UPDATE ARTICLE

Recent evidence and potential mechanisms underlying weight gain and insulin resistance due to atypical antipsychotics

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Objective: Atypical antipsychotics (AAPs) promote obesity and insulin resistance. In this regard, the main objective of this study was to present potential mechanisms and evidence concerning side effects of atypical antipsychotics in humans and rodents.

Method: A systematic review of the literature was performed using the MEDLINE database. We checked the references of selected articles, review articles, and books on the subject.

Results: This review provides consistent results concerning the side effects of olanzapine (OL) and clozapine (CLZ), whereas we found conflicting results related to other AAPs. Most studies involving humans describe the effects on body weight, adiposity, lipid profile, and blood glucose levels. However, it seems difficult to identify an animal model replicating the wide range of changes observed in humans. Animal lineage, route of administration, dose, and duration of treatment should be carefully chosen for the replication of the findings in humans.

Conclusions: Patients undergoing treatment with AAPs are at higher risk of developing adverse metabolic changes. This increased risk must be taken into account when making decisions about treatment. The influence of AAPs on multiple systems is certainly the cause of such effects. Specifically, muscarinic and histaminergic pathways seem to play important roles.

Keywords: Neuroendocrinology; schizophrenia; drug side effects; antipsychotics; biological markers

Introduction

A number of drugs exhibit unexpected side effects related to body weight changes in humans. Atypical antipsychotics (AAPs) are prescribed as a first-line intervention and represent a great advance in schizophrenia drug treatment.1 According to Reinke et al.,2 AAPs such as olanzapine (OL) seem to confer a lower risk of extrapyramidal side effects compared to typical antipsychotics, and provide good antipsychotic properties.

AAPs present an affinity for dopamine binding sites of dopamine receptors (DR), as well as serotonin (5HT), 2,3,6 muscarinic (MR), adrenergic, and histamine (H1) binding sites.3 In detail, OL and clozapine (CLZ), which are AAPs with strong association with obesity and insulin resistance, exhibit binding affinities for muscarinic receptors of at least two orders of magnitude higher than the other AAP.4 Similarly, both drugs exhibit a high antagonist affinity for histaminergic receptor type 1 (HR1).5 Therefore, the high affinity of CLZ and OL for HR and MR suggests the role of such receptors on the physiopathology of insulin resistance and obesity.

Specifically, histaminergic neurons influence the dopaminergic system6 and leptin signaling,7 resulting in hyperphagia and food craving. Moreover, the effects of acetylcholine (ACh) on pancreatic insulin release are mediated by activation of muscarinic receptor type 3 (MR3), leading to hyperglycemia.8 Considering these facts, we focused the present review on OL and CLZ as well as the role of histaminergic and muscarinic receptors.

Patients undergoing treatment with AAPs are at high risk of developing adverse metabolic changes. This risk must be taken into account when making decisions about treatment. Therefore, the aim of this review is to present evidence concerning the side effects of AAPs in humans and rodents. In addition, we also addressed the potential mechanisms involved, as they may potentially influence the future development of pharmacological strategies.

Methods

We searched articles published between 1981 and 2012, preferentially written in English and available in the PubMed database. The following keywords were used as search parameters: atypical antipsychotics, schizophrenia, olanzapine, clozapine, body weight, obesity,
overweight, adiposity, insulin resistance, glucose, and hyperglycemia. The inclusion criteria were: 1) articles reporting on human metabolic effects of AAPs; 2) articles using rodents treated with AAPs and focusing on central and metabolic changes; 3) previously published systematic reviews addressing the same topic.

Results
Some of the mechanisms associated with weight gain and insulin resistance induced by AAPs are illustrated in Figure 1. The action of AAPs as antagonists of many receptors results in increased expression of neuropeptide Y (NPY) and melanin-concentrating hormone receptor 1 (MCHR1); decreased expression of leptin-induced AMPK (AMP-activated protein kinase); reduction of lipolysis in white adipose tissue (WAT); and reduction of orexin and consequent thermogenesis. Hyperglycemia is caused by α2 antagonism and inactive muscarinic receptors, which reduce the release of insulin induced by ACh. These changes contribute to hyperphagic behavior, reduced thermogenesis, fat accumulation and consequent weight gain in this population.

Atypical antipsychotics and their effects on humans
Antipsychotic drugs are described to treat schizophrenia, episodes of mania, agitation and delirium, impulsivity and dissociation. There are two classes of antipsychotic medications referred as typical or atypical. Typical antipsychotic drugs, like haloperidol (HAL), act as high-affinity antagonists for type 2 dopamine (D2, D3, and D4 receptors) with a consequence of extrapyramidal side effects. Instead, AAPs, like OL, CLZ, quetiapine (QUET), risperidone (RIS), ziprasidone (ZIP), have lower incidence of extrapyramidal side effects than typical compounds. Probably, because AAPs have additional affinities for a variety of neurotransmitter receptor subtypes, including other serotonins (5HT1A, 5HT2C, 5HT6, and 5HT7) and DRs (D1, D3, and D4), as well as the histamine receptor H1, muscarinic receptors (M1, M2, M3, M4, and M5) and adrenergic receptors (α1 and α2). The main receptor-binding profiles of six marketed AAPs (aripiprazole, CLZ, OL, QUET, RIS, and ZIP) are shown in Table 1.

The decreased specificity for the DRs of the AAP has lessened the motor disorders associated with previous agents such as HAL, but this pharmacological feature may be responsible for the wide spread metabolic side effects associated with the drugs.

Because of the reduction of extrapyramidal side effects, AAPs have become the gold standard and the first treatment option for mental illness. However, after the introduction of atypicals, the growing collection of case reports and clinical trials describing metabolic complications and, particularly, body weight gain, increased food intake, increased amount of visceral fat, reduced locomotor activity and new-onset diabetes has drawn the attention over the high association and comorbidity between the risk of obesity and antipsychotic medication.

Weight gain
According to the US Food and Drug Administration guidelines, in most of the studies, body mass gain is considered clinically significant when an increase of total body weight of at least 7% from the baseline occurred. Also, the severity of adverse events differ according to drug tolerance as well as the types of medications, showing a rank order of liability in weight gain which can

Figure 1 Mechanism underlying weight gain and insulin resistance
ACh: acetylcholine; AMPK: AMP-activated protein kinase; ARC: arcuate nucleus; BAT: brown adipose tissue; LHA: lateral hypothalamic area; MCHR1: melanin-concentrating hormone receptor 1; NPY: neuropeptide Y; UCP1: uncoupling protein; WAT: white adipose tissue.
be described as follows: CLZ = OL > QUET > RIS > amisulpride (AMI) > aripiprazole (ARI) > ZIP.12,20-23

The relationship between CLZ treatment and susceptibility to weight gain is, in most cases, described in a time-related fashion, with both rapid and progressive effects.12 Chronic CLZ treatment causes an increase between 5.3 and 6 kg of weight after 10 weeks and up to 9.2 kg after 68 weeks.21 Notably, this study also underlined the potential gender-dependent effect of AAPs (an increase of 10.4 and 16.2 kg in men and woman, respectively, after 37-39 months of CLZ therapy). This observation is consistent with the former suggestion of a major vulnerability of women to the AAP-induced weight gain.24 Nevertheless, the effect of CLZ treatment upon women weight gain is still unclear and involves all the atypical drugs accountable for inducing weight gain.25

Similar as CLZ treatment, OL affects weight gain during the first year of treatment and induces a moderate increase in weight over time. This effect was reported by Newcomer,12 which indicated a mean weight gain of 10 kg during 7 months of treatment and a range of increase of 6-12 kg after 6-12 months. Another matter of debate is the distinction between AAP effects upon patients with chronic disease and patients with the first-episode of psychotic disorder. As described by Strassnig et al.,26 there was a higher magnitude of weight gain in psychotic patients by OL and, in a lesser degree, by RIS and HAL. Interestingly, both younger subjects and patients with negative symptoms (e.g., social withdrawal and poverty of speech) at baseline were more susceptible to weight gain. A recent comparison between OL, RIS, and the typical HAL indicated that weight gain was 3- to 4-fold greater in younger patients with limited previous exposure to antipsychotic agents in both short-term studies (7.1-9.2 kg for OL, 4.0-5.6 kg for RIS and 2.6-3.8 kg for HAL vs. 1.8-5.4 kg, 1.0-2.3 kg and 0.01-1.4 kg, respectively, in studies that included patients with chronic psychotic disorders) and long-term clinical trials (10.2-15.4 kg for OL, 6.6-8.9 kg for RIS and 4.0-9.7 kg for HAL vs. 2.0-6.2 kg, 0.4-3.9 kg and -0.7 to 0.4 kg, respectively).27 Hence, the possibility that younger subjects might be at a higher risk of being overweight or obese should be taken into consideration.

Impaired glucose homeostasis

Data from most studies suggest that the prevalence of diabetes in schizophrenic patients is almost 1.5-2 times greater than the prevalence reported in the general population.28 While there is an ongoing discussion as to whether the metabolic disease is part of the natural etiology of schizophrenia, there is great evidence of treatment side effects.29,30 The incidence of diabetes is nearly 10% greater in schizophrenic patients treated with AAPS when compared with those treated with typical antipsychotic drugs.31 Notably, OL and CLZ appear to have the highest tendency to disturb glucose metabolism compared with the other antipsychotic drugs available on the market.32 Also, the higher propensity of these drugs to induce diabetic ketoacidosis and new-onset type II diabetes mellitus had been generally related to increased adiposity. However, in line with other reports,33,34 Ramankutty provides evidence that OL can cause glucose dysregulation through a mechanism other than weight gain.35

The results of many studies concerning RIS treatment and glucose homeostasis led to some inconsistent conclusions. Schizophrenic patients who had preexisting risk factors for diabetes, developed insulin resistance in the context of weight gain during treatment with RIS.36 Recent pharmacoepidemiologic studies have recently confirmed significant rates of type II diabetes in patients receiving RIS.36,39 Also, another study suggests that AAP-induced diabetes does not always take a type 2 presentation in which weight gain and insulin resistance are implicated. Sometimes the presentation is with diabetic ketoacidosis.30 On the other hand, several studies have reported either reduced or absent risk of associated diabetogenic effects.31

Similar as RIS treatment, the link between QUET therapy and diabetes has led to inconclusive results. The examination of a retrospective database study conducted by Sernyak et al.31 concluded that patients who received atypicals were 9% more likely to have diabetes than those who received typical neuroleptics, and the prevalence of diabetes was significantly increased for patients who received CLZ, OL, and QUET, but not RIS. Moreover, for patients younger than 40 years old, all of the AAP were associated with a significantly increased prevalence of diabetes. Furthermore, a recent longitudinal investigation confirmed the time-dependent effect in worsening plasma glucose levels in subjects taking CLZ, OL, and also QUET.42 Of note, in comparison with CLZ and OL, the hyperglycemic and diabetogenic risk associated with QUET therapy can be estimated as lower, but still higher than RIS. Differently, in a 2-million member, managed-care system database, there was a

### Table 1: Atypical antipsychotics and their receptor subtype affinities

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
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<td>6 &lt; pKi &lt; 7</td>
<td>pKi &lt; 6</td>
<td>6 &lt; pKi &lt; 7</td>
<td>6 &lt; pKi &lt; 7</td>
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<tr>
<td>5HT₂C</td>
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<td>7 &lt; pKi &lt; 8</td>
<td>8 &lt; pKi &lt; 9</td>
<td>pKi &lt; 6</td>
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<td>₂₄₂A</td>
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<td>8 &lt; pKi &lt; 9</td>
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</tr>
</tbody>
</table>

5HT = serotonin receptor; D₂ = dopamine receptor type 2; M₃ = muscarinic receptor type 3; H₁ = histamine receptor. Bold font indicates greater affinities of clozapine and olanzapine for muscarinic and histamine receptors. Adapted from Nasrallah.10

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Adapted from .
1.4-fold increase in diabetes risk with OL, while RIS, QUET, and conventional antipsychotic agents did not significantly increase diabetes.\(^{14}\) In conclusion, there is consensus in the literature that CLZ and OL impair glucose homeostasis, possibly because of increased body weight and/or as a result of independent mechanisms. Although many studies concluded that also RIS and QUET were significantly associated with diabetes-related adverse events, opposite conclusions have been also reported.

**Adverse effects of AAP treatment on rodents**

Evidence concerning the effects of AAP treatment on rodents will be summarized in this section. Notably, the duplicability of results in mice and rats is dependent on various factors such as species, duration of treatment, and routes of administration.

A model of AAP-induced obesity was evaluated between different strains of rats (Sprague-Dawley and Wistar) and mice (C57BL6 and A/J).\(^{46}\) Chronically, OL or CLZ was self-administered via cookie dough to rodents. OL (1 to 8 mg/kg), but not CLZ, increased body weight and food intake in female rats only. Chronic administration (12 to 29 days) led to hyperphagia, hyperleptinemia, insulin resistance, and weight gain, which was reversed by topiramate. Also, in this study, acute OL-treated rats presented lower plasma leptin levels, both at baseline and 90-min after glucose challenge (by oral glucose tolerance test, OGTT). Such basal hypoleptinemia and blunted response to acute glucose challenge was interpreted as one of the potential mechanisms involved in the hyperphagia observed under chronic OL administration. A recent work from our group also described similar level of plasma leptin.\(^{46}\) In both studies, weight gain might have been a consequence of the initial hypoleptinemia-dependent hyperphagia.

The effects of OL on Wistar rats were also demonstrated by Goudie et al.\(^{47}\) In this study, female Wistar rats received OL twice daily, chronically at 4 mg/kg (b.i.d.). Such rats showed marked weight gain, after only a single day of treatment, although weight gain increased up to a plateau after 10 days of treatment. Nevertheless, cessation of treatment also demonstrated the reversibility of the effects produced on weight gain. In agreement, female Sprague-Dawley rats receiving OL at 1.2 mg/kg per day (orally via gavage) for 10 days exhibited significant decreases in gross motor activity, increases in body weight and food intake when compared with control rats. Also, body weight returned to normal levels once the treatment was discontinued.\(^{48}\) Some authors hypothesized that weight gain due to OL treatment, can be a result from feeding pattern abnormalities. Lee & Clifton, 2002 demonstrated that treatment with OL and CLZ did not increase meal size in Lister rats.\(^{46}\) Also, another study compared the effects of OL and CLZ on the microstructure of ingestive behavior. Both treatments promoted fat hyperphagia in male hooded Lister rats. A delay or reduction of the post-ingestive satiety signal combined with preserved palatability appears to be the mechanism responsible for altered ingestive behavior.\(^{30}\) Depending on the duration of chronic treatment, oral administration of AAP can affect feeding and metabolic function in different ways. Recently, Victoriano et al.\(^{51}\) evaluated the effects of a chronic OL treatment over feeding patterns in rats and the potential time-related association between feeding patterns and the appearance of glucose metabolism abnormalities. Specifically, in the first experimental design, OL-treated (2 mg/kg/day during 26 days) male rats showed increased meal number, without change in total food intake. After 31 days of treatment, glucose metabolism was affected, an indicative for insulin resistance. Those results were even more pronounced after 46 days of treatment, showing hyperglycemia and adiposity. As a whole, the results raise the hypothesis that long-term alteration of feeding pattern by OL may predispose to disturbances in the regulation of energy metabolism.

A recent work conducted by Choi et al.\(^{52}\) used osmotic mini-pumps to chronic treatment with antipsychotics. According to the study, since blood antipsychotic half-lives are short in rats when compared to humans, chronic administration by constant infusion may be necessary to see consistent weight gain in rats. Male and female rats received OL (5 mg/kg/day), CLZ (10 mg/kg/day) trough constant infusion for 11 days. OL increased food intake and body weight in female, but not male rats.

Regarding CLZ treatment and its effects upon glucose metabolism, a recent work analyzed many features after acute and subchronic administration of CLZ.\(^{53}\) CLZ administration caused hyperglycemia and hyperinsulinemia during intraperitoneal glucose tolerance test, suggesting reduced insulin sensitivity. Those effects were not related to changes in feeding behavior or fat accumulation. Moreover, daily treatment with CLZ (10 mg/kg subcutaneous [s.c.]), QUET (10 mg/kg s.c.) and HAL (0.25 mg/kg s.c.) in Sprague-Dawley rats impaired glucose tolerance that was not caused by a direct induction of insulin resistance but acted via an increase in glucagon secretion and thus stimulation of hepatic glucose production. The alterations in carbohydrate metabolism appeared independent of weight gain.\(^{54}\)

The effects of RIS and sulpiride (SULP) were evaluated in rats during 16 days in different doses (0.125, 0.25, or 0.5 mg/kg during 16 days) on body weight gain and food intake in male and female rats. In male rats, RIS did not significantly affect body weight gain, food intake, glucose tolerance or hormonal parameters. In females, both antipsychotics significantly increased body weight and food intake, and the effect was stronger with SULP. These results were significantly associated with an increase in body fat.\(^{55}\) In a parallel evaluation, treatment with subcutaneous RIS during 21 days induced different responses in rats. The lower dose (0.005 mg/kg) produced increased food intake and the rate of body weight gain, as well as the augmentation of leptin gene expression in WAT. Curiously, the injection of 0.5 mg/kg RIS caused a reduction in body weight gain, as well as enhanced uncoupling protein 1 (UCP1) gene expression in brown adipose tissue (BAT) and serum prolactin concentrations. The reduction in the rate of body weight
gain following injection of 0.5 mg/kg can be explained, in part, by increased energy expenditure, as revealed by the remarkable increase in the UCP-1 mRNA expression level in BAT.\textsuperscript{56} An association between hyperprolactinemia and weight gain has also been described for RIS therapy.\textsuperscript{57,58}

In order to compare the adverse side effects of treatment with atypicals among adults and juveniles, ZIP (2.5 mg/kg intraperitoneal [i.p.]) was administered in juvenile female hooded Lister rats during 21 days. No changes were observed in respect of body weight, food intake, and even fat mass depots.\textsuperscript{59} However, when ZIP (1 and 2.5 mg/kg i.p.) was administered for 28 days, significant weight gain was observed on day 28 at 2.5 mg/kg, with no effects on food intake, fat mass depots or plasma prolactin levels.\textsuperscript{60} In the same study, rats submitted to OL (4 mg/kg), RIS (0.5 mg/kg), SULP (10 mg/kg), or HAL (0.5 mg/kg) presented weight gain 1.5-2 times greater than that previously observed in adult rats.\textsuperscript{59}

As mentioned above, most results in respect of metabolic effects induced by antipsychotics were designed in rats. However, interesting results can be also found in mice.\textsuperscript{61} Three mouse strains (FVB/N, C57BL/6 and CD-1) with variable susceptibility to glucose challenge and hyperglycemia were compared with regard to their liability to different antipsychotic-induced changes on plasma glucose and insulin levels. Hyperglycemia (100%-140% greater than basal levels) was observed in all strains after acute high dose of CLZ, OL, and QUET, with no effects on insulin levels. In contrast, neither HAL nor the atypicals RIS, ARI, and ZIP altered glucose homeostasis in the FVB/N mouse strain. Among drugs that did not alter glycemic levels after acute administration, RIS was also showed to elevate insulin release and, consequently, reduce glucose levels (-30%).\textsuperscript{61} In CD-1 mice treated chronically with OL (0.75, 1.5, 3 mg/kg per osmotic pumps) during 36 days, the highest dose postponed the onset of satiation, which was confirmed by an increase in the actual food intake.\textsuperscript{62} These results suggest that alterations in hunger-satiety regulation can predict AAP-induced weight gain.

Potential mechanisms underlying AAP adverse effects

Animal models of atypical-induced adverse effects portray the considerable effort to reproduce the wide constellation of metabolic derangement occurring in psychotic patients. Most part of animal models described above, report metabolic consequences such as increased body weight and food intake, adiposity, and impaired glucose metabolism. In the view of mechanistic explanations, it appears that appetite stimulation, increased meal size, satiety inhibition and consequent incentive drive to eat are all involved. Hence, in this section, interesting data regarding the mechanisms involved will be addressed.

Hypothalamic orexigenic peptides

The interaction between atypical compounds and neurochemical systems involved in the regulation of appetite and body weight should be considered. The hypothalamic neuropeptides, neuropeptide-Y (NPY), orexin/hypocretin (HCRT), and melanin-concentrating hormone (MCH) are potent stimulators of food intake when administered centrally,\textsuperscript{63-65} while α-melanocyte-stimulating hormone (α-MSH) is a hypothalamic neuropeptide that inhibits feeding by acting at central melanocortin-4 receptors (MC4R).\textsuperscript{66} Hypothalamic neuropeptide mRNA levels of NPY, orexin, MCH and POMC (proopiomelanocortin) appeared unchanged after both acute and sub-chronic OL treatment, indicating that OL-induced hyperphagia and weight gain may not be mediated via alterations in the expression of the feeding-related hypothalamic neuropeptides.\textsuperscript{67} However, 3 weeks of treatment with CLZ (25 mg/kg i.p.) increased NPY expression in hypothalamic arcuate nucleus (ARC) of Sprague-Dawley rats.\textsuperscript{58} Guesdon et al. conducted a recent research providing evidence that treatment with OL and melanin-concentrating hormone receptor 1 (MCHR1) agonist produce additive effects on energy balance and selective effects on the brain expression of energy balance-related genes.\textsuperscript{68} After 13 days, OL and the MCHR1 agonist produced enhanced food intake and adiposity. Consistently, each treatment differently affected brain expression of genes influencing energy balance. While the MCHR1 agonist treatment increased NPY mRNA expression in the hypothalamic ARC, OL treatment specifically increased MCHR1 mRNA expression in the nucleus accumbens shell (NAcSh).\textsuperscript{69} This might suggest that some AAP drugs may enhance the incentive to eat by upregulating the MCH signal following the increase of the MCH-R1 mRNA expression in the nucleus accumbens (NAcc).

Compelling evidence of a possible convergent signaling pathway and functional interaction between MCH-R1, dopamine outflow, and atypical drugs have been recently addressed. In MCH knockout (KO) mice, a significantly elevated expression of the dopamine transporter and evoked dopamine release was found in NAcc of MCH KO mice.\textsuperscript{70} Besides, Chung et al.\textsuperscript{71} also pointed for the important modulatory role of MCH in cocaine reward and reinforcement by potentiating the dopaminergic system in the NAcc. MCH infusion increased dopamine activity (spike firing) when both dopamine receptor 1 (D1R) and dopamine receptor 2 (D2R) are activated. Also, MCH injection potentiates cocaine-induced hyperactivity in mice and the acute blockade of the MCH system not only reduces cocaine self-administration, but also attenuates cue- and cocaine-induced reinstatement. Therefore, it is possible that exacerbated food intake induced by antipsychotic treatment is due, at least in part, to the functional interaction between MCH and dopamine systems.

Histaminergic system

The monoamine histamine is another important chemical messenger that plays a physiological role in a wide variety of physiologic responses, including feeding behavior.\textsuperscript{72} Histaminergic neurons and histamine receptor (HR) 1 in mammalian brain are located exclusively in the tuberomammillary nucleus of the posterior hypothalamus and send their axons all over the central nervous system.
Four metabotropic HR subtypes have been cloned so far. HR1, HR2, and HR3 are expressed in abundance in the brain and HR4 mainly occurs in peripheral tissues. Intracerebroventricular (icv) infusion of selective histamine, HR1, HR2, and HR3 agonists were tested by Lecklin et al. HR1 agonist significantly decreased food intake, whereas HR2 antagonist had a diuretic effect and HR3 antagonist predominantly provoked drinking. Furthermore, reduction in food intake by histamine was accompanied by an increase in c-fos-like immunoreactivity in the paraventricular nucleus (PVN) of mice.

Several studies examining drug-binding profiles to various receptors showed that the AAP binding affinity for HR1 is a good predictor of AAP mediated weight gain. Specifically, OL was indicated as the atypical with greater affinity for the HR1. Accordingly, administration of OL increased body weight, fat depots, and reduced HR1 mRNA expression in ARC and ventromedial nucleus (VMH). There were significant negative correlations between the levels of HR1 mRNA expression and biometric data, which indicate that downregulation of VMH and ARC HR1 expression may be a key factor contributing to OL-induced obesity.

The histaminergic system also influences the dopaminergic system. Histamine can suppress the mesolimbic dopamine pathway, responsible for controlling palatable food intake via the HR3 autoreceptor and yet activate it through the histamine HR1. One study suggested that the effect of HR3 deletion is mediated by its ability to inhibit the HR1 pathway.

Also, strong evidence supports the view that leptin effects in the brain are mediated by histaminergic neurons. Central infusion of histamine improved energy unbalance and reduced visceral fat accumulation in rodent models of leptin resistance. A recent work showed that, in control mice, reduction of hypothalamic AMP-activated protein kinase (AMPK) and catalytic activity induced by leptin is reversed with CLZ treatment. Hence, evidence that histaminergic antagonism may disrupt central leptin signaling and accelerate the development of leptin resistance should be considered for the interpretation of AAP-induced adiposity. In addition, histaminergic neurons regulate peripheral lipid metabolism through the accelerating lipolytic in WAT by activation of sympathetic β-adrenergic receptor. Moreover, orexin is another peptide that contributes to modulation of lipolytic processes occurring in adipose tissue by the way of histaminergic transmission. Fadel brought evidence that a decrease of neural histaminergic signaling may attenuate the orexin-mediated BAT thermogenesis and acute CLZ, OL, and RIS administration increase the percentage of hypothalamic orexin-positive neurons. Under this context, the chronic infusion with OL in female rats reduced overall metabolic rate, which is associated with a decrease in temperature and expression of UCP1 in BAT. In summary, several studies suggest that selective blockade of HR1 by atypical drugs may contribute to the inhibition of sympathetic activity to WAT, which is influenced by orexin.

Notably, the co-administration with beta-histine has been considered in order to prevent body weight gain.

As a whole, there is clear evidence that the histaminergic system is associated with changes observed in patients treated with antipsychotics. The increased food intake observed in OL-treated animals is possibly a result of the interaction between histaminergic-dopaminergic system and histaminergic-leptin action. Conversely, decreased thermogenesis is due to the relationship between histaminergic system and orexins, which in physiological situation increase lipolytic activity.

Adrenergic receptors

As described above, the AAPs may decrease sympathetic response by blockade of histaminergic receptors. Additionally, the effects on the sympathetic nervous system may be also mediated by the adrenergic system. There are two main groups of adrenergic receptors, α and β, with several subtypes, and both have different effects on mechanisms implicated in fat cells. Adrenal receptor α1 has been detected in human properitoneal and omental adipocyte membranes. They activate the phosphoinositide pathway and increase Ca^2+ concentration. However, the physiological role of Ca^2+ in regulation of adipocyte lipolysis is unclear. Alpha 1-adrenergic receptors have been identified and extensively investigated in brown fat cells. A primary role of these cells is heat production. Some AAPs displayed higher affinity for adrenergic receptors α1A/B and α2A/B, specifically CLZ and RIS, which are negatively correlated with lipolysis rate and body weight. Flechtnet al. assessed adipose tissue of severely obese subjects and identified that adrenergic receptors α1 are involved in regulation of lipolysis rate and microcirculation of adipose tissue. Also, pharmacological stimulation of the adrenergic system has been reported to reduce OL-induced weight gain. Specifically, schizophrenic patients treated with OL and reboxetine (selective norepinephrine reuptake inhibitor) demonstrated a significant lower increase in body weight than those given OL. Furthermore, a role of α1 receptors in AAP-induced glucose dysregulation had been suggested by the hyperglycemic effects of α1 subtype blockade. In the same line, recent knowledge in respect to adrenoreceptor α2 and glucose metabolism was described. The pretreatment with adrenoreceptor α2 antagonist prevent the CLZ-induced hyperglycemia.

Conversely, the analysis of other candidate genes in the literature brought up new insights in respect to AAP-induced weight gain. Genetic variants of 5-HT2A/C receptors, the G-protein β2 subunit, and the adrenergic receptor β3 were described as genetic risk factors for OL-induced weight gain and they showed additive genetic effects on weight gain. Moreover, an association between adiposity and polymorphism in β3 receptor was described in a schizophrenic population. The gene for β3-adrenergic receptor is expressed predominantly in fat and adipocytes lining the gastrointestinal tract. The receptor’s primary role is thought to be the regulation of the resting metabolic rate and lipolysis. Overall, considerations regarding sympathetic activation leading to
lipolytic activity and the role of adrenoreceptors in mediate glucose homeostasis are hypothesized; however, consistent association between adrenergic system and AAP-induced metabolic alterations is still lacking.

Muscarinic receptors and glucose homeostasis

One likely mechanism underlying hyperglycemia and insulin resistance during AAP treatment is the upregulation of 11 beta-hydroxysteroid dehydrogenase type 1 (β-HSD-1) and phosphoenolpyruvate carboxykinase (PEPCK) in the liver. The increased expression of 11β-HSD-1 in CLZ treated rats favors the conversion of cortisone to active cortisol (corticosterone in rodents), thus catalyzing the reactivation of glucocorticoids and regulating the intracellular activation of glucocorticoid receptors (i.e., increasing local glucocorticoid concentrations). Consequently, an elevated expression of PECK is expected. PECK is a fundamental gluconeogenic enzyme, able to regulate the hepatic glucose output. In physiological conditions, insulin opposes gluconeogenesis mostly by inhibiting some gluconeogenic enzymes, among which, PECK.53

Glucose homeostasis should be also impaired in a different manner, which involves insulin release. Although relatively small compared with the total release of insulin after a meal, the ACh-mediated preabsorptive phase of insulin secretion has particular importance for maintaining normal glucose tolerance. Parasympathetic (vagal) nerve endings release ACh during the preabsorptive and, most likely, the absorptive phase of feeding.99,100 In addition, ACh/vagus effects on pancreatic insulin release are mediated by activation of muscarinic receptors. ACh binds to muscarinic receptors and activates phospholipase C resulting in hydrolysis of phosphoinositides. This intracellular pathway is activated by ACh and carbachol, a muscarinic agonist and inhibited by atropine, the muscarinic antagonist.99-101 Also, previous studies suggest that ACh can stimulate the secretion of glucagon by acting on muscarinic receptors located in the pancreas.99,100,102,103

Molecular cloning studies have revealed the existence of five molecularly distinct muscarinic receptor subtypes (M1-M5).104 Additionally, the muscarinic receptor type 3 (M3) appears to be the predominant subtype expressed by pancreatic β-cells.99-101,105-107 The role of muscarinic receptors in insulin release is well described in studies performed in M3 receptor-deficient mice (M3 -/ -). Specifically, the infusion of the muscarinic agonist oxotremorine in islet cells either failed to stimulate insulin release in M3 receptor-deficient mice (M3 -/-) or was strongly inhibited in islets from M3 +/- mice.108 Accordingly, a functional in vivo impairment of the increase in serum insulin levels after glucose load was also observed in M3 -/- receptor-deficient mice.109 Conversely, elevated free fatty acids postulated in the etiology of insulin resistance can inhibit the stimulatory effect of ACh on insulin release from pancreatic islets.110

OL and CLZ exhibit binding affinities for muscarinic receptors of at least two orders of magnitude higher than the other AAP (Table I).4,112 Similarly, both these drugs exhibit a high antagonist affinity for HR1.5 Therefore, the high affinity of CLZ and OL for M3 receptor suggests the role of such receptors on the pathophysiology of insulin resistance. Furthermore, a recent analysis indicates M3 receptor as the best predictor of diabetes induced by treatment with AAPs.8 In detail, another study described the inhibition of insulin secretion under carbachol stimulation in isolated rat islets after treatment with OL and CLZ. This inhibition of insulin secretion was paralleled by significant reductions in carbachol-potentiated inositol phosphate accumulation. Possibly, in case of persistent supranormal glycemic levels, the blockade of the M3 receptor may lead to β-cells adaptive response failure and further exacerbate hyperglycemia. Interestingly, in all procedures, RIS or ZIP had no adverse effects.113

Discussion

In this study, a systematic review regarding the adverse effects of treatment with AAPs was presented. The main effects reported in humans are weight gain and insulin resistance, in most cases due to OL and CLZ treatment. Both treatments cause rapid and progressive weight gain.12 Also, there is a greater susceptibility in the female population54 and in younger patients.26 Blood glucose control also shows up changed. The incidence of type II diabetes is 10% higher in patients treated with AAP, with the worst effect associated with OL and CLZ.38,39 Furthermore, there is greater susceptibility to development of diabetes in patients older than 40 years. The major vulnerability in women is still a matter of debate and involves not only OL and CLZ but also all the atypical drugs accountable for inducing weight gain. In experimental studies, animal models have a wide variability regarding the lineage of animals, dose, route of administration and duration of treatment. Despite the discrepancy in the results found in the literature, there is a consensus that OL and CLZ lead to worst effects on weight and glucose metabolism in rats.45,47 In some studies, the weight gain is immediate, but shows up reversible upon cessation of treatment.47 Females and young animals have a higher susceptibility changes.47,48

Histaminergic system and MR appear to be crucial to the onset of the observed changes. Among other mechanisms suggested, the high affinity of OL and CLZ for these receptors promotes increased expression of orexigenic peptides,62 reduced UCP-1,112 reduction in insulin secretion induced by ACh,111 leptin signaling failure,7 and reduction in lipolytic activity.83 Taken together, these mechanisms lead to obesity and insulin resistance, two chronic diseases that increase the risk of cardiovascular disease.

Patients undergoing treatment with AAP are at high risk of developing adverse metabolic changes. The influence of AAPs on multiple systems is certainly the cause of such effects. Specifically, muscarinic and histaminergic receptors seem to play important roles. Hence, the large diffusion and wide prescription of AAP in clinical practice requires the examination of the risk-benefit ratio of this unconventional class of compounds.113
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Disclosure

The authors report no conflicts of interest.

References

8. Teff KL, Kim SF. Atypical antipsychotics and the neural regulation of food intake and peripheral metabolism. Physiol Behav. 2011;104:590-8.
Obesity due to atypical antipsychotics


80 Han M, Deng C, Burbe TH, Newell KA, Huang XF. Short- and long-term effects of antipsychotic drug treatment on weight gain and H1 receptor expression. Psychoneuroendocrinology. 2008;33:569-80.

81 Brabant C, Aileva L, Querentmont E, Tirelli E. Involvement of the brain histaminergic system in addiction and addiction-related behaviors: a comprehensive review with emphasis on the potential therapeutic use of histaminergic compounds in drug dependence. Prog Neuropsihol. 2010;32:421-41.