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Leptin and Ghrelin Levels in Patients With Schizophrenia During Different Antipsychotics Treatment: A Review

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Energy homeostasis is achieved by the integration of peripheral metabolic signals by the neural circuits involving specific hypothalamic nuclei and brain stem regions. These neural circuits mediate many of the effects of the adipocyte-derived hormone leptin and gut-derived hormone ghrelin. The former is strongly anorexigenic while the latter is the only orexigenic agent active when administered by a peripheral route. Abnormal regulation of these 2 antagonistic regulatory peptides in patients with schizophrenia could play a role in the impairment in the regulation of food intake and energy balance. This bibliographical analysis aims to compare 27 prospective and cross-sectional studies published on circulating leptin and ghrelin levels during acute and chronic administration of antipsychotics treatment, especially atypical ones. Fasting morning leptin levels of schizophrenic patients increase rapidly in the first 2 weeks after atypical antipsychotic (AAP) treatment (mostly olanzapine and clozapine) and remain somehow elevated after that period up to several months. On the contrary, conventional antipsychotics (such as haloperidol) do not interfere with leptin levels. In contrast to leptin, fasting morning ghrelin levels decrease during the first few weeks after the beginning of AAPs treatment while they increase in the longer run. Surprisingly, body weight gain and correlations between the variation of these 2 peptides and adiposity and metabolism-related parameters such as the body mass index and abdominal perimeter were not systematically considered. Finally, an objective evaluation of feeding behavior during antipsychotic treatment remains to be determined.

Key words: leptin/ghrelin/antipsychotics/schizophrenia

Introduction

Atypical antipsychotics (AAPs) became the first-line treatment in schizophrenia and many other mental disorders due to better efficacy and more favorable side effect profile than the first-generation antipsychotics. As the number of AAP-treated patients and available data, higher incidence of significant weight gain (WG) was observed, with the higher risk associated with clozapine and olanzapine, followed by quetiapine and risperidone.[1–3] High blood glucose has also been reported with the use of AAP treatment particularly with clozapine and olanzapine.[4]

The higher risk of cardiovascular disease, leading to enhanced morbidity, important economic cost, and mortality (reducing quality of life [QOL] and lower compliance to treatment) can be linked to the obesitogenic and diabetogenic capacity of these drugs.[5–7]

The mechanisms by which some AAP drugs contribute to WG and cardiovascular risk are still poorly understood. It is believed that the interaction is probably multifactorially determined (eg, Brady[8]): increased appetite, energy intake and storage, metabolic and endocrine alterations, reduced energy expenditure and increased utilization, as well as lower physical activity (eg, Zipursky[9] and Levin and Rezvani[10]) have all been involved in AAP-induced WG. Many neuropeptides and hormones are involved in energy homeostasis and body weight (BW) regulation. Among those, leptin and ghrelin appears to play a crucial role in the energy balance (modulation of hunger and satiety) and appetite (food choice), during treatment with some AAP.[11,12]

It has been suggested that antipsychotics (AP) interact with the complex system of neurotransmitters, neuropeptides, and other modulators in brain neuronal circuits involving the hypothalamus and brain stem where a neuropeptidergic network mediates the actions of leptin and ghrelin to provoke disturbances in energy homeostasis, endocrine alterations, and BW control.[13,14]

The distribution of adipose tissue within the body is recognized as a key factor influencing the effect of increasing weight on health. Several studies have demonstrated a link between abdominal adiposity and overall mortality, with visceral adiposity associated with an increase risk of diseases as dyslipidemia and glucose intolerance.[15]

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The discovery in 1994 by Zhang and associates[16] of the adipocyte-derived circulating hormone leptin (from the Greek leptos, meaning thin) changed the status of the adipocyte from a mere storage compartment to a new endocrine organ. Leptin is the protein product of the obese (*ob*) gene located on chromosome 7 (7q31.3), a highly hydrophilic 167 amino acid protein with an N-terminal secretory signal sequence. Circulating leptin is found in human serum either in its free form as a 16-kDa protein or in its sOB-R (soluble form of the leptin receptor) bound form.[17] Leptin is produced by adipocytes in proportion to fat stores. Thus, it directly communicates the state of energy reserves to the brain in order to control feeding and metabolism, modulate satiety, energy intake, and energy expenditure. The effects of leptin in food intake and energy homeostasis are central and mediated via a network of orexigenic and anorexigenic neuropeptides containing neurons located in the mediobasal (tuberoinfundibular) portion of the hypothalamus (see figure 1). Leptin directly activates proopiomelanocortin (POMC) cells in the arcuate nucleus to increase the release of melanocortin peptides, including the POMC product α-melanocyte–stimulating hormone (α-MSH). Melanocortins (MCs) inhibit food intake and regulate metabolism, energy storage, insulin secretion, and gastrointestinal motility predominantly via projections to MC4 receptor neurons. Moreover, leptin also directly inhibits arcuate neurons, which produce agouti-related protein (AgRP) and neuropeptide Y (NPY). AgRP is an endogenous antagonist of α-MSH at MC4 receptors and, peripherally, has neuroendocrine functions involved in food consumption and weight regulation.[18,19] NPY is a potent orexigenic agent when injected intracerebrally. Leptin receptors are also present in the ventrotegmental area (VTA) and leptin targets dopaminergic and gamma-aminobutyric acid neurons of in this region critical to brain reward circuits, inducing phosphorylation of signal transducer and activator of transcription-3.[20] Direct administration of leptin in the VTA also caused decreased food intake (see figure 1).[21] Conversely, long-term RNAi-mediated knockdown of leptin receptor (ObR) in the VTA led to increased food intake, locomotor activity, and sensitivity to highly palatable food. These data support a critical role for VTA ObR in regulating feeding behavior and provide functional evidence for direct peripheral metabolic signaling on VTA dopamine neurons.

Peripheral administration of leptin reduces appetite and feeding while leptin deficiency (both mice and humans with mutations in the leptin or leptin receptor genes) causes extreme obesity and increased thermogenesis (eg, Considin et al[22] and Maffei et al[23]). The rate of leptin production is related to adiposity; it is secreted in a pulsatile fashion but without a marked circadian rhythm. It is influenced by gender, women having markedly higher leptin concentrations than men for any given

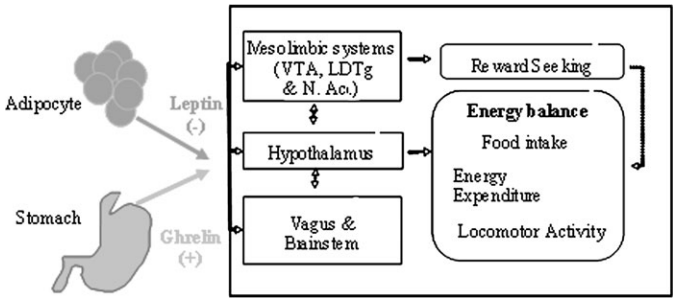

Fig. 1. Neural Circuits Involved in the Integration of Peripheral Metabolic Signals Controlling Homeostasis. Leptin and ghrelin act antagonistically within the hypothalamic circuits regulating energy metabolism. They also interact in the brain stem satiety center to regulate the dorsal vagal complex in the basal mesencephalon on reward-seeking mechanism.[20,21,30]

degree of fat mass.[17] It is decreased with older age, with physical activity and its secretion is stimulated by insulin, but a large portion of interindividual variability in leptin concentration is independent of body fat mass.[24]

Beside the very rare case of genetic leptin deficiency, the vast majority of obese humans have high plasma leptin concentrations related to the size of adipose tissue, but this elevated leptin signal does not induce the expected responses (ie, a reduction in food intake and an increase in energy expenditure), thus suggesting that most obese human subjects are resistant to the effects of endogenous leptin.[25]

In 1999, 5 years after the discovery of leptin, a novel gastrointestinal peptide hormone was characterized and named ghrelin (from the Sanskrit ghre, to grow),[26] based on its ability to bind to the growth hormone (GH) secretagogue receptor (GHS-R) and its capacity to release GH. The gene coding for human preproghrelin, growth hormone receptor ligand, is located on chromosome 3 (*3p25-26*). This 28 amino acid peptide has the particularity to present with an *n*-octanoyl modification on Ser 3, which makes it the natural endogenous ligand of the GHS-R and allows it to act as potent appetite-stimulating hormone (eg, Tschop[27]) probably by directly stimulating the activity of neurons expressing AgRP/NPY production (and possibly orexins) while indirectly inhibiting POMC and corticotropin releasing hormone neuronal activities.[28] GHS-R are also located in the VTA, and ghrelin administration in this ventral mesencephalic region stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens.[29]Ghrelin is mainly produced and released by the P/D1 cells, an enteroendocrine cells in the stomach, which also express the vesicular monoamine transporter 2, suggesting a role of monoaminergic transmission in the regulation of ghrelin.[30] Ghrelin also stimulates preadipocyte differentiation, increases the body fat mass, and inhibits the anorexigenic effect of leptin. Circulating ghrelin and leptin are inversely

related over the nychtemere in rats (eg, Anderson and Moore[28]), but this remains controversial in humans.

This food intake–stimulatory signal has opened a new era of understanding of anabolism feeding behavior and nutritional homeostasis for GH secretion and gastrointestinal motility through gut-brain interactions (see figure 1).

Tschop et al[27] investigated the possible involvement of ghrelin in the pathogenesis in human obesity in a population of 30 subjects (15 Caucasian: 7 lean and 8 obese and 15 Pima Indians: 7 lean and 8 obese). They observed that fasting plasma concentrations of octanoylated ghrelin was negatively correlated with percent body fat and leptin levels.

The secretion of ghrelin by the stomach depends largely on the nutritional state. Ghrelin levels show preprandial increases and postprandial decreases. In addition, ghrelin levels show a diurnal variation and seem to decrease in older age. It is higher in women and correlates negatively with body mass index (BMI) and GH while glucose and insulin seem to decrease its level.[31]

In 2 studies of a large sample of population-based cohort, a metabolic syndrome (MS) was associated with low ghrelin levels, suggesting a relationship of ghrelin in the metabolic disturbances of MS: waist circumference, blood pressure, high density lipoprotein cholesterol, and triglycerides (low ghrelin was a significant predictor of MS).[32,33]

Thus, both leptin and ghrelin play major roles in the control system for energy balance in humans. However, leptin appears more involved in long-term regulation of energy balance, being released into the circulatory system as a function of energy stores, whereas ghrelin can also be considered as a fast-acting hormone, of which the circulatory levels show clear meal-related changes. Based on genetically modified rodent models, another difference is that, in contrast to leptin, ghrelin does not seem to be critical for normal appetite and growth.[24] However, it is not yet fully understood whether the variations in circulating leptin and ghrelin concentrations are a direct effect of AAP administration or secondary to the AAP-induced WG.

Therefore, the main goal of this review was to analyze a large panel of recently published studies evaluating the impact of antipsychotic in leptin and ghrelin blood levels; it could exert potent disturbing effects in food intake attitudes, inducing BW control problems.

Methods

A literature search (MEDLINE/PubMed) was undertaken for the year ranging from 1998 (where leptin was first to be analyzed in schizophrenic patient with WG) to June 2007. The following key words were cross-referenced: ''leptin,'' ''ghrelin,'' ''schizophrenia,'' and ''antipsychotic.'' The clinically relevant reports (cross-sectional and prospective studies), dealing with the blood variation of leptin and ghrelin in adult schizophrenic patients treated with atypical and conventional antipsychotics, were analyzed. All applicable references were examined and scrutinized by 2 psychiatrist reviewers (M.F.P. and O.S.). To achieve a legitimate and workable summary of findings, data from prospective vs cross-sectional studies were separated and ranked according to variations in leptin blood level, ghrelin blood level, and both parameters in adult patients treated with antipsychotic drugs. This selection process resulted in 23 relevant articles concerning modification of leptin in schizophrenic or schizoaffective patients with AAP and conventional neuroleptic (17 prospective and 6 cross-sectional studies) and 8 articles about ghrelin (5 prospective and 3 cross-sectional studies). Four studies evaluated both leptin and ghrelin levels.

Commentary

Leptin

Table 1 summarizes 17 prospective and 6 cross-sectionals studies which evaluated the effects of AP on leptin concentration. It is organized according to the treatments given because our main objective was to evaluate the impact of antipsychotic treatments on circulating regulatory peptides over a period of time.

Concerning prospective studies, Bromel et al[34] evaluated 9 schizophrenic patients and 3 schizoaffective disorder patients, who were assigned to monotherapy with clozapine (only 8 were additionally treated with conventional neuroleptics and other psychotropic drugs). These authors reported that serum leptin levels (SLLs) prior to initiation of clozapine treatment differed significantly from levels measured afterward ($P < .0001$) with concentrations at least doubling in 8 clozapine-treated psychotic patients by week 2 ($P = .023$) vs baseline and no significant changes up to the 10th week vs week 2 ($P = .126$). In 3 patients, leptin levels remained similar to baseline. Moreover, the net differences in BW and BMI between baseline and week 2 revealed positive correlations ($r = .3$ and .75, respectively) to the relative increases in the SLL at week 2.

In 2002, Monteleone et al[35] prospectively measured plasma leptin levels (PPLs) in 22 chronic resistant schizophrenic patients treated with clozapine in monotherapy; blood samples were taken at baseline and after 1, 2, 4, 6, 8, 12, 16, 24, and 32 weeks. These authors found that plasma leptin concentrations doubled after only 2 weeks of clozapine administration. By the end of week 4, leptin levels abruptly fell to levels more strictly related to BW changes and, subsequently, progressively rose up to the 32nd week of treatment, paralleling the progressive increase of WG. Significant differences were observed between men and women in the mean baseline values in plasma leptin (5.0 ± 3.4 vs 14.7 ± 7.7 ng/ml), but it did not differ over time.

Table 1. Circulating Leptin Level Modifications during AP Treatment in Psychotic Patients (prospective and cross-sectional studies)

Authors	Washout Period (d)	Drug	Number of Patients	Duration (wk)	Mean Age (y) ± SD	Leptin Modifications
Prospective studies						
Bromel et al[34]	NA	CLZ	12 (6 w/6 m)	10	31(22–44)	W2 vs B: ↗, W10 vs W2: NS
Monteleone et al[35]	14	CLZ	22 (9 w/13 m)	32	(26–61)	W2 vs B:↗, W32 vs B: ↗, W4 vs W2: ↘
Kivircik et al[36]	2–5	CLZ	19 (11 w/8 m)	10	37.4 ± 10.5	W4 vs B: NS, W10 vs B: NS
Theisen et al[12]	NA	CLZ	12 (6 w/6 m)	10	31 ± 7.1	W2 vs B: ↗, W10 vs B: ↗, W10 vs W2: NS
Popovic et al[41]	Switch	CLZ/RISP	18 (9 w/9 m)	12	28.8 ± 1.6	W12 vs B: ↗
Graham et al[37]	NA	OLZ	09(3 w/6 m)	12	21.5 (20.8–27.3)	W12 vs B: NS
Murashita et al[38]	NA	OLZ	7 (3 w/4 m)	26	46.3 ± 15.7	W26 vs B: ↗
Hosojima et al[11]	28	OLZ	13 (4 w/9 m)	4	37 (20–56)	W4 vs B: ↗
Wang et al[39]	NA	OLZ	09 (4 w/5 m)	2	35 ± 10	H4 vs B: ↗, W2 vs B: NS
Baptista et al[40]	Switch	OLZ	60 (26 w/34 m)	16	46.5 ± 10.7	W8 vs B: ↗, W16 NS vs B
Eder et al[42]	3; 5 naive patients	OLZ	10 (2 w/8 m)	8	30.4 ± 7	W8 vs B: ↗
		HC	10			W8 vs B: NS
Ebenbichler et al[43]	3	OLZ	14	10		W10 vs B: ↗
		HC	14			W8 vs B: NS
Atmaca et al[44]	14	OLZ	21(7 w/14 m)	6	30.4 ± 7.8	W6 vs B: ↗
		HC	21			W6 vs B: NS
Atmaca et al[45]	14	OLZ	15	6	29.2 ± 11.8	W6 vs B: ↗
		QUET	15		28.6 ± 11.3	W6 vs B: ↗
		HAL	15		27.4 ± 10.6	W6 vs B: NS
Kraus et al[46]	NA	CLZ	11 (7 w/4 m)	4	37 ± 19	W2 vs B: ↗, W4 vs W2: NS
		OLZ	08 (5 w/3 m)		26 ± 6	W2 vs B: ↗, W4 vs W2: NS
		HAL	13 (7 w/6 m)		36 ± 16	W2 vs B: ↗, W4 vs W2: NS
		HC	12 (7 w/5 m)		30 ± 12	W2 vs B: NS, W4 vs B: NS
Fitzgerald et al[48]	NA	CLZ/RISP	22 (w)		34.6 ± 8.9	W12 vs B: ↗
Zhang et al[47]	Naive patients	CLZ/RISP/CPZ	46 (19 w/27 m)	10	26.5 ± 6.6	W10 vs B: ↗
		HC	38 (16 w/22 m)			
Cross-sectional studies						
Melkerson et al[50]		OLZ	14 (7 w/7 m)	20 (10–72)	44 (30–60)	OLZ vs CLZ vs CONV: NS
		CLZ	14 (7 w/7 m)	156 (26–384)	35 (26–47)	
		CONV	19 (9 w/10 m)	156 (15–104)	42 (28–72)	
Herran et al[51]		CLZ	5	26	38.2 ± 11.2	NS vs HC
		OLZ	7			NS vs HC
		RISP	5			NS vs HC
		CONV	34			NS vs HC
		HC	59		38.1 ± 9.6	
Haag et al[52]		CLZ	41 (20 w/21 m)	145 (124–171)	41 (39–44)	w vs HC: ↗, m vs HC: NS
		CONV	62 (24 w/38 m)	452 (369–530)	49 (46–51)	w vs HC: ↗, m vs HC: NS
		HC	189		46 (26–65)	
Haupt et al[53]		OLZ/RISP/CONV	27	(12–104)	38.1± 8.3	NS vs HC
		HC	124			
Murashita et al[54]		RISP	15 (10 w/5 m)	26	40.8 ± 11.8	↗ vs HC
		HC	25			

Note: NA, not available; CLZ, clozapine; w, women; m, men; W, week; B, baseline; NS, nonsignificant, $P > .05$; RISP, risperidone; OLZ, olanzapine; H, hour; HC, healthy control; QUET, quetiapine; HAL, haloperidol; CPZ, chlorpromazine; CONV, conventional.

Kivircik et al[36] reported on 19 in- and outpatients with schizophrenia who completed 10 weeks of treatment with clozapine that the analysis of variance did not reveal any significant change in leptin among baseline and the patient gained 5% of their BW (baseline: 11.87 ± 9.70 ng/ml, weight: 65.3 ± 15.9 kg vs week 4: 11.56 ± 10.80 ng/ml vs week 10: 13.11 ± 10.08 ng/ml, weight: 68.6 ± 16.4 kg). The increase in BMI was significant ($P < .001$), but the variation in SLL was not correlated with the change in BW and in BMI.

Theisen et al[12] investigated SLL and BMI in 12 patients with schizophrenia or schizoaffective disorders over a 10-week period after initiation of clozapine treatment (8 patients were additionally treated with other AP, benzodiazepines, and/or antidepressant). The investigators observed that both SLL and BMI increased significantly from baseline to week 2, and this increase stayed stable in week 10 (baseline: 8.3 ± 6.5 ng/ml vs week 2: 13.8 ± 11.9 ng/ml, $P < .05$, vs week 10: 13.6 ± 11.4 ng/ml, and for BMI, baseline: 25.2 ± 4.8 kg/m^2 vs week 10: 26.5 ± 5.0 kg/m^2, $P < .05$).

Concerning olanzapine treatment, Graham et al[37] evaluated anthropomorphic measures and leptin levels in the first and last visits (12 weeks apart) in 9 patients after a first psychotic episode. They did not observe any significant variation on SLL: 5.16 (range 3.90–7.42) to 7.58 ng/ml (range 5.27–14.69), and median change was not significant ($P < .16$) but a significant variation in BW ($P = .004$).

In contrast, Murashita et al[38] compared metabolic parameters before and after 6-month administration of olanzapine in 7 Japanese patients with schizophrenia, and the investigators reported that the SLL were significantly increased (baseline: 10 ± 1.9 ng/ml vs week 26: 12.9 ± 3.4 ng/ml, $P = .028$), but BW and BMI did not vary significantly after 6 month of treatment.

Hosojima et al[11] recruited 13 patients with schizophrenia (6 patients were AP naive) who received a monotherapy of olanzapine for 4 weeks. SLL increased from baseline to week 4 (baseline: 3.2 ± 2.7 ng/ml vs week 4: 4.6 ± 4.1 ng/ml, $P = .02$), and the patients had gained 1.7 kg of their baseline weight at week 4 ($P = .01$).

Wang et al[39] were the first to monitor the very early changes in leptin levels at baseline, after 2 h, 4 h, 3, 7, and 14 days olanzapine initiating treatment in 9 patients with schizophrenia. These investigators observed a significant increment in the PLLs as soon as at the fourth hour after the beginning of the treatment (baseline: 14.6 ± 16.6 ng/ml vs 4 h: 21.7 ± 23.8 ng/ml, $P = .003$), and this increment stayed stable in week 2 (21.5 ± 17.5 ng/ml). BMI did not increase significantly from baseline at week 2.

Baptista et al[40] explored a large sample of 60 schizophrenic patients, treated in monotherapy with olanzapine, after switching from conventional AP, during a period of 16 weeks. These investigators observed a significant increment in SLL at week 8 (baseline: 7.1 ± 6.8 ng/ml vs week 8: 9.2 ± 7.9 ng/ml, $P = .01$) and no changes in week 16 (6.1 ± 6.1 pg/ml) vs baseline. In addition, significant WG ($P = .001$) and BMI increase ($P = .001$) and a positive correlation between leptin levels, BMI, and WG were observed at week 8. During all measurements, leptin levels were significantly higher in women than in men ($P = .001$). However, these authors did not take into account the effect of the interruption of conventional antipsychotics on SLL, in addition to the subsequent effect of olanzapine, as also done by Popovic et al[41] In this last study, modifications of SLL were evaluated in 13 schizophrenic patients treated with conventional AP and switched to clozapine or risperidone during 12 weeks. These investigators observed a significant increase in SLL at week 12 comparing to baseline (baseline: 7.8 ± 3.2 ng/ml vs week 12: 15.8 ± 4.0 ng/ml, $P < .05$), but the leptin concentrations in 18 patients treated with conventional AP were not different as compared with 20 healthy controls (HCs).

In a longitudinal study, Eder et al[42] observed a concomitant significant increase in SLL over baseline and olanzapine-induced WG over baseline during an 8-week period in 10 schizophrenic inpatients, assigned to monotherapy with olanzapine and compared with healthy subjects (baseline: 2.5 ± 2.4 ng/ml to week 8: 4.6 ± 4.5 ng/ml, $P = .03$; weight: 68.8 ± 11.3 to 72.1 ± 10.5 kg, $P = .001$, vs baseline: 3.1 ± 2.2 ng/ml to week 8: 2.7 ± 2.0 ng/ml in HCs).

Ebenbichler and colleagues[43] determined whether WG induced by treatment with olanzapine was associated with changes in the soluble form of the leptin receptor (sOB-R) and whether such modification of the biological activity of leptin by sOB-R might contribute to WG. The authors assessed 14 schizophrenic inpatients assigned to a monotherapy with olanzapine during 10 weeks in comparison with HCs. Over a 10-week period, SLL increased from 4.3 ± 6.6 to 7.0 ± 8.8 ng/ml ($P = .002$), while there was no difference in the leptin level compared with the control group ($P = .175$), and there was an increase in BW (66.7 ± 11.3 to 69.7 ± 10.7 kg, $P = .001$).

In 2007, Atmaca et al[44] evaluated 21 schizophrenic patients, enrolled in olanzapine monotherapy during 6 weeks and compared with 21 HCs. These investigators reported that leptin levels were increased from the baseline in the patients, while no difference was observed in the control group during the same period (baseline: 5.9 ± 1.5 ng/ml vs week 6: 12.0 ± 3.1 ng/ml, $P < .01$, vs baseline: 5.7 ± 1.3 ng/ml vs week 6: 6.0 ± 1.7 ng/ml in controls). In addition, the mean change in weight for the olanzapine group throughout 6 weeks was 6.8 ± 3.0 kg ($P < .05$) and the change in leptin levels correlated with the change in BW ($r = .61$, $P < .05$) and in BMI ($r = .55$, $P < .05$).

In a previous longitudinal study, Atmaca et al[45] examined 45 inpatients with schizophrenia, treated by monotherapy with quetiapine ($n = 15$), olanzapine ($n = 15$), and haloperidol ($n = 15$). The patients were evaluated at base-

line and after 6 weeks of medication. These authors found a marked increase in leptin levels for the olanzapine vs the quetiapine group ($P < .05$) and for the olanzapine vs the haloperidol group ($P < .01$). The mean WG for the quetiapine, olanzapine, and haloperidol groups were 3.9, 8.4, and 0.5 kg, respectively.

In addition, Krauss and colleagues[46] measured PLLs, weight, and BMI at baseline and weekly (over 4 weeks) in schizophrenic inpatients who received clozapine ($n = 11$), olanzapine ($n = 8$), haloperidol ($n = 13$), and in an other group of patients with various psychiatric disorders ($n = 12$) which did not receive any psychopharmacological treatment. These investigators observed an increase PLL associated with clozapine-induced WG, as soon as the end of the first week after the beginning of the treatment (baseline: 6.7 ± 3.9 ng/ml vs week 1: 8.7 ± 5.8 ng/ml and week 2: 9.4 ± 6.0 ng/ml, $P < .05$). Olanzapine also induced a similar effect (baseline: 6.1 ± 4.2 ng/ml vs week 2: 9.5 ± 7.7 ng/ml, $P < .05$), whereas leptin level, weight, and BMI remained stable in patient receiving haloperidol or no psychopharmacological treatment.

In 2 studies, the effects on leptin concentration of 2 drugs were not analyzed separately. Zhang et al[47] assessed the effects of AP drug therapy on abdominal fat deposition and on leptin and insulin secretion in 46 schizophrenic patients in their first episode treated with risperidone ($n = 30$) and chlorpromazine ($n = 15$). These patients were matched with 38 HCs. These authors did not observe any significant difference in fasting PLL between the control group and patients on admission (11.07 ± 11.39 vs 7.68 ± 7.71 ng/ml) and a substantial elevation in PLL in the patient group after 10 weeks of medication (21.61 ± 17.13 ng/ml; $P < .001$, with significant interactions with gender). In addition, significant increases in all weight and fat indicators were observed 10 weeks after the beginning of the AP treatment in the patient group (mean BW: 61.3 ± 11.5 vs 56.7 ± 11.4 kg before treatment, $P < .05$, and mean BMI: 22.2 ± 3.4 vs 20.5 ± 3.5 kg/m^2 at baseline, $P < .01$). Finally, Fitzgerald et al[48] reported an increment in PLL and BMI in 22 schizophrenic women treated with risperidone or olanzapine at week 12, compared with baseline (baseline: 25.0 ± 10.1 ng/ml vs week 12: 28.9 ± 13.9 ng/ml, $P = .06$, and for BMI, $P = .03$).

Six cross-sectional studies also evaluated the effects of AP on leptin concentrations. In 2000, Melkersson et al[49] investigated the influence of olanzapine on SLL in 14 patients meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for schizophrenia or related psychosis and treated for 0.4 years (0.2–1.4 years). The authors reported a median SLL of 24.2 ng/ml (range 6.7–39.5), and for all patients, SLL were increased in 57%, and no correlation between leptin and BMI was found. Later on Melkersson and Hulting[50] conducted a study in 47 patients with schizophrenia and schizoaffective disorder receiving conventional AP ($n = 19$) during 3.0 years (0.3–20.0 years), olanzapine ($n = 14$) during 0.4 years (0.2–1.4 years), or clozapine ($n = 14$) during 3.0 years (0.5–7.4 years). No significant difference on SLL occurred among the 3 groups of patients (conventional AP, median leptin level [MLL]: 20.1 μg/l [range 1.4–46.3]; clozapine, MLL: 10.3 μg/l [range 2.4–46.9]; and olanzapine, MLL: 24.2 μg/l [range 6.7–39.5]). In addition, elevated BMI was found in 47% of the patients in the conventional AP group, in 50% of patients in the clozapine group, and in 57% of the patients in the olanzapine group.

Herran et al[51] determined the effects of long-term antipsychotic treatment (at least 6 months) on SLL of 59 outpatients with chronic schizophrenia treated with AP (phenothiazines: $n = 26$, mean SLL = 11.30 ± 7.92 ng/ml; haloperidol: $n = 8$, SLL = 10.74 ± 9.30 ng/ml; olanzapine: $n = 7$, SLL = 26.60 ± 20.02 ng/ml; clozapine: $n = 5$, SLL = 10.86 ± 9.25 ng/ml; risperidone: $n = 5$, SLL = 5.64 ± 3.96 ng/ml compared with 59 HCs (11.5 ± 10.2 ng/ml). The SLL did not differ significantly between patients and HC ($P = .8$). Differences in leptin levels were significant when comparing patients taking AAP ($P = .03$), and the levels were higher in females than in males both in patients and in control group. Moreover, the authors added that SLL in patients correlated significantly with WG ($P < .001$) and showed a trend for an association with BMI gains ($P < .07$).

Hagg et al[52] compared 87 schizophrenic patients and related psychosis treated with clozapine ($n = 41$) during 2.8 years (2.4–3.3 years) as well as with conventional AP ($n = 62$) during 8.7 years (7.1–10.2 years) to the general population ($n = 189$). The authors reported an increase of PLL; in separate multiple regression analyses, leptin levels were significantly associated with clozapine treatment in both men and women and with AP treatment only in men (HC: men, 4.5 ng/ml; women, 13.7 ng/ml vs clozapine: men, 6.7 ng/l [$P = .002$]; women, 20.6 ng/ml [$P = .023$] vs conventional: men, 6.4 ng/ml [$P = .027$]; women: 19.8 ng/ml [$P = .11$]). In addition, partial correlation coefficients between leptin concentrations and BMI controlling for sex and age were relatively high in all groups ($r = .67$–$.73$).

Haupt and colleagues[53] indicated no evidence of modification in plasma leptin concentration in 72 patients with schizophrenia compared with 124 HCs; the patients were treated with olanzapine ($n = 27$), risperidone ($n = 24$), or conventional AP ($n = 21$) with medication duration greater than 3 months (mostly from 6 months to 2 years), and polytherapy was allowed (antidepressant, mood regulators, conventional antipsychotic, and benzodiazepine). There was no interaction with BMI and treatment or subject groups.

Finally, in 2007, Murashita et al[54] evaluated 15 schizophrenic patients treated with risperidone monotherapy for at least 6 months ($r = .5$–8.3 years) and compared them with HCs ($n = 25$). They also measured glucose

Table 2. Circulating Ghrelin Level Modifications during AP Treatment in Psychotic Patients (prospective and cross-sectional studies)

Authors	Washout Period (d)	Drug	Number of Patients	Duration (wk)	Mean age (y) ± SD	Ghrelin Modifications
Prospective studies						
Murashita et al[38]	NA	OLZ	7 (3 w/4 m)	26	46.3 ± 15.7	W26[a] vs B: ↗
Hosojima et al[11]	28	OLZ	13 (4 w/9 m)	4	37 (20–56)	W4[a] vs B: ↘
Theisen et al[12]	NA	CLZ	12 (6 w/6 m)	10	31 ± 7.1	W10[a] vs B: NS
Himmerich et al[55]	7	OLZ/CLZ	6 (3 w/3 m)	2	49.83 ± 11.02	W2[b] vs B: NS
		Others	17(8 w/9 m)		35.35 ± 12.51	W2[b] vs B: NS
Popovic et al[41]	Switch	CLZ/RISP	18 (9 w, 9 m)	12	28.8 ± 1.6	W4[a], W12[a] vs B: NS
Cross-sectional studies						
Togo et al[56]		OLZ	19	9 (4–68)	43.7 ± 14.2	↘[a] vs HC
		RISP	15	79 (4–294)	41.3 ± 13.7	↘[a] vs HC
		HC	18		35.3 ± 6.5	
Palik et al[57]		CLZ	15	52	50.6 ± 5.6	↗[a] vs HC
		OLZ	14			↗[a] vs HC
		RISP	15			↗[a] vs HC
		QUET	12			↗[a] vs HC
		HC	75		51.1 ± 5.8	
Murashita et al[54]		RISP	15 (10 w/5 m)	26	40.8 ± 11.8	↗[a,b] vs HC
		HC	25			

Note: Abbreviations are explained in the first footnote to table 1.
[a]Octanoylated ghrelin.
[b]Total ghrelin.

and lipid parameters. The authors reported that SLL and BMI were significantly higher in risperidone group (10.4 ± 4.1 vs 6.4 ± 4.2 ng/ml for HC, $P = .0243$, and 25.2 ± 3.5 vs 22.8 ± 2.1 kg/m^2 for HC, $P = .015$).

Ghrelin

More recently, ghrelin levels of antipsychotic-treated patients with schizophrenia were assessed in 5 prospective and 3 cross-sectional studies (Table 2).

In a first prospective clinical study, Murashita et al[38] evaluated 7 Japanese patients with schizophrenia and compared metabolic parameters before and after 6-month administration of olanzapine. Both plasma total ghrelin (baseline: 164.5 ± 82.9 fmol/ml to week 26: 227.6 ± 117.6 fmol/ml, $P = .018$) and active ghrelin (baseline: 9.1 ± 7.0 fmol/ml to week 26: 21.1 ± 12.1 fmol/ml, $P = .0057$) were increased significantly after the olanzapine treatment; the variation of BMI and WG was not significant after 6 months of treatment.

Hosojima et al[11] recruited 13 patients with schizophrenia without medications for at least 4 weeks (6 patients were AP naive) and receiving olanzapine for 4 weeks in monotherapy. Serum bioactive (octanoylated) ghrelin levels decreased significantly from baseline at week 4 (baseline: 92.6 ± 62.6 pg/ml vs week 4: 61.2 ± 42.8 pg/ml, $P = .03$).

Theisen et al[12] reported that bioactive serum ghrelin level (SGL) did not differ significantly in 12 psychotic patients during 10 weeks (baseline: 749 ± 493 pg/ml vs week 10: 777 ± 394 pg/ml, $P > .05$).

Himmerich et al[55] reported on an open-labeled longitudinal study of 52 patients free of medication for at least 1 week. Twenty-three schizophrenic patients received AP among whom 6 received olanzapine or clozapine and 17 conventional AP, while 29 mood disorders patients received antidepressants (13 patients receiving mirtazapine or trimipramine). Total immunoreactive ghrelin levels were measured at baseline and in the second week of the treatments. Total ghrelin levels did not differ among medication groups and did not relate to age or gender (601 ± 535.3 pg/ml for AAP group vs 502.18 ± 279.9 pg/ml for conventional AP). BMI at the time of blood measurement was significantly and inversely correlated with ghrelin level. Finally, patients taking clozapine or olanzapine showed a larger WG than did patients with other AP medications.

Finally, Popovic et al[41] measured the modifications of total SGL and BMI in 13 schizophrenic patients treated with conventional AP and switched to clozapine or risperidone during 12 weeks. The authors reported no modifications in SGL at weeks 4 and 12 as compared with baseline and a significant increase in BMI (baseline: 947.5 ± 140.3 pg/ml vs week 4: 890.1 ± 72.7 pg/ml vs week 12: 900.3 ± 110.7 pg/ml, and for BMI, baseline: 22.4 ± 0.9 kg/m^2 vs week 12: 23.1 ± 0.8 kg/m^2, $P < .01$); the total ghrelin concentrations in 18 patients treated with conventional AP were not different as compared with 20 HCs.

Three cross-sectional studies also evaluated the effects of AP on ghrelin concentrations. Togo and colleagues[56] analyzed the effect of psychopharmacological treatment

on ghrelin levels; they compared 34 schizophrenic patients treated, respectively, with olanzapine (n = 19) and risperidone (n = 15) for at least 4 weeks (4–294 weeks), with 18 HCs. The investigators reported significant differences in serum bioactive octanoylated ghrelin concentrations between patients treated with olanzapine (50.5 ± 23.7 pg/ml, $P < .001$) or risperidone (96.5 ± 57 pg/ml, $P < .001$) vs HC (162.5 ± 117.8 pg/ml).

While Palik et al[57] determined ghrelin levels in 56 AAP patients treated continuously for at least 1 year (clozapine n = 15, olanzapine n = 14, risperidone n = 15, quetiapine n = 12). BMI and carbohydrate metabolism were compared with those of 75 HCs to evaluate the possible contribution of ghrelin to a possible increase in appetite. The active forms of SGLs in patients treated with AAP for at least 1 year were similar among the 4 groups of treatment and notably higher than in HCs (1333 ± 659 vs 368 ± 103 pg/ml, $P < .0001$). BMI of the total patient group was significantly higher that the controls (29.3 ± 7.2 vs 24.3 ± 3.7 kg/m^2, $P < .01$). Patients had a much higher ghrelin level with the same BMI than controls, suggesting a possible abnormality in the regulation of ghrelin secretion.

Finally, a third cross-sectional study (Murashita et al[54]) reported a significant increase in total ghrelin (271.4 ± 182.3 vs 159.2 ± 57.4 fmol/ml, P = .0067), in active ghrelin levels (24.2 ± 20.8 vs 13.5 ± 7.5 fmol/ml, P = .0241), and in BMI (P = .01) in 15 schizophrenic patients treated with risperidone monotherapy during 2.5 ± 1.9 years (r = .5–8.3 years) as compared with 25 healthy volunteers.

Synthesis

The aim of this review was to analyze the effects of antipsychotic drugs on leptin and ghrelin circulating levels.

In all studies, leptin levels were measured in the early morning in human plasma or serum in fasting patients. The dosage was homogeneously performed in most of the studies with commercial radioimmunoassay (RIA) kits, an intraassay coefficient of variance (CV) varied from 4.4% to 7% and an interassay CV from 5.2% to 10%. In 4 studies, ELISA method was used.

Women have more elevated PPLs than men,[22] in keeping with the fact that women have more adipose tissues. Surprisingly, only 3 of 19 prospective studies took this gender effect into account when analyzing SLL. When evaluated, a significant higher SLL was reported in women in mean baseline values as well as in AAP-treated subjects. However, in 2 cross-sectional studies and 1 prospective, SLL did not differ between male and female group.

A majority of the 22 studies, either prospective or cross-sectional, focused their analysis on the effects of clozapine and olanzapine on SLL. When prospective studies are compared, a significant increase in SLLs (from baseline or compared with HCs) occurs only a few hours after the beginning of the treatment, seems to peak between 6 and 10 weeks after, and remains somehow elevated after that period up to several months. (Some studies analyzed SLL in patients treated during long periods.) These results are only partially confirmed in cross-sectional studies with longer duration of clozapine or olanzapine treatments (20–452 weeks). Indeed, Herran et al[51] did not observe any difference in SLL between patients treated with antipsychotic drugs (clozapine, olanzapine, risperidone, and conventional antipsychotics) compared with HCs, but the number of patients was small.

One study (Sporn et al[58]) was not included in table 1 because it evaluated SLL in psychotic children and could not be easily compared with modifications as observed in adult patients. In this study, however, increased values of SLL were also observed in psychotic children vs HCs, 6 weeks after clozapine initiation.

In contrast to olanzapine and clozapine, in 3 of 4 studies (1 prospective and 3 cross-sectional), risperidone was not effective on SLL.

In addition, SLL were not significantly modified in patients treated with conventional neuroleptic treatment who displayed less BW modifications when compared with atypical ones. But it should be mentioned that only a few studies (2 prospective[45,46] and 2 cross-sectional[51,52]) with a small number of patients addressed this comparison.

Even if some authors regularly interviewed their patients regarding appetite and food intake, no study considered the feeding behavior of schizophrenic patients treated with antipsychotic based on a sensitive and validated food scale.

Only half of the studies reported the duration of washout treatment before evaluating the effect of AAP on SLL. When reported, washout duration varied from 3 days to 4 weeks and did not seem to affect leptin levels. Only 2 studies[37,47] evaluated naive patients. Arranz and colleagues[59] reported a higher increase in leptin concentrations in schizophrenia patients off AP treatment for 17.8 ± 2.8 months than antipsychotic naive patients.

AAP doses varied from small to high doses of the treatment. This did not seem to interact on the modulation of leptin secretion (small doses of the drug are apparently sufficient to induce this phenomenon).

Ten studies in treated psychotic patients assessed WG and BMI and 3 studies demonstrated a significant positive correlation between BMI and SLL modifications; this relationship was shown in lean and obese subjects as well.[22]

Ghrelin levels were measured in the early morning in fasted patients and subjects in human serum by conventional RIA methods, but only 3 studies indicated the intraassay (5.3% to 8%) and interassay (7.8% to 13.6%) CVs. As mentioned earlier, ghrelin in plasma or serum

samples can occur under 2 forms: an octanoylated (active) one and a desoctanoylated one which represents the bulk of the activity but which is not able to bind to GHS-R receptors. It is noteworthy that when both active and total ghrelin are measured in the same studies, the effects appear somehow clearer with the octanoylated form. Different results for octanoylated and total ghrelin levels may depend on the types of assay or RIA kits.[60] To date, only a few studies ($n = 8$) evaluated the effects of AAP (olanzapine, clozapine, risperidone, and quetiapine) on ghrelin concentrations in schizophrenic patients. In fact, when the duration of the antipsychotic treatment is brief, from 2 to 9 weeks, there is a decrease in serum-active ghrelin levels compared with baseline and an increase during longer periods (26 and 52 weeks). The latter occurred in the case of 4 different AAPs. However, Himmerich et al[55] did not observe a variation in SGL after 2 weeks of olanzapine or clozapine treatment in 6 patients.

Periods of wash out were not systematically specified except for 2 studies (eg, Hosojima et al[11] and Arranz et al[59]) in which all the patients included had been free from medication for at least 1 week to 1 month. It may be noted that it was also the only study reporting a negative relation between BMI and SGL.

Leptin and ghrelin in olanzapine-treated patients interact competitively (an increase on SLL and a decrease in SGL[11,61]). But this is not always observed and may depend on the time course at which the measurements are made.[43]

Finally, and as for leptin, the relationships between fasting plasma ghrelin concentrations and various anthropometric variables, such as the correlation between SGL and BMI, were seldom evaluated (except Himmerich and Palik studies[55,57]). When it was, this correlation was negative.

Conclusion

The comparison of the literature allows to conclude that an elevation on leptin levels of schizophrenic patients during some AAP treatment (olanzapine and clozapine) occurs very early after the onset of medication, and this increase remains stable after a period of several weeks. On the contrary, conventional antipsychotic treatments do not interfere with leptin levels as seems also to be the case with risperidone; but, for this last agent, only a few studies are available. In addition, AAP monotherapy is not systematically evaluated, and other drugs such as aripiprazole and amisulpride have not been studied as yet.

In contrast to leptin, a biphasic evolution on ghrelin levels is observed, depending on the AAP treatment duration: a decrease at earlier time intervals and an elevation in longer ones.

Surprisingly, body WG and correlations between peptide levels and BMI were not systematically considered, and to our knowledge, no study so far evaluated feeding behavior during antipsychotic treatment.

Owing to continuing of increased prevalence of weight modification and obesity in schizophrenia, future prospective and follow-up studies in larger patients samples are warranted to (1) determine the mechanistic basis of these clinical effects and their potential for contributing to the development of comorbid illness as well as (2) study the hormonal responses to food intake, involving ghrelin leptin and other satiety signals as insulin and adinopectin, considering dynamic measurement and their impact on weight during AAP treatment.

Future researches should carefully evaluate, before and during AP treatment, the very complex aspects of eating behavior which depends not only on hormonal regulation but also on other factors such as emotion, learning, and cognitive impairments. Possible correlations between BMI and satiety signals should be taken into account to identify those subjects who need special clinical attention to prevent or minimize WG during AP treatment. Monitoring of metabolic and feeding parameters may be useful in preventing metabolic abnormality, thereby improving health and maintaining a good QOL and the observance of APP treatment by the patients.

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