Mechanisms and Genetics of Antipsychotic-Associated Weight Gain

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Antipsychotic medications, which comprise one of the most widely prescribed medication classes, have proven effective in many psychiatric conditions. However, these agents can also be associated with obesity and other metabolic abnormalities, the mechanisms of which have been partially elucidated. We review here the current state of knowledge of the effects of these medications on weight and appetite, as well as genetic markers that may help predict weight gain and prevent the undesirable cardiometabolic effects of these agents.

Atypical antipsychotic medications are the mainstay of treatment for schizophrenia and have also come into widespread use in the management of mood disorders and other indications. Unlike conventional, first-generation antipsychotics, which are characterized by high dopamine D2 receptor antagonism, atypical agents demonstrate higher serotonin 5-HT2 receptor antagonism, are less likely to cause extrapyramidal side effects at therapeutic doses, and generally have beneficial effects on both the positive and negative symptoms of schizophrenia.

However, atypical antipsychotic medications frequently cause weight gain and other adverse metabolic effects, which contribute to the morbidity of schizophrenia and may affect medication adherence.[1] One-year mean weight increases, for example, range from 1 kg (with aripiprazole and ziprasidone)[2] to nearly 14 kg (with olanzapine).[3] This review focuses on atypical antipsychotic medications and their role in weight gain and obesity, summarizing the current state of knowledge regarding the neurochemistry of appetite and weight gain, the known effects of atypical antipsychotics on receptors and neuroendocrine pathways involved in weight regulation, and efforts to identify genotypes and other baseline features of patients that predispose to antipsychotic-associated weight gain (AAWG).

NEURAL REGULATORS OF APPETITE RELEVANT TO AAWG

Appetite and food intake are regulated by input to the brain from the periphery and by the action of hypothalamic neurotransmitters and neuropeptides (see **Figure 1**). The hypothalamus integrates messages from higher cortical levels, brain pathways involved in motivation and reward, and peripheral messengers. The hypothalamic nucleus most involved with appetite is the arcuate nucleus (AN). One population of cells in the AN expresses neuropeptide Y (NPY) and Agouti-related protein (AgRP), two highly orexigenic (appetite-enhancing) peptides whose expression is increased by ghrelin and inhibited by leptin. Another population of neurons expresses pro-opiomelanocortin (POMC), a precursor protein whose peptide products include α-melanocyte-stimulating hormone (α-MSH). Central injection of α-MSH results in decreased food intake, presumably by binding to melanocortin 3 and 4 receptors (MC3R and MC4R); MC4R deficiency is the most common genetic cause of obesity (~5%) in humans.[4]

Peripheral messengers also regulate food intake at the level of the hypothalamus. Ghrelin, a peptide hormone secreted from the stomach mucosa, induces NPY and AgRP expression, thereby stimulating appetite. Other messengers inhibit food intake; these include leptin, a hormone that is released by adipose tissue and has the effect of suppressing NPY/AgRP expression and increasing POMC activity.[5] Exogenously administered leptin, however, has little to no effect in humans with obesity. Other anorexigenic peptides include the cytokine tumor necrosis factor-α (originally known as cachectin), which also activates POMC neurons and insulin from pancreatic β cells.

The neurotransmitters serotonin and histamine also regulate food intake. Serotonin enhances satiety by stimulating POMC secretion from AN neurons, an effect mediated by 5-HT2C receptors.[6] Serotonergic agents such as fenfluramine and sibutramine decrease food intake in humans and animals; 5-HT2C receptor knockout mice are obese[7] and show elevations in glucose, leptin, and insulin levels. Histamine from the tuberomammillary nucleus in the posterior hypothalamus acts on H1 receptors to suppress food intake and increase thermogenesis; it also increases sympathetic activation of adipose tissue to enhance lipolysis. Histamine and the H1 signaling pathway appear to be required for leptin function, as seen from the fact

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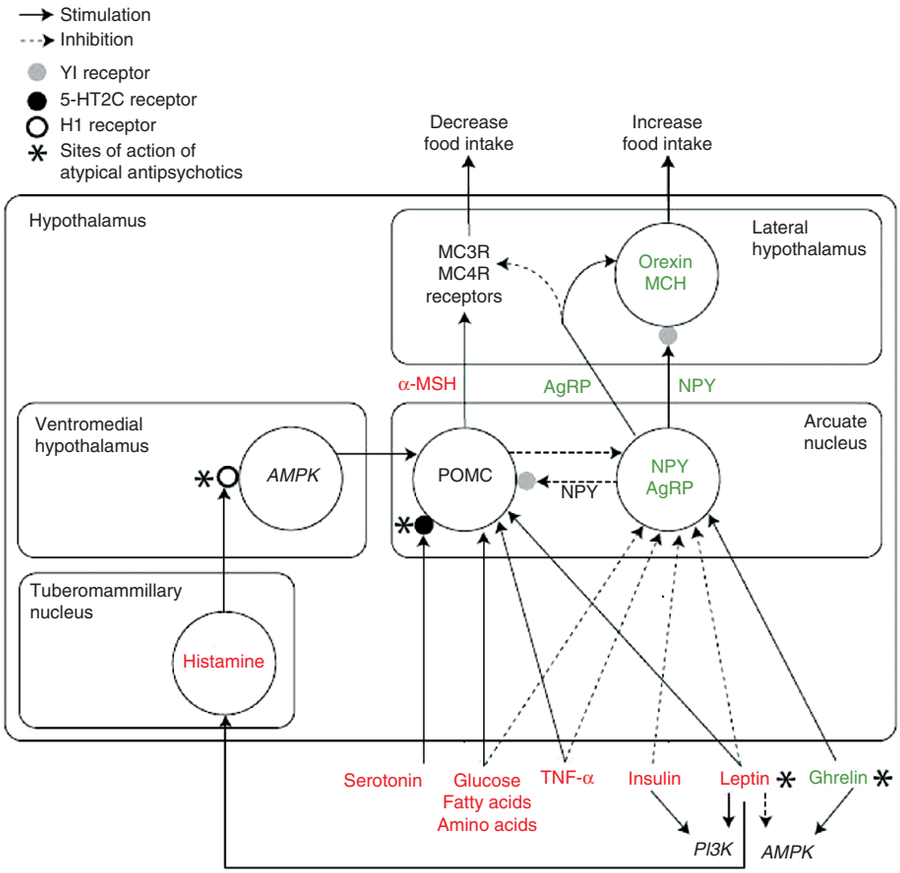

Figure 1 Schematic diagram of hypothalamic pathways involved in appetite regulation. Names in green indicate peptides or monoamines that stimulate or enhance food intake. Names in red indicate peptides or monoamines involved in the inhibition of food intake or reduction in appetite. Solid lines indicate a stimulatory effect; dashed lines indicate an inhibitory effect. Italicized names denote intracellular second-messenger systems. Receptors (small circles) are depicted only at sites thought to be involved in appetite regulation. *Sites of action of atypical antipsychotic medications. α-MSH, α-melanocyte-stimulating hormone; AgRP, Agouti-related peptide; AMPK, AMP-related kinase; MCH, melanocyte concentrating hormone; MCxR, melanocortin receptor; NPY, neuropeptide Y; PI3K, phosphoinositide 3-kinase; POMC, pro-opiomelanocortin; TNF-α, tumor necrosis factor-α.

[Q1]

that leptin's anorexiant effects are attenuated in H1 receptor knockout mice. Histamine release is inhibited by H3 autoreceptor activation, and selective H3 antagonists cause hypophagia in rats and other mammals.[8]

EFFECTS OF ANTIPSYCHOTIC MEDICATION

Atypical antipsychotic medications show affinity for serotonin (5-HT1A, 5-HT2A, 5-HT2C, 5-HT6, and 5-HT7), dopamine (D2 and D4), muscarinic (M1 and M3), histamine (H1), and adrenergic receptors,[9] giving rise to a variety of potential adverse effects despite their clear clinical efficacy (see **Table 1**). The risk of AAWG correlates to an extent with affinity for the H1 receptor and 5-HT2C receptor;[10] olanzapine and clozapine show high affinity for each of these receptors.

Histamine H1 receptor blockade activates hypothalamic AMPK, indicating negative energy balance and increasing appetite, an effect not observed in H1 receptor knockout mice.[11] The H1 receptor also seems to be required for leptin's anorexiant effect, as mentioned earlier. Antagonists of the 5-HT2C receptor prevent or delay the onset of satiety, thereby increasing the size of the meal. This process is probably mediated by inhibition [Q2]

of hypothalamic POMC neurons,[6] with a resultant decrease in α-MSH activity (as seen in 5-HT2C knockout mice), as well as disinhibition of NPY activity in AN neurons.

In addition to 5-HT2C and H1 antagonism, however, the dopamine D2 receptor itself has been implicated in AAWG. D2 receptor antagonism may, in fact, be a common factor [Q3] underlying weight gain with respect to all antipsychotic medications; for instance, more than half of the subjects in a recent open-label trial gained >7% of their baseline body weight when treated with haloperidol or amisulpride (D2 and D3 antagonists).[3] D2 blockade also causes hyperprolactinemia, which in turn may decrease insulin sensitivity and increase fat deposition; this may also be necessary for the orexigenic effect of 5-HT2C antagonism, given that a pure 5-HT2C antagonist requires concomitant D2 blockade to induce weight gain in rats.[12]

Other receptors, including the 5-HT1A and 5-HT2A subtypes and the muscarinic M3 receptor, have been implicated in other cardiometabolic effects of atypical antipsychotic medications, as summarized in **Table 1**.

In addition to their effects on specific receptors, atypical antipsychotics appear to affect the levels of neuropeptide hormones

Table 1 Summary of key receptors bound by atypical antipsychotics and their associated side effects

Receptor	Side effect	Mechanism
Serotonin 5-HT 2C	Diabetes	Antagonists disrupt sympathetic regulation of peripheral glucose metabolism; also inhibit skeletal muscle and hepatic glucose uptake
	Weight gain	Antagonists disinhibit hypothalamic NPY neurons (resulting in elevated NPY) and inhibit POMC neurons (resulting in decreased α-MSH); may also play a role in leptin resistance
Serotonin 5-HT 1A	Diabetes	Antagonists inhibit skeletal muscle and hepatic glucose uptake and downregulate pancreatic β-cell sensitivity to glucose
	Weight gain	Agonists increase food intake; partial agonists may mitigate 5-HT2C antagonism; partial agonists may also decrease carbohydrate craving
Histamine H1	Weight gain	Antagonists cause increased hypothalamic AMPK activity, mimicking depletion of cellular energy stores and causing increased appetite
	Diabetes	Antagonists disrupt sympathetic regulation of adipose tissue
	Sedation	Antagonists inhibit cholinergic neurons of basal forebrain and serotonergic neurons of dorsal raphe
Dopamine D2	Weight gain	Antagonists cause overall decrease in limbic dopaminergic activity, possibly leading to increased engagement reward-seeking behaviors such as food intake; agonists (psychostimulants, cocaine) are appetite suppressants
	Extrapyramidal side effects	Antagonists disinhibit indirect descending motor pathway in basal ganglia
	Endocrine effects	Antagonists disinhibit prolactin release from posterior hypothalamus, also contributing to weight gain
Muscarinic M1	Anticholinergic effects	Antagonists cause dry mouth, urinary retention, cognitive dysfunction, urinary retention, and constipation
Muscarinic M3	Diabetes	Antagonists cause impaired glucose tolerance and reduced insulin secretion from pancreatic β cells

α-MSH, α-melanocyte-stimulating hormone; AMPK, AMP-related kinase; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

involved in weight regulation. Reversible elevations in serum leptin concentration have been observed, probably as a consequence of increased adipose mass rather than a direct effect on leptin secretion.[13] This hyperleptinemia does not cause the expected suppression of food intake, suggesting the presence of leptin resistance. This may be mediated either by concurrent antipsychotic effects on histamine or serotonin pathways or the inability of leptin to cross the blood–brain barrier, perhaps as a consequence of dyslipidemia.

Levels of the orexigenic hormone ghrelin may decrease during the first few weeks of antipsychotic treatment and subsequently increase.[14] One recent study showed that all antipsychotic medications except quetiapine gave rise to a sustained increase in ghrelin levels.[15] Likewise, adiponectin levels fall during antipsychotic treatment; it is unclear whether antipsychotics directly affect adiponectin synthesis or secretion, or whether this is a result of adipogenesis and insulin resistance.[16] Expression of melanin-concentrating hormone and its receptor are also upregulated by antipsychotic treatment, possibly enhancing the incentive salience and rewarding aspects of food.[17] [Q4]

Finally, antipsychotic medications may act directly on adipose tissue. Olanzapine may directly inhibit lipolysis,[18] and other antipsychotics may induce protein kinase C-β activity in preadipocytes, thereby inducing their differentiation.[19]

PREDICTING AND MANAGING AAWG

AAWG is frequently, but not always, a side effect of antipsychotic medications. Unfortunately, reliable biomarkers for prediction of weight gain (or other adverse effects) do not yet exist, and therefore personalized therapy to reduce risk remains an elusive goal. Weight gain appears to be a multifactorial phenomenon resulting from interactions among drug effects, patient characteristics, and other as-yet unidentified factors.[16]

On the basis of data from US antipsychotic drug product labels (except where noted), the agents most likely to cause clinically significant weight gain (defined as >7% increase in body weight from baseline) in short-term (4–8 week) trials are clozapine (≤50%)[20] and olanzapine (29%), followed by quetiapine (8–23%) and risperidone (18%), and finally ziprasidone (10%) and aripiprazole (2–8%, 20% in a 52-week trial).[21] With respect to newer agents, the incidence in short-term trials is 12–18% for iloperidone, 4.9–5.8% for asenapine (14.7% over a 1-year, open-label comparator-controlled study), and 5.6% for lurasidone.

This rank order roughly correlates with affinity for H1 and 5-HT2C receptors, although other mechanisms are clearly involved. For instance, ziprasidone has a high affinity for 5-HT2C receptors but is essentially weight neutral, and iloperidone has relatively low affinity for H1 receptors. Nevertheless, all atypical antipsychotics have potential to cause increases in body mass, diabetes, and dyslipidemia; consequently, receptor-binding affinities do not currently guide treatment selection. Current practice guidelines[22] for the use of any atypical antipsychotic call for measurements of the following parameters: body weight at 4-week intervals and then quarterly; fasting plasma glucose at baseline, 12 weeks, and annually; lipid profile at baseline, 12 weeks, and every 5 years; and waist circumference at baseline and annually. [Q5]

Few studies have assessed individual patient characteristics that may predispose to weight gain. Possible risk factors for AAWG include younger age (children and adolescents seem to be at greater risk than adults), female gender, first episode

Table 2 Polymorphisms found to be significantly associated with antipsychotic-induced weight gain

Category	Gene	Mutation or polymorphism	Comment
Receptors	*HTR2C*	−759C/T	−759T carriers have less weight gain than C carriers; studied in Han Chinese with olanzapine, clozapine; in Caucasians with multiple antipsychotics; and in Japanese with risperidone; C allele also associated with obesity in general population
	HTR2C	Cys23Ser	23 Cys allele associated with olanzapine-induced weight gain in Japanese
	HTR2A	102T/C	102T allele associated with risperidone-induced weight gain in Chinese, also with olanzapine-induced weight gain in Japanese; TT genotype associated with weight gain in Caucasians with multiple antipsychotics
	HTR6	267C/T	TT genotype associated with risperidone-induced weight gain in Japanese
	DRD2	−141C Ins/Del	Deletion-allele carriers show more weight gain (and worse treatment response) with risperidone or olanzapine
	ADRB3	Trp64Arg	64 Arg allele associated with olanzapine-induced weight gain in Japanese
	ADRA2A	−1291C/G	GG genotype and G allele significantly associated with weight gain
	LEPR	Gln223Arg	Arg/Arg associated with risperidone-induced weight gain in females only
	CNR1	−4558C/T	T allele carriers associated with greater weight gain with multiple antipsychotics
Peptides	*LEP*	−2548G/A	AA genotype significantly associated with weight gain in Chinese with risperidone and chlorpromazine; GG genotype associated with weight gain in Caucasians with multiple antipsychotics
	BDNF	Val66Met	Val/Val associated with weight gain with multiple antipsychotics; Val allele associated with risperidone-induced weight gain in Japanese
	TNF-α	−308G/A	−308 GG associated with clozapine-induced weight gain
Intracellular molecules	*GNB3*	C825T	TT genotype associated with more weight gain than CT or CC in Chinese with multiple antipsychotics; also found in olanzapine-induced weight gain in Japanese; however, meta-analysis shows nonsignificant effect
	SNAP25	TaiI and MnlI polymorphisms (in 3′ UTR)	Polymorphisms significantly associated with weight gain and with treatment response
Transporters	*5HTT* (LPR)	Long/short (L/S) promoter	S allele associated with weight gain in Caucasians with multiple antipsychotics
Metabolic enzymes	*CYP2D6*	188C/T	CC genotype associated with risperidone-induced weight gain in Japanese
	CYP2D6	Alleles *3, *4	Associated with olanzapine-induced weight gain
Other	*MDR1*	G2677T, C3435T	2677T and 3435T alleles associated with risperidone-induced weight gain

[Q6] α-MSH, α-melanocyte-stimulating hormone; LPR, linked polymorphic region; UTR, untranslated region.

of antipsychotic therapy, longer duration of treatment, high parental body mass index (BMI), and high BMI prior to first antipsychotic treatment. Patients with low baseline BMI may gain weight more rapidly in the early stages of treatment, but this is not predictive of long-term gain.[23] Finally, the magnitude of increase in serum leptin level (but not the baseline level) during antipsychotic treatment seems to be correlated with increase in BMI.[24]

The management of antipsychotic-induced weight gain can take the form of cognitive behavioral therapy interventions, nutritional or dietary changes, and switching of antipsychotic medications. Pharmacological strategies (reviewed in ref. 25) include H2 antagonists, serotonin reuptake inhibitors, sympathomimetics, and metformin. Topiramate, which may downregulate NPY receptors, has shown some promise; others include amantadine, which blocks dopamine reuptake, and orlistat, which inhibits fat absorption from the gastrointestinal tract. Other agents that have demonstrated efficacy in the past but are not currently available for use include rimonabant, a selective cannabinoid receptor, and sibutramine, a serotonergic agent.

PHARMACOGENETICS OF AAWG

There has been much work over the past decade to attempt to identify genetic contributions to AAWG, particularly in target genes implicated in weight regulation and the mechanism of antipsychotic action (reviewed in ref. 26). The genes with which significant correlations have been identified are listed in **Table 2**. Notably, the genes associated with AAWG are numerous, and not all are directly involved in the pathways of weight and appetite regulation discussed earlier.

The most extensively studied gene is the X-linked 5-HT2C receptor gene (*HTR2C*). Carriers of the −759T allele have been found to gain less weight than those with the wild-type C allele,[27] a finding that has been replicated in several, but not all, populations studied.[28] The T allele is associated with lower expression of the gene *in vitro* and may influence levels of circulating leptin.[29] An independent polymorphism, Cys23Ser, has also been associated with AAWG in some studies.

The −2548A/G polymorphism in the leptin gene (*LEP*) promoter region, known to be associated with obesity and alterations in leptin secretion, has also been associated with AAWG. When

combined with the *HTR2C* mutation above, this polymorphism might explain more than 25% of the variance in weight gain.[29]

Results from more recent work have begun to elucidate genetic associations that may underlie weight gain specific to particular antipsychotics; for instance, weight gain due to olanzapine may be associated with apolipoprotein and scavenger receptor genes, whereas weight profiles in patients taking risperidone may be associated with genes for the leptin receptor NPY receptor and paraoxonase 1.[30]

DISCUSSION

The widespread use of atypical antipsychotic medications has been associated with weight gain and related metabolic abnormalities in many, but not all, patients. Although certain antipsychotics are implicated in AAWG to a greater extent than others, there are, unfortunately, no clear biomarkers or predictors of AAWG to guide clinical decision making. Genetic testing, although still not widely available, may in the future help clinicians identify patients with mutations predisposing to AAWG, such as the *HTR2C* −759C and the *LEP* −2548G alleles. In addition to current metabolic monitoring, future practice guidelines may include measurement of leptin or ghrelin levels and rates of change during early treatment. The selection and use of antipsychotics with less H1 antagonism, minimal M3 antagonism, and partial agonist properties at the 5-HT1A receptor may also be protective.

Obesity is well known to be associated with adverse medical outcomes and poor quality of life, as well as depression, low self-esteem, and medication nonadherence; these effects could be devastating in patients with schizophrenia or bipolar disorder who are receiving treatment with an atypical antipsychotic. A greater understanding of the pathways that underlie appetite and food intake, as well as of the interactions between antipsychotic drug action and these pathways, may help to minimize the morbidity, mortality, and other societal costs associated with AAWG, while continuing to manage and treat the psychotic symptoms for which these agents remain the treatment of choice.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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