Effects of long-term treatment with antipsychotics on serum leptin levels

ANDRÉS HERRÁN, MARÍA TERESA GARCÍA-UNZUETA, JOSÉ ANTONIO AMADO, MARÍA TERESA DE LA MAZA, CONCEPCIÓN ÁLVAREZ and JOSÉ LUIS VÁZQUEZ-BARQUERO

Background Abnormal regulation of the adipocyte-derived hormone leptin could play a role in body weight gain induced by antipsychotics.

Aims To study the effects of long-term antipsychotic treatment on leptin levels in patients with schizophrenia.

Method Serum leptin levels were determined in 59 out-patients with chronic schizophrenia and in the same number of healthy subjects controlled by gender, age and body mass index.

Results Leptin levels did not differ between patients and controls. Leptin levels in patients with schizophrenia correlated with weight gain, even after controlling for current weight, but did not show any association with clinical variables. Antipsychotic class tended to exert different effects over leptin levels (among atypicals, olanzapine induced a greater increase).

Conclusions Elevation of leptin levels induced by chronic antipsychotic treatment can be attributed to weight gain, but other mechanisms could be involved.

Declaration of interest This study was supported by a grant from the Fundación Marqués de Valdecilla, 1996.

Body weight gain is a common side-effect of antipsychotics that affects up to 50% of the patients under chronic treatment with these drugs (Allison *et al*, 1999; Baptista, 1999; Ganguli, 1999). The factors influencing body weight regulation are rather complex (Yanovski & Yanovski, 1999), but a major advance was the discovery of the adipocyte-derived hormone leptin (Zhang *et al*, 1994). The level of this hormone is correlated positively with body fat. Leptin acts by binding to specific receptors in the hypothalamus; this decreases food intake and increases energy expenditure (Friedman & Halaas, 1998). Clozapine and olanzapine (Brömel *et al*, 1998; Kraus *et al*, 1999) have been shown to increase the levels of leptin over short-term treatment, but the effects of long-term treatment are unknown. Our aim has been to study serum leptin levels in out-patients with chronic schizophrenia, to determine the effects of long-term treatment with different antipsychotics on this hormone and to test if clinical symptoms are associated with leptin levels.

METHOD

Subjects

All out-patients treated at one department in Santander (a city in the North of Spain), and fitting DSM–IV criteria of schizophrenia (American Psychiatric Association, 1994) by agreement of two senior psychiatrists were asked to participate in the study. In addition, patients were evaluated with the Item Group Checklist section of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing *et al*, 1990; Vázquez-Barquero *et al*, 1994) in order to confirm the diagnosis. Exclusion criteria were acute or chronic illnesses known to affect the immune, endocrine or metabolic systems. From the initial sample of 81 patients, 12 patients were excluded because of not fitting schizophrenia criteria and 4 were excluded because of physical reasons (two patients with diabetes mellitus, one with AIDS and one pregnant). In addition, three patients were not accessible when the study was performed and three did not give informed consent. Thus 22 patients were excluded from the initial sample, leaving 59 patients entered in the study. This sample has been analysed previously in other reports (Herrán *et al*, 1999; 2000*a*,*b*).

Fifty-nine healthy subjects without current or past psychiatric disorder and controlled by gender and age were selected as controls. In addition, they were matched by the current body mass index (BMI) of the patients. Exclusionary criteria were the same as for patients. Neither patients nor controls had alimentary restriction or evidence of clinical malnutrition. After a complete description of the study, all patients and healthy controls gave informed consent to participate in the investigation.

Clinical data were obtained from the patients and blood samples were obtained from patients and controls.

Clinical measures

Demographic, social and medical antecedent variables were assessed using a specifically created questionnaire. Clinical information included DSM–IV schizophrenia subtype and the Spanish version of the Positive and Negative Syndrome Scale (PANSS; Peralta & Cuesta, 1994; for English version see Kay *et al*, 1987). Additional data regarding clinical evolution and treatment were derived from the clinical records.

Chlorpromazine equivalents were calculated according to commonly used equivalent doses (American Psychiatric Association, 1997). All patients had been on treatment with their current antipsychotic for at least 6 months. Patients ($n=5$) on treatment with fluphenazine depot and another antipsychotic drug were considered as taking only phenothiazines. Four patients were treated exclusively with behavioural psychotherapy and were not taking antipsychotic medication.

Height and weight were assessed immediately before blood sample extraction. For patients, weight at the onset of the illness was derived from clinical records. The BMI was expressed in kg/m^2.

Serum measures

Fasting blood samples were withdrawn from an antecubital vein between 08.00 and 09.00 h. Samples were centrifuged

https://doi.org/10.1192/bjp.179.1.59 Published online by Cambridge University Press

immediately and serum was stored at −40°C until assayed. Samples were obtained simultaneously for patients and controls within a 6-month period to avoid seasonality.

Serum leptin levels were determined by radioimmunoassay (RIA) from Linco (Linco Research Inc., St Charles, MO, USA). Precisions within and between assay variation were 4.9 and 4.5%, respectively. Normal values are: <10 ng/ml for males and <20 ng/ml for females, with BMI <25 kg/m^2.

Analysis

Data were analysed with the Statistical Package for the Social Sciences (SPSS) version 8.0. Given the skewed distribution of leptin levels, a base-10 logarithm transformation was used for analysis. Comparisons between schizophrenia and control groups were made by *t*-test. Group mean differences among schizophrenia subtypes (clinical, treatment) were checked by means of *t*-test or analysis of variance (ANOVA). The General Linear Model (Factorial) command of the SPSS was used when controlling for covariates. For the relationship between leptin levels, weight and BMI, Pearson's correlation was used (and partial correlation when controlling for the effects of other additional variables). For the relationship with clinical (ordinal) variables, Spearman's correlation was used.

RESULTS

Fifty-nine patients with schizophrenia and the same number of healthy subjects entered the study (32 males and 27 females in each group). Patients and controls were controlled for age (mean=38.2 years and s.d.=11.2 *v.* mean=38.1 years and s.d.=9.6, respectively), and BMI (mean=26.4 kg/m^2 and s.d.=4.2 *v.* mean=25.7 kg/m^2 and s.d.=4.0, respectively).

Sample description

The sample consisted of patients with chronic schizophrenia, with a mean of 13.7 years of evolution of the illness (s.d.=11.1). There was a predominance of patients with residual schizophrenia. Clinical subtypes were as follows: paranoid, 19 (32.3%); disorganised, 7 (11.9%); undifferentiated, 9 (15.5%); and residual schizophrenia, 24 (40.7%). Mean scores on the PANSS scale reflect a moderate severity of the illness and a predominance of negative symptoms. Mean scores were: positive sub-scale, 10.9 (s.d.=4.9); negative sub-scale, 17.6 (s.d.=7.3); general sub-scale, 27.4 (s.d.=9.9); and total PANSS score, 55.8 (s.d.=18.3). Mean weight gain in patients since the onset of the illness was 10.6 kg (s.d.=9.3) and mean BMI gain was 3.8 kg/m^2 (s.d.=3.3).

Mean antipsychotic dose (as chlorpromazine equivalents) was 317.8 mg/day (s.d.=206.8). Seventeen patients (30.9% of those taking antipsychotic treatment) were taking long-acting depot neuroleptics and the same number of patients were on atypical antipsychotics. Twenty-six patients were on treatment with phenothiazines (perphenazine, fluphenazine, trifluoperazine), eight with haloperidol, two with zuclopenthixol, one with loxapine, one with pimozide, five with risperidone, five with clozapine and seven with olanzapine. Some of the patients also received benzodiazepines and/or anticholinergic drugs, but none received antidepressants or mood stabilisers.

Table 1 Serum levels of leptin (ng/ml) in patients and controls

	n	Mean (ng/ml)	s.d.
Patients with schizophrenia	59	12.4	10.9
Male	32	8.1	9.2
Female	27	17.5	10.7
Healthy controls	59	11.5	10.2
Male	32	6.4	2.9
Female	27	17.4	12.5

Serum leptin levels

Serum leptin levels did not differ significantly between patients and controls, either in the total sample (t=0.150; d.f.=116; P=0.8) or when they were compared by gender. Levels were higher in females than in males, both in patients (t=−5.602; d.f.=57; P=0.000) and control groups (t=−5.968; d.f.=57; P=0.000) (Table 1). The BMI did not differ significantly between male and female groups. Age did not correlate with leptin levels.

Relationships between leptin levels and weight, BMI, gain in weight and gain in BMI are shown in Table 2. In both patients and controls, leptin showed a strong correlation with BMI, and in the case of patients leptin also correlated with weight gain and BMI gain. Because weight gain correlated strongly with current weight (r=0.740; P=0.000) and BMI gain correlated with current BMI (r=0.767; P=0.000), the effects of weight and BMI gain were controlled for current weight and BMI. Leptin levels in patients with schizophrenia correlated significantly with weight gain and showed a trend for an association with BMI gain.

Neither clinical variables (age at the onset of the illness, years of evolution, PANSS scores) nor schizophrenia subtype (F=0.048; d.f.=3; P=0.9) exerted any effect over leptin levels. Also, antipsychotic dosage and method of treatment (oral *v.* depot) did not show any association with leptin levels. Patients on typical antipsychotic treatment did not differ from those on atypical drugs (clozapine, olanzapine, risperidone) (t=−0.572; d.f.=53; P=0.5). Serum leptin levels, weight and BMI according to antipsychotic class are shown in Table 3. Patients taking clozapine and olanzapine tended to show a higher BMI than patients taking other antipsychotic drugs.

Serum leptin levels did not differ among patients taking different antipsychotics when controlling for current BMI. When comparing patients taking atypical drugs (clozapine, olanzapine, risperidone) the differences in leptin levels were significant (F=4.442; d.f.=2; P=0.03). Patients on treatment with olanzapine had the highest leptin levels, patients on risperidone had the lowest and patients taking clozapine

Table 2 Pearson's correlation coefficients between leptin levels (log-transformed) and current weight, body mass index (BMI), weight gain and BMI gain

	Patients	Controls
Weight (kg)	0.206	0.104
BMI (kg/m^2)	0.545**	0.448**
Weight gain (kg)[1]	0.508**	
BMI gain (kg/m^2)[2]	0.246*	

1. Controlled for the effects of current weight.
2. Controlled for the effects of current BMI.
*P=0.07; **P<0.001.

https://doi.org/10.1192/bjp.179.1.59 Published online by Cambridge University Press

Table 3 Serum leptin levels, weight, weight gain, body mass index (BMI) and BMI gain by drug class[1]

Antipsychotic	Leptin[2] (ng/ml)			Weight (kg)			Weight gain (kg)			BMI (kg/m^2)			BMI gain (kg/m^2)		
	n	Mean	s.d.	*n*	Mean	s.d.	*n*	Mean	s.d.	*n*	Mean	s.d.	*n*	Mean	s.d.
Phenothiazines	26	11.30	7.92	26	71.42	14.25	23	10.22	10.36	26	25.73	3.45	23	3.58	3.43
Haloperidol	8	10.74	9.30	8	68.50	10.09	8	7.75	7.59	8	24.37	2.74	8	2.74	2.62
Clozapine	5	10.86	9.25	5	81.00	7.52	5	15.60	8.50	5	27.92	4.43	5	5.48	3.22
Olanzapine	7	26.60	20.02	7	80.57	16.31	7	14.71	11.46	7	29.46	6.28	7	5.55	4.49
Risperidone	5	5.64	3.96	5	73.60	6.23	5	7.40	5.55	5	25.30	2.37	5	2.50	1.79
ANOVA	F=2.316; P=0.07[3]			F=0.540; P=0.7			F=0.982; P=0.4			F=2.095; P=0.09			F=1.210; P=0.3		

1. Patients taking loxapine (n=1), pimozide (n=1) and zuclopenthixol (n=2) are not shown.
2. Differences are calculated with log-transformed leptin levels.
3. When controlling for current BMI: F=1.442; P=0.2.

had intermediate values. The difference in leptin levels between patients taking olanzapine and risperidone remained at the limit of statistical significance, even after controlling for BMI (F=4.877; d.f.=1; P=0.05).

DISCUSSION

This is the first study analysing the effects of chronic antipsychotic medication on serum leptin levels. In addition, we assessed an unselected, representative sample of outpatients with schizophrenia. Given the prevalence of weight gain in patients taking antipsychotics, and its impact over patients' health and quality of life, the knowledge of the physiological basis of this weight gain is an essential area of research.

The present study focused on the relationship between leptin levels and psychopathology, the effects of chronic treatment with antipsychotic drugs on weight and serum leptin levels and the differential effects of antipsychotic subgroups (particularly the newer atypical ones) over this hormone. The main findings were: serum leptin levels do not differ between patients with schizophrenia taking chronic antipsychotic medication and healthy subjects controlled by gender, age and BMI; leptin levels in patients with schizophrenia correlated with weight gain; leptin levels did not show any association with clinical variables; and among atypical antipsychotics olanzapine appeared to induce a greater increase in leptin independently of weight gain.

There are a number of limitations to the present study. First, given the transverse design of the study, we must be cautious with the conclusions: correlation does not imply causal association. In addition, we cannot exclude a number of confounding factors, such as other pharmacological treatments (anticholinergic drugs, etc.), and we did not assess the patients' eating behaviour. Additionally, there was a limited number of patients in each group (clinical and treatment groups).

Weight gain

As has been stated (Wirshing *et al*, 1999), the antipsychotics clozapine and olanzapine caused the most weight gain. In our sample, patients taking these drugs tended to show higher BMI. Weight gain and BMI gain were also higher for patients on these drugs, but without statistical significance, probably owing to the small size of the sample. It is atypical in this sample that the group of patients on risperidone had gained less weight than those on haloperidol and phenothiazines, because previous trials have shown the opposite findings (Allison *et al*, 1999; Wirshing *et al*, 1999). This could be attributed to the low number of patients in each group, or it could be that the patients have not been on risperidone long enough for their weight to have increased.

Although there are reports suggesting a link between body weight gain and clinical efficacy of antipsychotics (Jalenques *et al*, 1996), some authors do not agree with this hypothesis (Baptista, 1999). On the other hand, it has been suggested that leptin could exert central nervous system effects involved in the beneficial effect of antipsychotics (Kraus *et al*, 1999). This particular issue has not been analysed, but our results suggest that it is unlikely. Leptin levels were not associated with any clinical variable included in the present study, and given the chronic nature of the sample it would be expected that, if leptin were associated with the beneficial effect of antipsychotics, it would be correlated with clinical measures.

Leptin and antipsychotic treatment

Leptin levels did not differ between patients and healthy subjects matched by BMI. At least two studies have analysed the behaviour of leptin over short-term antipsychotic treatment. Brömel *et al* (1998) found that leptin increased in a 10-week period of treatment with clozapine. Kraus *et al* (1999) found an increase in leptin levels in patients taking clozapine or olanzapine over 4 weeks, but not in patients taking haloperidol. Both groups suggested that the most probable reasons for these increases in leptin levels were overeating and weight gain, which induce increased leptin secretion. Our results of unchanged levels in a sample of long-term treated patients compared with BMI-matched controls support this hypothesis. However, the difference in leptin levels between patients on olanzapine and those on risperidone is intriguing. Perhaps most of the effect of antipsychotics on leptin levels could be attributed to weight gain, but other mechanisms could be involved. Leptin is known to be affected by several neurotransmitters, such as histamine (Morimoto *et al*, 1999) and serotonin (Yamada *et al*, 1999). The serotonin reuptake inhibitor fluoxetine decreased plasma leptin levels in rats (Dryden *et al*, 1999). It is possible that, given the different pharmacological profile of antipsychotics (including the atypical ones) over these receptors (Moore, 1999), diverse drugs could exert differential effects over leptin levels irrespective of induced weight gain. This could support the hypothesis of Baptista (1999) regarding different ways in which

https://doi.org/10.1192/bjp.179.1.59 Published online by Cambridge University Press

antipsychotics induce weight gain: olanzapine, for example, could exert some direct effect over leptin. None the less, given that the main finding of the present study is that the leptin levels are raised in association with body weight, we must keep in mind the limitations discussed about the weight gain of patients on risperidone (low number of patients, not sufficiently long taking this drug). Prospective studies with larger samples are necessary to elucidate these issues.

CLINICAL IMPLICATIONS

- Body weight gain is a common side-effect of antipsychotics that could contribute to the increased morbidity and mortality in schizophrenia.
- Leptin levels did not differ between patients and healthy subjects matched by body mass index.
- Most of the effect of antipsychotics on leptin levels could be attributed to weight gain, although diverse drugs could exert differential effects over leptin.

LIMITATIONS

- Given the transverse design of the study, conclusions should be treated with caution.
- In the present work the patients' eating behaviour was not assessed.
- The number of patients was relatively low for assessing differences between groups of antipsychotics.

REFERENCES

Allison, D. B., Mentore, J. L., Heo, M., *et al* (1999) Antipsychotic-induced weight gain: a comprehensive research synthesis. *American Journal of Psychiatry*, **156**, 1686–1696.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

___ (1997) Practice guideline for the treatment of patients with schizophrenia. *American Journal of Psychiatry*, **154**, 10.

Baptista, T. (1999) Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatrica Scandinavica*, **100**, 3–16.

Brömel, T., Blum, W. F., Ziegler, A., *et al* (1998) Serum leptin levels increase rapidly after initiation of clozapine therapy. *Molecular Psychiatry*, **3**, 76–80.

Dryden, S., Brown, M., King, P., *et al* (1999) Decreased plasma leptin levels in lean and obese Zucker rats after treatment with the serotonin reuptake inhibitor fluoxetine. *Hormone Metabolism and Research*, **31**, 363–366.

Friedman, J. M. & Halaas, J. L. (1998) Leptin and the regulation of body weight in mammals. *Nature*, **395**, 763–770.

Ganguli, R. (1999) Weight gain associated with antipsychotic drugs. *Journal of Clinical Psychiatry*, **60** (suppl. 21), 20–24.

Herrán, A., García-Unzueta, M. T., Amado, J. A., *et al* (1999) Folate levels in psychiatric outpatients. *Psychiatry and Clinical Neurosciences*, **53**, 531–534.

___, de Santiago, A., Sandoya, M., *et al* (2000*a*) Determinants of smoking behaviour in outpatients with schizophrenia. *Schizophrenia Research*, **41**, 373–381.

___, García-Unzueta, M. T., Fernández-González, M. D., *et al* (2000*b*) Higher levels of serum copper in schizophrenic patients treated with depot neuroleptics. *Psychiatry Research*, **94**, 51–58.

Jalenques, Y., Tauveron, Y., Albuisson, E., *et al* (1996) Weight gain as a predictor of long-term clozapine efficacy. *CNS Drugs*, **12**, 16–25.

Kay, S. R., Fiszbein, A. & Opler, L. A. (1987) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, **13**, 261–276.

Kraus, T., Haack, M., Schuld, A., *et al* (1999) Body weight and leptin plasma levels during treatment with antipsychotic drugs. *American Journal of Psychiatry*, **156**, 312–314.

Moore, N. A. (1999) Behavioural pharmacology of the new generation of antipsychotic agents. *British Journal of Psychiatry*, **174** (suppl. 38), 5–11.

Morimoto, T., Yamamoto, Y., Mobarakeh, J. I., *et al* (1999) Involvement of the histaminergic system in leptin-induced suppression of food intake. *Physiology and Behavior*, **67**, 679–683.

Peralta, V. & Cuesta, M. J. (1994) Validación de la Escala de los Síndromes Positivo y Negativo (PANSS) en una muestra de esquizofrénicos españoles. *Actas Luso-Españolas de Neurología, Psiquiatría y Ciencias Afines*, **22**, 171–177.

Vázquez-Barquero, J. L., Gaite, L., Artal, J., *et al* (1994) Desarrollo y Verificación de la Versión Española de la Entrevista Psiquiátrica "Sistema SCAN" (Cuestionarios para la Evaluación Clínica en Neuropsiquiatría). *Actas Luso-Españolas de Neurología, Psiquiatría y Ciencias Afines*, **22**, 109–120.

Wing, J. K., Babor, T., Brugha, T., *et al* (1990) SCAN: Schedules for Clinical Assessment in Neuropsychiatry. *Archives of General Psychiatry*, **47**, 589–593.

Wirshing, D. A., Wirshing, W. C., Kysar, L., *et al* (1999) Novel antipsychotics: comparison of weight gain liabilities. *Journal of Clinical Psychiatry*, **60**, 358–363.

Yamada, J., Sugimoto, Y. & Ujikawa, M. (1999) The serotonin precursor 5-hydroxytryptophan elevates serum leptin levels in mice. *European Journal of Pharmacology*, **383**, 49–51.

Yanovski, J. A. & Yanovski, S. Z. (1999) Recent advances in basic obesity research. *Journal of the American Medical Association*, **282**, 1504–1506.

Zhang, Y., Proenca, R., Maffei, M., *et al* (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature*, **372**, 425–432.

ANDRÉS HERRÁN, MD, Clinical and Social Psychiatry Research Unit, Department of Psychiatry, MARÍA TERESA GARCÍA-UNZUETA, MD, JOSÉ ANTONIO AMADO, MD, Department of Endocrinology, MARÍA TERESA DE LA MAZA, MD, CONCEPCIÓN ÁLVAREZ, MD, Department of Biochemistry, JOSÉ LUIS VÁZQUEZ-BARQUERO, FRCPsych, Clinical and Social Psychiatry Research Unit, Department of Psychiatry, University Hospital Marqués de Valdecilla, Santander, Spain

Correspondence: Andrés Herrán, Clinical and Social Psychiatry Research Unit, Department of Psychiatry, University Hospital Marqués de Valdecilla, Avda. de Valdecilla s/n, 39008 Santander, Spain. Tel: 34 942 202545; Fax: 34 942 203447; e-mail: herran@humv.es

(First received 9 May 2000, final revision 29 January 2001, accepted 31 January 2001)

https://doi.org/10.1192/bjp.179.1.59 Published online by Cambridge University Press