

# Appetite Regulation: Hormones and Antipsychotics

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**A**ntipsychotics induce unwanted weight gain and metabolic abnormalities in some patients, referred to as the metabolic syndrome. Second-generation antipsychotics (SGAs) have a greater propensity than first-generation antipsychotics (FGAs) to produce these untoward effects. Black box warnings in their product labeling which caution about long-term risk of metabolic abnormalities with drug treatment have been mandated by the Food and Drug Administration for most of the antipsychotics. These metabolic aberrations resulting from antipsychotic therapy are currently the target of intense investigation. However, definitive research findings so far remain quite limited, and data in children and adolescents, who are particularly susceptible, are scanty.<sup>1</sup>

Clozapine and olanzapine in particular are prone to produce excessive weight gain. Olanzapine mainly increases body fat, while both antipsychotics are associated with disturbances of glucose metabolism. Recent findings indicate it is unlikely these SGAs have direct effects on pancreatic  $\beta$  cells to alter glucose homeostasis, but rather induce insulin resistance of peripheral tissues by some mechanism other than purely weight gain.<sup>2</sup>

## PHYSIOLOGIC SYSTEMS REGULATING WEIGHT AND APPETITE

One line of research being actively pursued is whether antipsychotics have direct hormonal effects on appetite control. Two hormones, ghrelin and leptin, with opposite effects on appetite and weight control, are being scrutinized as likely candidates for causing the metabolic syndrome induced by antipsychotics.

The body has several physiologic systems in place for maintaining body weight.<sup>3</sup> One such system is primar-

ily concerned with short-term regulation of appetite and weight (ghrelin), while the other (leptin) primarily mediates longer-term regulation of body weight. The peptide hormone ghrelin produced in the stomach is linked to short-term feeding behavior and acts as an appetite stimulant. Long-term weight maintenance, on the other hand, is largely regulated by leptin, a hormone secreted by adipose tissue cells ("white fat"), which functions to inhibit feeding behavior.

The arcuate nucleus of the hippocampus contains ligand-specific receptors for the appetite-regulating hormones. When these hormones bind to their respective receptors in the arcuate nucleus, they stimulate the hippocampus to signal the body to adjust food intake and the metabolic expenditure of energy, accordingly. It has been observed that the weight control systems of the body that have evolved in humans tend to protect better against weight loss than weight gain.<sup>4</sup> It is postulated that food scarcity, rather than overabundance, has represented the greater threat to survival of man, until modern times.

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## GHRELIN

Appetite is known to be influenced by the gastrointestinal hormone cholecystokinin, a peptide released into the bloodstream by the intestine and labeled the “satiety hormone” because it notifies a person when he or she has had enough to eat. Recently, ghrelin has been identified as a key appetite-regulating hormone following its discovery by a group of Japanese investigators in 1999.<sup>5</sup> It is regarded as a key peptide hormone in the regulation of normal and abnormal body weight. Ghrelin has emerged as the first circulating “hunger” hormone. Ghrelin levels rise sharply before a meal or when weight loss is present. Ghrelin levels tend to be lower in obese individuals than in lean individuals.

In its acylated form, ghrelin acts in the central nervous system (CNS) to stimulate growth hormone secretion and promote food intake. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R 1a) in the CNS, also affecting prolactin and cortisol release. A second action of ghrelin described following its discovery is its role in regulating appetite, feeding behavior, and energy utilization. Circulating ghrelin levels are inversely correlated with body mass index and body fat percentage. Normally, ghrelin production and secretion into the blood stream is reduced in the presence of obesity. Decreased ghrelin levels of the morbidly obese are presumed to be the reason for the acute decrease in appetite that occurs following bariatric surgery.

In plasma, ghrelin has been found to exist in two forms—an unacylated and an acylated form. The former is present at approximately 2.5 times greater concentration than the latter. The acetylated form (active ghrelin) is thought to be critical in order to enable penetration of the blood brain barrier so as to allow modulation of GH release, appetite, and other endocrine functions by the hippocampus. The unacylated form of ghrelin has non-endocrine functions mediated by ghrelin receptors distributed throughout peripheral cardiovascular tissues and other functions related to adipogenesis and cell proliferation.

## LEPTIN

In 1994, a team of researchers<sup>4</sup> discovered the first true anti-obesity hormone, leptin, which has led to an explosion in obesity research and fostered the search by the pharmaceutical industry for an effective and safe anti-obesity drug. While leptin inhibits feeding behaviors and is, therefore, useful to treat a mutant strain of obese mice lacking this

hormone as well as humans with leptin gene deficiency, most obese humans have elevated, not reduced, blood levels of leptin. To date, only leptin and insulin fulfill the criteria for a physiologic adiposity signal.

Evidence suggests that the main role of leptin physiologically is to protect against weight loss in times of food deprivation rather than to prevent weight gain in times of plenty. As fat stores of an individual shrink, leptin production declines and, in response, appetite increases and body energy utilization diminishes.

However, the reverse does not seem to be the case. Leptin is known to be elevated in obesity. It is postulated that both leptin resistance and an overabundance of leptin secretion occurs consequent to an enlarged fat compartment. High levels of leptin associated with increased fat stores do not appear to inhibit appetite or increase metabolic utilization of energy proportionately. Although leptin therapy is ineffective in treating garden variety obesity, its discovery has led to better understanding of the body’s weight control mechanisms and dysregulation by antipsychotic therapy.<sup>3</sup>

## ANTIPSYCHOTICS AND APPETITE REGULATION

Both FGAs and SGAs can cause unwanted weight gain; however, treatment with FGAs appears significantly less likely to result in weight gain than SGAs, which differ substantially in their propensity to induce unwanted weight gain and the metabolic syndrome.<sup>6</sup> There is considerable evidence that clozapine and olanzapine carry the greatest risk, risperidone and quetiapine an intermediate risk, and ziprasidone and aripiprazole the least risk of these adverse effects.

The potential impact of the SGAs, especially clozapine and olanzapine, on the appetite hormones leptin and ghrelin is currently being actively pursued in drug-treated patients, especially those patients who experience excessive weight gain. The effects of long-term therapy on these appetite hormones are being compared in patients with schizophrenia and age-matched normal controls, but preliminary findings are as yet inconclusive with respect to possible direct effects of antipsychotics on hormones central to controlling appetite and regulating weight.

Numerous large sample size studies of schizophrenia patients find elevated levels of plasma leptin in subjects treated with SGAs as well as some conventional antipsychotics.<sup>7-9</sup> Increased plasma leptin levels within 6 weeks of starting clozapine therapy in children is reported.<sup>10</sup> Patterns of changes in ghrelin levels during treatment

with antipsychotics are less clearcut. Studies in patients with schizophrenia have reported increases,<sup>11</sup> decreases,<sup>12</sup> and no change<sup>9</sup> in plasma ghrelin concentrations during antipsychotic therapy.

A potential reason for the discrepant findings of ghrelin levels during antipsychotic therapy may be the methodologic importance of measuring only the active (acylated) fraction of ghrelin rather than total plasma concentrations of hormone, as has been the case with many studies.<sup>1,13</sup> Until it is acylated, ghrelin does appear to penetrate the blood-brain barrier with resulting effects on appetite. How SGAs, in particular, may affect ghrelin secretion remain to be established.

## CONCLUSION

Two recently discovered hormones, ghrelin and leptin, have opposing effects on appetite and weight control, acting on different receptors located in the arcuate nucleus of the hypothalamus. Ghrelin, secreted primarily by the gastric fundus, has emerged as the first circulating hunger hormone. Leptin, secreted predominantly by adipose tissue cells, maintains a balance between food intake and energy utilization and has an inhibitory effect on body. Changes in circulating plasma

levels of these hormones are reported with antipsychotic drug therapy, especially clozapine and olanzapine. It remains unclear whether these hormonal aberrations are primary drug effects or represent secondary effects due to changes in body weight and glucose metabolism. **PP**

## REFERENCES

1. Winsberg B, Usubiaga H, Cooper T. Ghrelin and leptin response to oral glucose challenge among antipsychotic drug-treated children. *J Clin Psychopharmacol.* 2007;27(6):590-594.
2. Laimer M, Ebenbichler CF, Kranebitter M, et al. Olanzapine-induced hyperglycemia: role of humoral insulin resistance-inducing factors. *J Clin Psychopharmacol.* 2005;25(2):183-185.
3. Marx J. Cellular warriors at the battle of the bulge. *Science.* 2003;299(5608):846-849.
4. Friedman J. A war on obesity, not the obese. *Science.* 2003;299(5608):856-858.
5. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature.* 1999;402(6762):656-660.
6. Weiden PJ, Buckley PF. Reducing the burden of side effects during long-term antipsychotic therapy: the role of "switching" medications. *J Clin Psychiatry.* 2007;68(suppl 6):14-23.
7. Hägg S, Söderberg S, Ahrén B, Olsson T, Mjörndal T. Leptin concentrations are increased in subjects treated with clozapine and conventional antipsychotics. *J Clin Psychopharmacol.* 2001;62(11):843-884.
8. Hosojima H, Togo T, Odawara T, et al. Early effects of olanzapine on serum levels of ghrelin, adiponectin and leptin in patients with schizophrenia. *J Psychopharmacol.* 2006;20(1):75-79.
9. Popovic V, Doknic M, Maric N, et al. Changes in neuroendocrine and metabolic hormones induced by atypical antipsychotics in normal-weight patients with schizophrenia. *Neuroendocrinology.* 2007;85(4):249-256.
10. Sporn A, Bobb A, Gogtay N, et al. Hormonal correlates of clozapine-induced weight gain in psychotic children: an exploratory study. *J Am Acad Child Adolesc Psychiatry.* 2005;44(9):925-933.
11. Palik E, Birkás KD, Faludi G, Karádi I, Cseh K. Correlation of serum ghrelin levels with body mass index and carbohydrate metabolism in patients treated with atypical antipsychotics. *Diabetes Res Clin Pract.* 2005;68(suppl 1):S69-64.
12. Togo T, Hasegawa K, Miuri S, et al. Serum ghrelin concentrations in patients receiving olanzapine or risperidone. *Psychopharmacology.* 2004;172(3):230-232.
13. Rindi G, Torsello A, Locatelli V, et al. Ghrelin expression and actions: a novel peptide for an old cell type of the diffuse endocrine system. *Exp Biol Med.* 2004;229(10):1007-1016.