Leptin Concentrations Are Increased in Subjects Treated With Clozapine or Conventional Antipsychotics

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Background: Overweight is a considerable clinical problem in patients treated with antipsychotic agents. Recent results suggest that insulin resistance with increased insulin levels is also associated with treatment with the atypical antipsychotic agent clozapine. Leptin is important for the control of body weight and has been proposed to be a link between obesity and the insulin resistance syndrome. This study examined if clozapine-treated subjects and subjects treated with conventional antipsychotics had increased leptin levels compared with the general population and whether there was a gender difference in this respect.

Method: Clozapine-treated patients (N = 41), patients treated with conventional antipsychotic drugs (N = 62), and healthy subjects from the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project (N = 189) were investigated with a cross-sectional study design. Weight, body mass index (BMI), and plasma leptin concentrations were measured, and all study subjects were investigated for the presence of diabetes mellitus. Drug treatment, health status, and smoking habits were registered.

Results: After adjustment for gender, BMI, smoking habits, age, and diabetes, hyperleptinemia was independently ($p < .001$) associated with clozapine treatment and with treatment with conventional antipsychotics ($p < .005$) within a multiple regression analysis. In separate multiple regression analyses, leptin levels were significantly associated with clozapine treatment in men ($p = .002$) and women ($p = .023$) and with conventional antipsychotic treatment in men ($p = .027$) but not in women.

Conclusion: Treatment with clozapine as well as with conventional antipsychotics is associated with increased levels of circulating leptin. Hyperleptinemia can be an important link in the development of overweight and the insulin resistance syndrome in subjects receiving antipsychotic drugs, especially atypical agents like clozapine.

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Overweight is a well-documented adverse effect of antipsychotic agents.[1–6] Conventional antipsychotic agents promote weight gain in varying degrees. The mechanism is poorly understood. Reduced physical activity and less energy utilization as well as increased thirst and appetite have been proposed as possible mediators for this effect.[1,2] Low-potency drugs such as chlorpromazine and thioridazine are more often associated with weight gain compared with high-potency antipsychotics such as haloperidol.[1,2] However, excessive weight gain has also been related to treatment with atypical antipsychotics such as clozapine and olanzapine.[3–6]

Antipsychotic drugs, especially clozapine and olanzapine, have also been reported to affect the glucose-insulin homeostasis.[7–10] Since it was recently reported that clozapine concentrations were closely linked to insulin levels in 13 clozapine-treated patients,[11] it may be anticipated that clozapine induces insulin resistance, which is associated with a compensatory increase in insulin secretion. Subjects with failure of this compensatory hyperinsulinemia might then develop diabetes. Clozapine and olanzapine have also been associated with hypertriglyceridemia.[12–14] Indeed, clozapine has thus been associated with several of the risk factors of the metabolic syndrome, which are linked to an increased risk for cardiovascular disease.[15] Components of this syndrome are impaired glucose regulation or diabetes, insulin resistance, dyslipidemia, hypertension, central obesity, and microalbuminuria.[15]

The adipocyte-derived protein leptin is important for body weight homeostasis.[16] The hormone is secreted from the adipocyte in relation to the degree of adiposity and recent food intake, and it induces satiety and stimulates

energy expenditures.[16] Leptin may also mediate adverse metabolic effects associated with obesity, i.e., the insulin resistance syndrome.[17,18] However, whether the association between obesity and diabetes in patients treated with clozapine is accompanied by increased leptin levels is not established. In a small longitudinal study,[19] serum leptin levels at least doubled in 8 of 12 patients treated with clozapine. In another small longitudinal study,[20] significant increases in weight, body mass index (BMI), and leptin levels were found in patients receiving clozapine or olanzapine, but remained stable in patients who received haloperidol or no pharmacologic treatment. Unfortunately, gender aspects were not addressed in these studies, which are important considering the profound gender differences in circulating leptin levels.[21] The aim of our study was therefore to examine if clozapine-treated subjects and subjects treated with conventional antipsychotics have increased leptin levels compared with the general population and whether there is a gender difference in this respect.

METHOD

Subjects

The psychiatric patients included in our study participated in a previous study.[7] By September 1, 1995, 64 patients between 22 and 65 years old were treated with clozapine at the psychiatric clinic at Gällivare Hospital, in northern Sweden. Due to practical reasons, blood samples could not be obtained in 14 of those subjects. Nine of the remaining subjects concomitantly treated with conventional antipsychotics were excluded and thus 41 patients remained for this study.

At the same time, 125 patients between 26 and 65 years of age were treated with depot injections of various conventional antipsychotics. Forty-six of these patients were living in remote places and were excluded for practical reasons, 12 did not want to participate in the study, and blood samples were not obtained from 5 subjects. Thus, 62 patients were finally included. They were treated with the following depot antipsychotics: haloperidol (N = 20), zuclopenthixol (N = 21), fluphenazine (N = 10), perphenazine (N = 7), and flupenthixol (N = 4). Some of these patients had additional treatment with oral antipsychotic medications (N = 36), most often levomepromazine (N = 25). To compare the doses of different antipsychotics, the patient's daily dose of depot injections or oral medication was transformed into oral chlorpromazine equivalents. The daily dose of depot injections was first adjusted for proportion of active substance. For haloperidol, 100% of the fluid is active substance whereas for zuclopenthixol, 72.2%; for perphenazine decanoate, 72.4%; for fluphenazine decanoate, 73.9%; and for flupenthixol decanoate, 74.0% constitute the active substance. The daily active dose was then adjusted according to its bioavailability: 70% for perphenazine, 60% for haloperidol, 50% for zuclopenthixol, 50% for flupenthixol, and 30% for fluphenazine.[22] Thereafter the dose was transformed into chlorpromazine equivalents according to a table for oral equipotency.[23] Oral antipsychotic dose was directly transformed into chlorpromazine equivalents.

Table 1. Psychiatric Diagnosis According to DSM-IV Criteria in 103 Psychiatric Patients Treated With at Least 1 Antipsychotic Drug

	Clozapine Group (N = 41)		Conventional Antipsychotic Group (N = 62)	
Diagnosis	N	%	N	%
Schizophrenia	37	90	50	81
Delusional disorder	3	7	3	5
Schizoaffective disorder	0	0	2	3
Psychotic disorder	1	2	0	0
Personality disorder	0	0	3	5
Bipolar disorder	0	0	4	6

For all psychiatric patients, the following variables were registered: age, sex, body weight, height, drug therapy, and duration of underlying disease. Weight and height were obtained from the medical records, and BMI was calculated as weight (kg)/height squared (m^2). Information about drug therapy, medical history, and smoking habits was collected from the medical records and from a supplementary interview. The onset of the psychiatric disease was defined as the first time the patient presented symptoms consistent with the diagnosis. The psychiatric diagnoses were set and confirmed independently by 2 psychiatrists according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[24] and the distribution of diagnosis is shown in Table 1.

The control group was a population-based sample from the 2 northernmost counties in Sweden (Västerbotten and Norrbotten), which was obtained within the framework of the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) study. The selection of this sample has recently been described in detail.[25] In this study, 189 individuals between 25 and 65 years of age were included. The participating subjects were interviewed about medical history and their smoking habits.

The study was approved by the regional Ethics Committee at Umeå University Hospital and the data handling procedures by the National Computer Data Inspection Board. Informed consent was obtained from all subjects.

Sampling and Analysis

A blood sample for the leptin analysis was collected between 7:00 a.m. and 9:00 a.m. in the subjects of the MONICA population and between 7:00 a.m. and noon in the majority of the psychiatric patients. In 12 subjects (10 with clozapine treatment and 2 with conventional antipsychotic treatment), the sample was obtained be-

Table 2. Subject Characteristics[a]

Characteristic	MONICA Population (N = 189)	Clozapine Group (N = 41)	Conventional Antipsychotic Group (N = 62)	p Value	Comparison[b]
Men, N (%)	84 (44)	21 (51)	38 (61)	.07[c]	
Diabetes mellitus, N (%)	7 (3.7)	4 (9.8)	4 (6.5)	.24[c]	
Smokers, N (%)	38 (20)	20 (51)	28 (59)	< .001[c]	
1–20 cigarettes/d	38 (20)	13 (33)	18 (38)		
21–40 cigarettes/d	0 (0)	7 (18)	8 (17)		
> 40 cigarettes/d	0 (0)	1 (3)	2 (4)		
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		
Age, y	46 (44 to 48)	41 (39 to 44)	49 (46 to 51)	.006[d]	ac
Weight, kg	74 (72 to 77)	79 (74 to 84)	80 (75 to 85)	.03[d]	b
Height, m	1.70 (1.69 to 1.71)	1.70 (1.67 to 1.73)	1.66 (1.60 to 1.72)	.17[d]	
BMI, kg/m^2	25.7 (25.0 to 26.4)	27.4 (25.8 to 29.0)	27.9 (26.4 to 29.4)	.004[d]	b
Dose, mg/d					
Men		451 (388 to 514)	348 (248 to 448)[e]	…	
Women		300 (216 to 384)	397 (295 to 498)[e]	…	
Duration of disease, y		14.4 (11.6 to 17.2)	21.7 (19.6 to 23.8)	< .001[f]	
Duration of current neuroleptic treatment, y		2.8 (2.4 to 3.3)	8.7 (7.1 to 10.2)	< .001[f]	
Leptin level, ng/mL[g]					
Men	4.5 (3.9 to 5.1)	6.7 (5.0 to 8.9)	6.4 (5.0 to 8.1)	.007[d]	ab
Women	13.7 (11.9 to 15.7)	20.6 (15.8 to 26.8)	19.8 (14.8 to 26.5)	.009[d]	

[a]Abbreviations: BMI = body mass index, CI = confidence interval, MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease, a study by the World Health Organization.[25]
[b]Significant differences between groups in ANOVA analysis after Bonferroni correction: a = MONICA population vs. clozapine, b = MONICA population vs. conventional antipsychotics, c = clozapine vs. conventional antipsychotics.
[c]Pearson chi-square test.
[d]Analysis of variance.
[e]Dose in mg oral chlorpromazine equivalents.
[f]Independent t test for the equality of means.
[g]Geometric means.

tween noon and 2:00 p.m. The plasma samples of leptin were stored at –80ºC (–176ºF) until analysis. The leptin analysis was performed by use of a double antibody radioimmunoassay with rabbit antihuman leptin antibodies, I^{131}-labeled human leptin as tracer and human leptin as standard. Interassay coefficients of variations were 1.9% at low levels (< 5 ng/mL) and 3.2% at high levels (10–l5 ng/mL) (Linco Research, Inc., St. Louis, Mo.).

An abbreviated oral glucose tolerance test was performed according to the standard of WHO in all subjects from the MONICA population and in all psychiatric patients with a random blood glucose above 5.0 mmol/L.[25] Diabetes mellitus was defined as a fasting capillary blood glucose value exceeding 6.7 mmol/L or a 2-hour post–oral glucose tolerance test blood glucose value above 11.0 mmol/L.[26]

Statistical Analysis

All calculations were made with the statistical program SPSS version 9.0 (SPSS, Inc., Chicago, Ill.). Since the distributions of the leptin concentrations were highly skewed, data were log transformed (natural logarithm, ln). After the transformation, skewness and kurtosis improved. Means (geometric for transformed values) are presented. Differences between groups were tested by chi-square test, independent t test, and by 1-way analysis of variance (ANOVA) with Bonferroni correction. Multiple linear regression analyses were performed with fixed entries of independent variables. Possible interactions between study variables were explored with bivariate and partial (adjusted for BMI) correlation analysis with ln-transformed values of leptin. The presence of outliers was checked by visual inspection of scatterplots, plotting of leverage, and DfBeta values (the difference between the standard regression coefficients when a case is included in the model compared to when it is excluded). A significant p value was set at .05.

RESULTS

Baseline characteristics of the 3 groups are presented in Table 2. Leptin concentrations were more than 3 times higher in women than in men. Analyses were therefore performed separately for women and men. The mean concentration of leptin in women was 50% higher in clozapine-treated subjects and 44% higher in subjects treated with conventional antipsychotics compared with the MONICA population. In men, the mean leptin concentration was 49% higher in clozapine-treated subjects and 42% higher in subjects treated with conventional antipsychotics compared with the MONICA population. Partial correlation coefficients between leptin concentrations and BMI controlling for sex and age were relatively high in all 3 study groups (r = 0.67–0.73).

Table 3. Linear Regression Model for Variables Associated With Circulating Leptin Concentrations[a]

Variable[b]	B	SE	β	p Value	Adjusted R^2
Whole population					72%
Male sex	1.16	0.06	0.68	< .001	
BMI	0.09	0.01	0.53	< .001	
Clozapine	0.33	0.09	0.13	< .001	
Conventional antipsychotics	0.24	0.08	0.11	.005	
Smoking	–0.12	0.05	–0.09	.013	
Age	0.004	0.002	0.060	.12	
Men					52%
BMI	0.11	0.01	0.65	< .001	
Clozapine	0.38	0.12	0.204	.002	
Conventional antipsychotics	0.25	0.11	0.15	.027	
Smoking	–0.06	0.08	–0.05	.41	
Age	0.007	0.003	0.13	.045	
Women					56%
BMI	0.09	0.01	0.72	< .001	
Clozapine	0.30	0.13	0.15	.023	
Conventional antipsychotics	0.22	0.13	0.11	.11	
Smoking	–0.16	0.07	–0.15	.023	
Age	0.001	0.003	0.021	.71	

[a]Abbreviations: B = regression coefficient; β = standardized regression coefficient, BMI = body mass index, SE = standard error of the regression coefficient.
[b]Variables are listed in the order they were introduced in the model.

Table 3 shows the results from multiple regression analyses with leptin concentrations as the dependent variable. High leptin levels were significantly associated with clozapine treatment and conventional antipsychotics after adjustments for sex, BMI, smoking, and age. After stratification for sex, this effect was statistically significant in both men and women treated with clozapine, but with conventional antipsychotics, it was significant in only men. In clozapine-treated subjects, the mean daily dose was significantly higher in men than in women (451 vs. 300 mg, p = .005), whereas in subjects treated with conventional antipsychotics, there was no significant difference in mean daily dose expressed as oral chlorpromazine equivalents (348 vs. 397 mg, p = .51).

Introducing diabetes and glucose variables or presence of other diseases including hypertension, coronary disease, stroke, and hyperlipidemia did not influence the results, neither did the variables clozapine dosage and dosage expressed as oral chlorpromazine equivalents in the specific analysis for the groups treated with clozapine and conventional antipsychotics, respectively (data not shown).

DISCUSSION

Treatment with clozapine and conventional antipsychotics was found to be independently and significantly associated with high circulating leptin levels. Increased leptin levels have been reported previously during treatment with clozapine and olanzapine,[19,20] but conventional antipsychotics have not been associated with increased leptin levels. Treatment with haloperidol does not seem to increase leptin levels in humans,[20] and leptin and insulin concentrations did not increase despite a significant weight gain in rats receiving treatment with sulpiride.[27]

Treatment with clozapine was associated with high levels of circulating leptin concentrations in men as well as in women. However, a significant association between treatment with conventional antipsychotics and high levels of circulating leptin was only found in men. This finding might be explained by a lack of power to detect a significant association between conventional antipsychotic therapy and leptin levels in the linear regression model used. However, other explanations may be possible. Similar gender differences with respect to the association between leptin and components of the insulin resistance syndrome seem to exist, and we have recently reported that hyperleptinemia is associated with waist circumference and hyperinsulinemia in men and in postmenopausal women, but not in premenopausal women.[25] Thus, a gender difference is likely to exist not only with regard to the absolute concentrations of leptin, but also with respect to regulation of leptin production. Interestingly, testosterone replacement reduces leptin levels in hypogonadal men,[28] and leptin levels correlate inversely to testosterone levels in healthy nonobese men and directly in nonobese women.[29] Speculatively, interaction between conventional antipsychotic treatment and androgens might contribute to gender differences in leptin levels in our study.

There were no relationships between leptin levels and doses administered of clozapine and conventional antipsychotics (expressed in oral doses of chlorpromazine equivalents). In a previous study,[19] only weak correlations between increases in leptin concentrations and serum levels of clozapine and its metabolites were found, indicating that there is no direct relationship between leptin levels and doses of antipsychotic medication.

The clinical implications of hyperleptinemia are not fully understood. Importantly, leptin is a main regulator of body weight[16] and can be a link between treatment with antipsychotic drugs and development of obesity and insulin resistance. The interaction of antipsychotic drugs with neuronal receptors for serotonin and histamine may also relate to weight gain induced by antipsychotic treatment. It has been thus demonstrated that the serotonin-2C (5-HT_{2C}) receptor subtype is of importance in regulating appetite,[30–32] and the atypical antipsychotics clozapine and olanzapine, which are high-affinity 5-HT_{2C} receptor antagonists,[33] appear to cause the greatest gain in mean body weight.[6] Interestingly, recent data suggest that leptin secretion is modified by serotonergic mechanisms.[34,35]

Leptin has also recently been suggested to affect feeding behavior through activation of the central histaminergic system via histamine H_1 receptors,[36] and H_1 receptors

have been proposed to be of major importance in the mechanism of antipsychotic-induced weight gain since there is a strong correlation between the affinity for the H_1 receptor and weight gain liability of various antipsychotic agents.[6] Thus, the hyperleptinemic action of clozapine may be instituted through influence of 5-HT_{2C} and H_1 receptors.

Other possible links also may exist between clozapine treatment, leptin, and the development of obesity and insulin resistance. Clozapine may increase insulin secretion,[11] thereby increasing leptin levels, as chronic hyperinsulinemia increases leptin concentrations.[21] Finally, whether direct effect of clozapine treatment secretion of leptin and leptin receptor sensitivity exists remains to be studied. Hyperleptinemia may interfere with the secretion of insulin.[37,38] The net result would be an alteration in peripheral insulin sensitivity, thus contributing to hyperinsulinemia and increased risk of type 2 diabetes mellitus.[39–42]

A potential drawback in this study is that the blood sampling for leptin was performed between 7:00 a.m. and 9:00 a.m. in the MONICA population and between 7:00 a.m. and 2:00 p.m. in the patients treated with antipsychotic drugs. Moreover, the subjects of the MONICA population were instructed to be fasting, while the subjects treated with antipsychotic agents were not. However, since leptin concentrations decrease approximately 20% between 8:00 a.m. and noon despite intake of breakfast and level off during the following hours,[43] one should expect lower values of leptin in the groups treated with antipsychotic drugs. It is therefore possible that our present results actually underestimate the true effect of antipsychotic drugs on leptin concentrations.

CONCLUSIONS

The present study demonstrates clearly that treatment with clozapine and conventional antipsychotics is associated with significantly increased concentrations of leptin. This effect was seen in both men and women in clozapine-treated subjects but only in men receiving conventional antipsychotics. Increased leptin levels may be an important link in the development of overweight and the insulin resistance syndrome seen in subjects receiving antipsychotic drugs, especially in those receiving atypical agents like clozapine.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others).

REFERENCES

1. Brady KT. Weight gain associated with psychotropic drugs. South Med J 1989;82:611–617
2. Stanton JM. Weight gain associated with neuroleptic medication: a review. Schizophr Bull 1995;21:463–472
3. Lamberti JS, Bellnier T, Schwarzkopf SB. Weight gain among schizophrenic patients treated with clozapine. Am J Psychiatry 1992;149: 689–690
4. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72
5. Gupta S, Droney T, Al Samarrai S, et al. Olanzapine-induced weight gain [letter]. Ann Clin Psychiatry 1998;10:39
6. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363
7. Hägg S, Joelsson L, Mjörndal 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;59:294–299
8. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108–111
9. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778–783
10. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000;34:865–867
11. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999,60: 783–791
12. Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999;156:1270–1272
13. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999;60:767–770
14. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, pt 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–553
16. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999; 341:879–884
17. Girard J. Is leptin the link between obesity and insulin resistance? Diabetes Metab 1997;3:16–24
18. Haynes WG, Sivitz WI, Morgan DA, et al. Sympathetic and cardiorenal actions of leptin. Hypertension 1997;30:619–623
19. Brömel T, Blum WF, Ziegler A, et al. Serum leptin levels increase rapidly after initiation of clozapine therapy. Mol Psychiatry 1998;3:76–80
20. Kraus T, Haack M, Schuld A, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. Am J Psychiatry 1999;156: 312–314
21. Ahrén B, Larsson H, Wilhelmsson C, et al. Regulation of circulating leptin in humans. Endocrine 1997;7:1–8
22. Balant-Gorgia AE, Balant LP, Andreoli A. Pharmacokinetic optimisation of the treatment of psychosis. Clin Pharmacokinet 1993;25:217–236
23. Davis JM. Comparative doses and costs of antipsychotic medication. Arch Gen Psychiatry 1976;33:858–861
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
25. Söderberg S, Olsson T, Eliasson M, et al. Plasma leptin levels are associated with abnormal fibrinolysis in men and postmenopausal women. J Intern Med 1999;245:533–543
26. WHO Study Group on Diabetes Mellitus. World Health Organization Technical Reports Series 727. Geneva, Switzerland: World Health Organization; 1985
27. Lacruz A, Baptista T, Mendoza S, et al. Antipsychotic drug-induced obesity in rats: correlation between leptin, insulin and body weight during sulpiride treatment. Mol Psychiatry 2000;5:70–76
28. Jockenhövel F, Blum WF, Vogel E, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. J Clin Endocrinol Metab 1997;82:2510–2513
29. Söderberg S, Olsson T, Eliasson M, et al. A strong association between biologically active testosterone and leptin in non-obese men and women is lost with increasing (central) adiposity. Int J Obes Relat Metab Disord 2001;25:98–105
30. Curzon G, Gibson EL, Oluyomi AO. Appetite suppression by commonly used drugs depends on 5-HT receptors but not on 5-HT availability. Trends Pharmacol Sci 1997;18:21–25
31. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice

lacking 5-HT_{2C} serotonin receptors. Nature 1995;374:542–546
32. Nonogaki K, Strack AM, Dallman MF, et al. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT_{2C} receptor gene. Nat Med 1998;4:1152–1156
33. Bymaster FP, Rasmussen K, Calligaro DO, et al. In vitro and in vivo biochemistry of olanzapine: a novel, atypical antipsychotic drug. J Clin Psychiatry 1997;58(suppl 10):28–36
34. Yamada J, Sugimoto Y, Ujikawa M. The serotonin precursor 5-hydroxytryptophan elevates serum leptin levels in mice. Eur J Pharmacol 1999; 383:49–51
35. Dryden S, Brown M, King P, et al. Decreased plasma leptin levels in lean and obese Zucker rats after treatment with the serotonin reuptake inhibitor fluoxetine. Horm Metab Res 1999;31:363–366
36. Morimoto T, Yamamoto Y, Mobarakeh JI, et al. Involvement of the histaminergic system in leptin-induced suppression of food intake. Physiol Behav 1999;67:679–683
37. Seufert J, Kieffer TJ, Leech CA, et al. Leptin suppression of insulin secretion and gene expression in human pancreatic islets: implications for the development of adipogenic diabetes mellitus. J Clin Endocrinol Metab 1999;84:670–676
38. Tanizawa Y, Okuya S, Ishihara H, et al. Direct stimulation of basal insulin secretion by physiological concentrations of leptin in pancreatic beta cells. Endocrinology 1997;138:4513–4516
39. Zimmet P, Hodge A, Nicolson M, et al. Serum leptin concentration, obesity, and insulin resistance in Western Samoans: cross sectional study. BMJ 1996;313:965–969
40. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292–295
41. Segal KR, Landt M, Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. Diabetes 1996;45: 988–991
42. Haffner SM, Miettinen H, Mykkanen L, et al. Leptin concentrations and insulin sensitivity in normoglycemic men. Int J Obes Relat Metab Disord 1997;21:393–399
43. Schoeller DA, Cella LK, Sinha MK, et al. Entrainment of the diurnal rhythm of plasma leptin to meal timing. J Clin Invest 1997;100: 1882–1887