhibitors of NO synthase (NOS) activity produce anorectic effects and reduce body-weight gain when administered in both lean and obese rats (Squadrito et al., 1993). More recently, it has been demonstrated that NO overproduction is reduced by leptin in cultured islets isolated from obese Zucker diabetic fatty rats (Wang et al., 1998), and intracerebroventricular (ICV) leptin injection has been reported to be capable of inhibiting diencephalic NOS activity in mice (Calapai et al., 1998). It has been concluded that the brain L-arginine/NO pathway is involved in leptin effects on food intake and body-weight gain and has been indicated that leptin-induced inhibition of brain NO synthesis is involved in determining leptin effects on central regulation of feeding behavior (Calapai et al., 1999). Moreover, it has been concluded that both central and peripheral leptin administration cause an increase in 5-HT turnover, and the experiments reported demonstrate for the first time that nNOS activity is required for the effects of leptin on 5-HT turnover in the brain (Calapai et al., 1999).

As to relationship between leptin and NO values, and improving psychopathology, decrease in total PANSS scores were negatively correlated with increase in leptin and NO levels in the present study. It has been reported that weight gain has some predictive value for a positive response to the patients under the clozapine treatment (Jalenques et al., 1996). On the other hand, it has been proposed that leptin mediates the beneficial effects of antipsychotics (Kraus et al., 1999).

There are some methodological limitations of the present study that must be acknowledged. Firstly, the relatively small sample size might not be representative of the patients treated with atypical antipsychotics. Secondly, some factors which might be related to olanzapine-induced weight gain, such as cytokines and soluble cytokine receptors, *soluble leptin receptors* and some neuroendocrine factors, strictly related with

energy homeostasis, such as insulin and adinopectin were not assessed in the present study. Furthermore we could not test if poor economic status and other psychosocial factors might be related to serum leptin levels. *In addition, the study has relatively simple not complex design.* Finally, it is worth mentioning that some confounding factors related to outpatient habits, i.e., exercise, life style and so on, and dietary changes may affect the production of NO. In conclusion, our results suggest that both leptin and NO increases with olanzapine-induced weight gain and these results need to be confirmed by more comprehensive and detailed further studies to decipher the exact roles of leptin and NO concurrently in atypical antipsychotic-induced weight gain.

References

Andersson K, Gaudiot N, Ribiere C, Elizalde M, Giudicelli Y, Arner P. A nitric oxide-mediated mechanism regulates lipolysis in human adipose tissue in vivo. British Journal of Pharmacology 1999;126:1639–45.

Andreasen NC. Scale for the assessment of negative symptoms (SANS). The University of Iowa: Department of Psychiatry College of Medicine; 1983.

Andreasen NC. Scale for the assessment of positive symptoms (SAPS). The University of Iowa: Department of Psychiatry College of Medicine; 1984.

Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum cholesterol and leptin levels in patients on lithium treatment. Neuropsychobiology 2002a;46:67–9.

Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Gecici O. Weight gain, serum leptin and triglyceride levels in the patients with schizophrenia on antipsychotic treatment with quetiapine, olanzapine and haloperidol. Schizophrenia Research 2002b;60:99–100.

Auwerx J, Staels B. Leptin. Lancet 1998;351:737–42.

Baptista T, Lacruz A, De Mendoza S, Mendoza Guillen JM, Silvera R, Angeles F, et al. Body weight gain after administration of antipsychotic drugs: correlation with leptin, insulin and reproductive hormones. Pharmacopsychiatry 2000;33:81–8.

Black MD, Selk DE, Hitchcock JM, Wettstein JG, Sorensen SM. On the effect of neonatal nitric oxide synthase inhibition in rats: a potential neurodevelopmental model of schizophrenia. Neuropharmacology 1999;38:1299–306.

Calapai G, Corica F, Allegra A, Corsonella A, Sautebin L, De Gregorio T, et al. Effects of intracerebroventricular leptin administration on food intake, body-weight gain and diencephalic nitric oxide synthase activity in the mouse. British Journal of Pharmacology 1998;125:798–802.

Calapai G, Corica F, Corsonello A, Sautebin L, Di Rosa M, Campo GM, et al. Leptin increases serotonin turnover by inhibition of brain nitric oxide synthesis. Journal of Clinical Investigation 1999;104:975–82.

Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse Ob protein; evidence for a peripheral signal linking adiposity and central neural networks. Science 1995;269:546–9.

Coddington RD, Bruch H. Gastric perceptivity in normal, obese, and schizophrenic subjects. Psychosomatics 1970;9:571–9.

Das I, Khan NS, Puri BK, Hirsch SR. Elevated endogenous nitric oxide synthase inhibitor in schizophrenic plasma may reflect abnormalities in brain nitric oxide production. Neuroscience Letters 1996;13(215):209–11.

Eder U, Mangweth B, Ebenbichler C, Weiss E, Hofer A, Hummer M, et al. Association of olanzapine-induced weight gain with an increase in body fat. American Journal of Psychiatry 2001;158:1719–22.

Eder-Ischia U, Ebenbichler C, Fleischhacher WW. Olanzapine-induced weight gain and disturbances of lipid and glucose metabolism. Essent Psychopharmacol 2005;6:112–7.

Evans PH. Free radicals in brain metabolism and pathology. British Medical Bulletin 1993;49:577–87.

Fitzgerald PB, Scaffidi A, Morris MJ, de castella AR, Kulkarni J. The relationship of changes in leptin, neuropeptide Y and reproductive hormones to antipsychotic induced weight gain. Human Psychopharmacology 2003;18:551–7.

Frühbeck G. Pivotal role of nitric oxide in the control of blood pressure after leptin administration. Diabetes 1999;48:903–8.

Frühbeck G, Gomez-Ambrosi J. Modulation of the leptin-induced white adipose tissue lipolysis by nitric oxide. Cell Signal 2001;13:827–33.

Gaudiot N, Jaubert AM, Charbonnier E, Sabourault D, Lacasa D, Giudıcelli Y, et al. Modulation of white adipose tissue lipolysis by nitric oxide. Biological Chemistry 1998;273:13475–81.

Graham KA, Gu H, Lieberman JA, Harp JB, Perkins DO. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. American Journal of Psychiatry 2005;162:1744–6.

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543–6.

Himms-Hagen J. Physiological roles of the leptin endocrine system: differences between mice and humans. Critical Reviews in Clinical Laboratory Sciences 1999;36:575–655.

Hosojima H, Togo T, Odawara T, Hasegawa K, Miura S, Kato Y. Early effects of olanzapine on serum levels of ghrelin, adiponectin and leptin in patients with schizophrenia. Journal of Psychopharmacology 2005 [Epub ahead of print].

Jalenques I, Tauveron I, Albuisson E, et al. Weight gain as a predictor of long term clozapine efficiency. Clinical Drug Investigation 1996;12:16–25.

Kapur S, Picard F, Perreault M, Deshaies Y, Marette A. International Journal of Obesity Related Metabolic Disorders 2000;24:S36–40.

Kraus T, Haack M, Schuld A, Hinze-Selch D, Kuhn M, Uhr M, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. American Journal of Psychiatry 1999;156:312–4.

Lee GH, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI, et al. Abnormal splicing of the leptin receptor in diabetic mice. Nature 1996;379:632–5.

Mahadik SP, Evans D, Lal H. Oxidative stress and role of antioxidant and ω-3 essential fatty acid supplementation in schizophrenia. Progress in Neuropsychopharmacology and Biological Psychiatry 2001;25:463–93.

Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. Journal of Clinical Psychiatry 2000;61:742–9.

Morley JE, Flood JF. Effect of competitive antagonism of NO synthetase on weight and food intake in obese and diabetic mice. American Journal of Physiology 1994;266:164–8.

Murashita M, Kusumi I, Inoue T, tkahashi Y, Hosoda H, Kangawa K, et al. Olanzapine increases plasma ghrelin level in patients with schizophrenia. Psychoneuroendocrinology 2005;30:106–10.

Nash JF, Meltzer HY, Gudelsky GA. Elevation of serum prolactin and corticosterone concentrations in the rat after the administration of 3,4-methylenedioxy metamphetamine. Journal of Pharmacology and Experimental Therapeutics 1988;245:873–9.

Nathan C. Inducible nitric oxide synthase: what difference does it make? Journal of Clinical Investigation 1997;100:2417–23.

Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. Journal of Clinical Psychiatry 1999;60:767–70.

Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995;269:540–3.

Perreault M, Marette A. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. Nature Medicine 2001;7:1138–43.

Prolo P, Wwong ML, Licinio J. Leptin. Internatonal Journal of Biochemistry and Cell Biology 1998;130:1285–90.

Ribiere C, Jaubert AM, Gaudiot N, Sabourault D, Marcus ML, Boucher JL, et al. White adipose tissue nitric oxide synthase: a potential source for NO production. Biochemical and Biophysical Research Communications 1996;222:706–12.

Richelson E. Preclinical pharmacology of neuroleptics: focus on new generation compounds. Journal of Clinical Psychiatry 1996;57:4–11.

Schulman H. Nitric oxide: a spatial second messenger. Molecular Psychiatry 1997;2:296–9.

Squadrito F, Calapai G, Cucinotta D, Altavilla D, Zingarelli B, Ioculano M, et al. Anorectic activity of NG-nitro-L-arginine, an inhibitor of brain nitric oxide synthase, in obese Zucker rats. European Journal of Pharmacology 1993;230:125–8.

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Seth PK, et al. Nitrite content and antioxidant enzyme levels in the blood of schizophrenia patients. Psychopharmacology (Berl) 2001;158:140–5.

Stahl SM. Neuropharmacology of obesity: my receptors made me eat it. Journal of Clinical Psychiatry 1998;59:447–8.

Stephens TW, Basinski M, Bristow PK, Bue-Valleskey JM, Burgett SG, Craft L, et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature 1995;377:530–2.

Suzuki E, Nakaki T, Nakamura M, Miyaoka H. Plasma nitrate levels in deficit versus non-deficit forms of schizophrenia. Journal of Psychiatry and Neuroscience 2003;28:288–92.

Taneli F, Pirildar S, Akdeniz F, Uyanik BS, Ari Z. Serum nitric oxide metabolite levels and the effect of antipsychotic therapy in schizophrenia. Archives of Medical Research 2004;35:401–5.

Ueta Y, Levy A, Chowdrey HS, Lightman SL. Inhibition of hypothalamic nitric oxide synthase gene expression in the rat paraventricular nucleus by food deprivation is independent of serotonin depletion. Journal of Neuroendocrinology 1995;7:861–5.

Wang MY, Koyama K, Shimabukuro M, Newgard CB, Unger RH. OB-Rb gene transfer to leptin-resistant islets reverses diabetogenic phenotype. Proceedings of the National Academy of Sciences of the United States of America 1998;95:714–8.

Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, et al. Novel antipsychotics: comparison of weight gain liabilities. Journal of Clinical Psychiatry 1999;60:358–63.

Zoroglu SS, Herken H, Yurekli M, Uz E, Tutkun H, Savas HA, et al. The possible pathophysiological role of plasma nitric oxide and adrenomedullin in schizophrenia. Journal of Psychiatric Research 2002;36:309–15.