Revista Brasileira de Psiquiatria. 2013;35:295–304
© 2013 Associação Brasileira de Psiquiatria
doi:10.1590/1516-4446-2012-1052

UPDATE ARTICLE

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

Ana Maria Volpato,[1] Alexandra Ioppi Zugno,[1,2,3] João Quevedo[1,2,3]

[1]*Laboratory of Neurosciences, Universidade do Extremo Sul Catarinense (UNESC), Criciúma, SC, Brazil.* [2]*National Science and Technology Institute for Translational Medicine (INCT-TM).* [3]*Center of Excellence in Applied Neurosciences of Santa Catarina (NENASC), Graduate Program in Health Sciences, Health Sciences Unit, UNESC, Criciúma, SC, Brazil.*

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 system[6] 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,

Correspondence: Prof. João Quevedo, Laboratório de Neurociências, PPGCS, UNASAU, Universidade do Extremo Sul Catarinense, CEP 88806-000 Criciúma, SC, Brazil.
E-mail: quevedo@unesc.net
Submitted Nov 14 2012, accepted Dec 20 2012.

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 $\alpha 2$ 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,[1] 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)-like receptors (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.[3] 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 ($\alpha 1$ and $\alpha 2$).[9] 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.[11]

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,[12] increased food intake,[13,14] increased amount of visceral fat,[15,16] reduced locomotor activity[17,18] 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.[19] 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

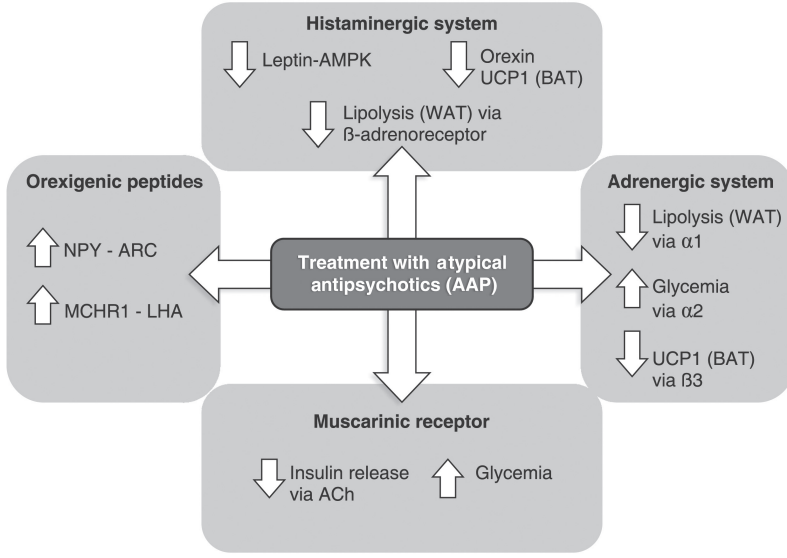


Figure 1 Mechanism underlying weight gain and insulin resistance

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.

Table 1 Atypical antipsychotics and their receptor subtype affinities

Receptor	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
$5HT_{1A}$	$8 < pKi < 9$	$6 < pKi < 7$	$pKi < 6$	$6 < pKi < 7$	$6 < pKi < 7$	$7 < pKi < 8$
$5HT_{2C}$	$6 < pKi < 7$	$7 < pKi < 8$	$8 < pKi < 9$	$pKi < 6$	$7 < pKi < 8$	$7 < pKi < 8$
α_{1A}	$7 < pKi < 8$	$8 < pKi < 9$	$6 < pKi < 7$	$7 < pKi < 8$	$8 < pKi < 9$	$7 < pKi < 8$
α_{2A}	$7 < pKi < 8$	$8 < pKi < 9$	$6 < pKi < 7$	$7 < pKi < 8$	$8 < pKi < 9$	$8 < pKi < 9$
D2	$pKi > 9$	$6 < pKi < 7$	$7 < pKi < 8$	$6 < pKi < 7$	$8 < pKi < 9$	$8 < pKi < 9$
M3	$pKi < 6$	**$7 < pKi < 8$**	**$7 < pKi < 8$**	$pKi < 6$	$pKi < 6$	$pKi < 6$
H1	$7 < pKi < 8$	**$8 < pKi < 9$**	**$8 < pKi < 9$**	$8 < pKi < 9$	$7 < pKi < 8$	$6 < pKi < 7$

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]

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 studies that included young 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.[32-34] 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,[35,36] Ramankutty provides evidence that OL can cause glucose dysregulation through a mechanism other than weight gain.[36]

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.[37] Recent pharmacoepidemiologic studies have recently confirmed significant rates of type II diabetes in patients receiving RIS.[38,39] 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.[40] On the other hand, several studies have reported either reduced or absent risk of associated diabetogenic effects.[41,42]

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.[43] 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

1.4-fold increase in diabetes risk with OL, while RIS, QUET, and conventional antipsychotic agents did not significantly increase diabetes.[44]

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).[45] 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.[49] 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.[50]

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.[56] An association between hyperprolactinemia and weight gain has also been described for RIS therapy.[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.[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.[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.[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.[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%).[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.[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,[63-65] while αmelanocyte-stimulating hormone (α-MSH) is a hypothalamic neuropeptide that inhibits feeding by acting at central melanocortin-4 receptors (MC4R).[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.[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.[68] 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.[69] 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).[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.[70] Besides, Chung et al.[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.[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.[73] Four metabotropic HR subtypes have been cloned so far.[74] HR1, HR2, and HR3 are expressed in abundance in the brain and HR4 mainly occurs in peripheral tissues.[75] 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.[76] Furthermore, reduction in food intake by histamine was accompanied by an increase in c-fos-like immunoreactivity in the paraventricular nucleus (PVN) of mice.[77]

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.[78] Specifically, OL was indicated as the atypical with greater affinity for the HR1.[79] 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.[80]

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.[81] One study suggested that the effect of HR3 deletion is mediated by its ability to inhibit the HR1 pathway.[6]

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.[7] 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.[82] 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-adrenoceptor.[83] 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.[84] Under this context, the chronic infusion with OL in female rats reduced overall metabolic rate,[85] which is associated with a decrease in temperature and expression of UCP1 in BAT.[86] In summary, several studies suggest either directly or indirectly 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 betahistine has been considered in order to prevent body weight gain.[87]

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.[88]

Adrenoreceptor α1 has been detected in human properitoneal[89] and omental adipocyte membranes.[90] 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-adrenoceptors have been identified and extensively investigated in brown fat cells. A primary role of these cells is heat production.[88] Some AAPs displayed higher affinity for adrenoreceptors $\alpha 1_{A/B}$ and $\alpha 2_{A/B}$, specifically CLZ and RIS [9], which are negatively correlated with lipolysis rate and body weight. Flechtner et al.[91] assessed adipose tissue of severely obese subjects and identified that adrenoreceptors 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.[92] Furthermore, a role of α1 receptors in AAP-induced glucose dysregulation had been suggested by the hyperglycemic effects of α1 subtype blockade.[93] 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.[61]

Conversely, the analysis of other candidate genes in the literature brought up new insights in respect to AAP-induced weigh gain. Genetic variants of $5\text{-}HT_{2A/2C}$ receptors, the G-protein β subunit, and the adrenergic receptor β_3 were described as genetic risk factors for OL-induced weight gain and they showed additive genetic effects on weight gain.[94] Moreover, an association between adiposity and polymorphism in β_3 receptor was described in a schizophrenic population.[95] The gene for β_3-adrenergic receptor[96,97] is expressed predominantly in fat and adipocytes lining the gastrointestinal tract.[98] The receptor's primary role is thought to be the regulation of the resting metabolic rate and lipolysis.[96] 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. PEPCK 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, PEPCK.[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 1).[4,10] 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 ß-cells adaptive response failure and further exacerbate hyperglycemia. Interestingly, in all procedures, RIS or ZIP had no adverse effects.[111]

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 population[24] 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,[82] 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]

Acknowledgements

This research was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado de Santa Catarina (FAPESC), Instituto Cérebro e Mente, and UNESC. Ana Maria Volpato receives a research grant from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). Alexandra I. Zugno and João Quevedo receive research grants from CNPq, Conselho de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), UNESC, Instituto Cérebro e Mente, and National Science and Technology Institute for Translational Medicine (INCT-TM).

Disclosure

The authors report no conflicts of interest.

References

1 Meltzer HY. Illuminating the molecular basis for some antipsychotic drug-induced metabolic burden. Proc Natl Acad Sci U S A. 2007; 104:3019-20.
2 Reinke A, Martins MR, Lima MS, Moreira JC, Dal-Pizzol F, Quevedo J. Haloperidol and clozapine, but not olanzapine, induces oxidative stress in rat brain. Neurosci Lett. 2004;372:157-60.
3 Tajima K, Fernandez H, Lopez-Ibor JL, Carrasco JL, Diaz-Marsa M. Schizophrenia treatment. Critical review on the drugs and mechanisms of action of antipsychotics. Actas Esp Psiquiatr. 2009;37:330-42.
4 Bymaster FP, Felder CC, Tzavara E, Nomikos GG, Calligaro DO, McKinzie DL. Muscarinic mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27:1125-43.
5 Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. From the cover: antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci U S A. 2007;104:3456-9.
6 Yoshimatsu H. Hypothalamic neuronal histamine regulates body weight through the modulation of diurnal feeding rhythm. Nutrition. 2008;24:827-31.
7 Masaki T, Yoshimatsu H, Chiba S, Watanabe T, Sakata T. Targeted disruption of histamine H1-receptor attenuates regulatory effects of leptin on feeding, adiposity, and UCP family in mice. Diabetes. 2001;50:385-91.
8 Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. Methods Find Exp Clin Pharmacol. 2005;27:289-304.
9 Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov. 2004;3:353-9.
10 Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry. 2008;13:27-35.
11 Teff KL, Kim SF. Atypical antipsychotics and the neural regulation of food intake and peripheral metabolism. Physiol Behav. 2011;104:590-8.
12 Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 2005;19:1-93.
13 Eder U, Mangweth B, Ebenbichler C, Weiss E, Hofer A, Hummer M, et al. Association of olanzapine-induced weight gain with an increase in body fat. Am J Psychiatry. 2001;158:1719-22.
14 Gothelf D, Falk B, Singer P, Kairi M, Phillip M, Zigel L, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. Am J Psychiatry. 2002;159:1055-7.
15 Ryan MC, Flanagan S, Kinsella U, Keeling F, Thakore JH. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naive patients with schizophrenia. Life Sci. 2004;74: 1999-2008.
16 Zhang ZJ, Yao ZJ, Liu W, Fang Q, Reynolds GP. Effects of antipsychotics on fat deposition and changes in leptin and insulin levels. Magnetic resonance imaging study of previously untreated people with schizophrenia. Br J Psychiatry. 2004;184:58-62.
17 Allison DB, Newcomer JW, Dunn AL, Blumenthal JA, Fabricatore AN, Daumit GL, et al. Obesity among those with mental disorders: a National Institute of Mental Health meeting report. Am J Prev Med. 2009;36:341-50.
18 Archie S, Wilson JH, Osborne S, Hobbs H, McNiven J. Pilot study: access to fitness facility and exercise levels in olanzapine-treated patients. Can J Psychiatry. 2003;48:628-32.
19 Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. J Clin Psychiatry. 1999;60:16-9.
20 Nasrallah HA, Newcomer JW. Atypical antipsychotics and metabolic dysregulation: evaluating the risk/benefit equation and improving the standard of care. J Clin Psychopharmacol. 2004;24:S7-14.
21 Taylor DM, McAskill R. Atypical antipsychotics and weight gain--a systematic review. Acta Psychiatr Scand. 2000;101:416-32.
22 Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry. 2001;62:22-31.
23 Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-23.
24 Bai YM, Lin CC, Chen JY, Lin CY. Weight gain among patients on clozapine. Psychiatr Serv. 1999;50:704-5.
25 Hummer M, Kemmler G, Kurz M, Kurzthaler I, Oberbauer H, Fleischhacker WW. Weight gain induced by clozapine. Eur Neuropsychopharmacol. 1995;5:437-40.
26 Strassnig M, Miewald J, Keshavan M, Ganguli R. Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. Schizophr Res. 2007;93:90-8.
27 Alvarez-Jimenez M, Gonzalez-Blanch C, Crespo-Facorro B, Hetrick S, Rodriguez-Sanchez JM, Perez-Iglesias R, et al. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs. 2008;22:547-62.
28 Mathews M, Muzina DJ. Atypical antipsychotics: new drugs, new challenges. Cleve Clin J Med. 2007;74:597-606.
29 Vestri HS, Maianu L, Moellering DR, Garvey WT. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. Neuropsychopharmacology. 2007;32:765-72.
30 Yang LH, Chen TM, Yu ST, Chen YH. Olanzapine induces SREBP-1-related adipogenesis in 3T3-L1 cells. Pharmacol Res. 2007;56:202-8.
31 Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry. 2002;159:561-6.
32 Muench J, Hamer AM. Adverse effects of antipsychotic medications. Am Fam Physician. 2010;81:617-22.
33 Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naive schizophrenia patients. Neuropsychopharmacology. 2010;35:1997-2004.
34 Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment--pharmacological mechanisms. Pharmacol Ther. 2010;125:169-79.
35 Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. J Clin Psychiatry. 2002;63:425-33.
36 Ramankutty G. Olanzapine-induced destabilization of diabetes in the absence of weight gain. Acta Psychiatr Scand. 2002;105:235-6; discussion 236-7.
37 Wirshing DA, Pierre JM, Eyeler J, Weinbach J, Wirshing WC. Risperidone-associated new-onset diabetes. Biol Psychiatry. 2001;50:148-9.
38 Buse JB, Cavazzoni P, Hornbuckle K, Hutchins D, Breier A, Jovanovic L. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J Clin Epidemiol. 2003;56:164-70.
39 Lambert BL, Cunningham FE, Miller DR, Dalack GW, Hur K. Diabetes risk associated with use of olanzapine, quetiapine, and

risperidone in veterans health administration patients with schizophrenia. Am J Epidemiol. 2006;164:672-81.
40 Dibben CR, Kalavalapalli SS, Linnington HE, Hynes FA, Dinneen SF, Adler AI, et al. Diabetes associated with atypical antipsychotic treatment may be severe but reversible: case report. Int J Psychiatry Med. 2005;35:307-11.
41 Fuller MA, Shermock KM, Secic M, Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. Pharmacotherapy. 2003;23:1037-43.
42 Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. J Clin Psychiatry. 2002;63:920-30.
43 van Winkel R, De Hert M, Wampers M, Van Eyck D, Hanssens L, Scheen A, et al. Major changes in glucose metabolism, including new-onset diabetes, within 3 months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2008;69:472-9.
44 Gianfrancesco F, White R, Wang RH, Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. J Clin Psychopharmacol. 2003;23:328-35.
45 Albaugh VL, Henry CR, Bello NT, Hajnal A, Lynch SL, Halle B, et al. Hormonal and metabolic effects of olanzapine and clozapine related to body weight in rodents. Obesity (Silver Spring). 2006;14:36-51.
46 Zugno AI, Barcelos M, Oliveira L, Canever L, Luca RD, Fraga DB, et al. Energy metabolism, leptin, and biochemical parameters are altered in rats subjected to the chronic administration of olanzapine. Rev Bras Psiquiatr. 2012;34:168-75.
47 Goudie AJ, Smith JA, Halford JC. Characterization of olanzapine-induced weight gain in rats. J Psychopharmacol. 2002;16:291-6.
48 Arjona AA, Zhang SX, Adamson B, Wurtman RJ. An animal model of antipsychotic-induced weight gain. Behav Brain Res. 2004;152:121-7.
49 Lee MD, Clifton PG. Meal patterns of free feeding rats treated with clozapine, olanzapine, or haloperidol. Pharmacol Biochem Behav. 2002;71:147-54.
50 Hartfield AW, Moore NA, Clifton PG. Effects of clozapine, olanzapine and haloperidol on the microstructure of ingestive behaviour in the rat. Psychopharmacology (Berl). 2003;167:115-22.
51 Victoriano M, Hermier D, Even PC, Fromentin G, Huneau JF, Tome D, et al. Early perturbation in feeding behaviour and energy homeostasy in olanzapine-treated rats. Psychopharmacology (Berl). 2009;206:167-76.
52 Choi S, DiSilvio B, Unangst J, Fernstrom JD. Effect of chronic infusion of olanzapine and clozapine on food intake and body weight gain in male and female rats. Life Sci. 2007;81:1024-30.
53 Tulipano G, Rizzetti C, Bianchi I, Fanzani A, Spano P, Cocchi D. Clozapine-induced alteration of glucose homeostasis in the rat: the contribution of hypothalamic-pituitary-adrenal axis activation. Neuroendocrinology. 2007;85:61-70.
54 Smith GC, Chaussade C, Vickers M, Jensen J, Shepherd PR. Atypical antipsychotic drugs induce derangements in glucose homeostasis by acutely increasing glucagon secretion and hepatic glucose output in the rat. Diabetologia. 2008;51:2309-17.
55 Baptista T, Araujo de Baptista E, Ying Kin NM, Beaulieu S, Walker D, Joober R, et al. Comparative effects of the antipsychotics sulpiride or risperidone in rats. I: bodyweight, food intake, body composition, hormones and glucose tolerance. Brain Res. 2002;957:144-51.
56 Ota M, Mori K, Nakashima A, Kaneko YS, Fujiwara K, Itoh M, et al. Peripheral injection of risperidone, an atypical antipsychotic, alters the bodyweight gain of rats. Clin Exp Pharmacol Physiol. 2002;29:980-9.
57 Goodnick PJ, Rodriguez L, Santana O. Antipsychotics: impact on prolactin levels. Expert Opin Pharmacother. 2002;3:1381-91.
58 Rourke C, Starr KR, Reavill C, Fenwick S, Deadman K, Jones DN. Effects of the atypical antipsychotics olanzapine and risperidone on plasma prolactin levels in male rats: a comparison with clinical data. Psychopharmacology (Berl). 2006;184:107-14.
59 Fell MJ, Neill JC, Rao C, Marshall KM. Effects of sub-chronic antipsychotic drug treatment on body weight and reproductive function in juvenile female rats. Psychopharmacology (Berl). 2005;182:499-507.
60 Fell MJ, Gibson R, McDermott E, Sisodia G, Marshall KM, Neill JC. Investigation into the effects of the novel antipsychotic ziprasidone on weight gain and reproductive function in female rats. Behav Brain Res. 2005;160:338-43.
61 Savoy YE, Ashton MA, Miller MW, Nedza FM, Spracklin DK, Hawthorn MH, et al. Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: evidence for the involvement of sympathetic regulation. Schizophr Bull. 2010;36:410-8.
62 Coccurello R, D'Amato FR, Moles A. Chronic administration of olanzapine affects Behavioral Satiety Sequence and feeding behavior in female mice. Eat Weight Disord. 2008;13:e55-60.
63 Edwards CM, Abusnana S, Sunter D, Murphy KG, Ghatei MA, Bloom SR. The effect of the orexins on food intake: comparison with neuropeptide Y, melanin-concentrating hormone and galanin. J Endocrinol. 1999;160:R7-12.
64 Levine AS, Morley JE. Neuropeptide Y: a potent inducer of consummatory behavior in rats. Peptides. 1984;5:1025-9.
65 Qu D, Ludwig DS, Gammeltoft S, Piper M, Pelleymounter MA, Cullen MJ, et al. A role for melanin-concentrating hormone in the central regulation of feeding behaviour. Nature. 1996;380:243-7.
66 Ludwig DS, Mountjoy KG, Tatro JB, Gillette JA, Frederich RC, Flier JS, et al. Melanin-concentrating hormone: a functional melanocortin antagonist in the hypothalamus. Am J Physiol. 1998;274:E627-33.
67 Davoodi N, Kalinichev M, Korneev SA, Clifton PG. Hyperphagia and increased meal size are responsible for weight gain in rats treated sub-chronically with olanzapine. Psychopharmacology (Berl). 2009;203:693-702.
68 Kirk SL, Cahir M, Reynolds GP. Clozapine, but not haloperidol, increases neuropeptide Y neuronal expression in the rat hypothalamus. J Psychopharmacol. 2006;20:577-9.
69 Guesdon B, Denis RG, Richard D. Additive effects of olanzapine and melanin-concentrating hormone agonism on energy balance. Behav Brain Res. 2010;207:14-20.
70 Pissios P, Frank L, Kennedy AR, Porter DR, Marino FE, Liu FF, et al. Dysregulation of the mesolimbic dopamine system and reward in MCH-/- mice. Biol Psychiatry. 2008;64:184-91.
71 Chung S, Hopf FW, Nagasaki H, Li CY, Belluzzi JD, Bonci A, et al. The melanin-concentrating hormone system modulates cocaine reward. Proc Natl Acad Sci U S A. 2009;106:6772-7.
72 Sakata T, Fukagawa K, Ookuma K, Fujimoto K, Yoshimatsu H, Yamatodani A, et al. Hypothalamic neuronal histamine modulates ad libitum feeding by rats. Brain Res. 1990;537:303-6.
73 Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev. 2008;88:1183-241.
74 Martinez-Mir MI, Pollard H, Moreau J, Arrang JM, Ruat M, Traiffort E, et al. Three histamine receptors (H1, H2 and H3) visualized in the brain of human and non-human primates. Brain Res. 1990;526:322-7.
75 Nguyen T, Shapiro DA, George SR, Setola V, Lee DK, Cheng R, et al. Discovery of a novel member of the histamine receptor family. Mol Pharmacol. 2001;59:427-33.
76 Lecklin A, Etu-Seppala P, Stark H, Tuomisto L. Effects of intracerebroventricularly infused histamine and selective H1, H2 and H3 agonists on food and water intake and urine flow in Wistar rats. Brain Res. 1998;793:279-88.
77 Masaki T, Chiba S, Yasuda T, Noguchi H, Kakuma T, Watanabe T, et al. Involvement of hypothalamic histamine H1 receptor in the regulation of feeding rhythm and obesity. Diabetes. 2004;53:2250-60.
78 Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology. 2003;28:519-26.
79 Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci. 2000;68:29-39.
80 Han M, Deng C, Burne 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, Alleva L, Quertemont 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 Neurobiol. 2010;92:421-41.

82 Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. Cell Metab. 2005;1:15-25.
83 Tsuda K, Yoshimatsu H, Niijima A, Chiba S, Okeda T, Sakata T. Hypothalamic histamine neurons activate lipolysis in rat adipose tissue. Exp Biol Med (Maywood). 2002;227:208-13.
84 Fadel J, Bubser M, Deutch AY. Differential activation of orexin neurons by antipsychotic drugs associated with weight gain. J Neurosci. 2002;22:6742-6.
85 Coccurello R, Brina D, Caprioli A, Conti R, Ghirardi O, Schepis F, et al. 30 days of continuous olanzapine infusion determines energy imbalance, glucose intolerance, insulin resistance, and dyslipidemia in mice. J Clin Psychopharmacol. 2009;29:576-83.
86 Stefanidis A, Verty AN, Allen AM, Owens NC, Cowley MA, Oldfield BJ. The role of thermogenesis in antipsychotic drug-induced weight gain. Obesity (Silver Spring). 2009;17:16-24.
87 Poyurovsky M, Pashinian A, Levi A, Weizman R, Weizman A. The effect of betahistine, a histamine H1 receptor agonist/H3 antagonist, on olanzapine-induced weight gain in first-episode schizophrenia patients. Int Clin Psychopharmacol. 2005;20:101-3.
88 Arner P. Adrenergic receptor function in fat cells. Am J Clin Nutr. 1992;55:228S-36S.
89 Burns TW, Langley PE, Terry BE, Bylund DB, Hoffman BB, Tharp MD, et al. Pharmacological characterizations of adrenergic receptors in human adipocytes. J Clin Invest. 1981;67:467-75.
90 Seydoux J, Muzzin P, Moinat M, Pralong W, Girardier L, Giacobino JP. Adrenoceptor heterogeneity in human white adipocytes differentiated in culture as assessed by cytosolic free calcium measurements. Cell Signal. 1996;8:117-22.
91 Flechtner-Mors M, Jenkinson CP, Alt A, Adler G, Ditschuneit HH. In vivo alpha(1)-adrenergic lipolytic activity in subcutaneous adipose tissue of obese subjects. J Pharmacol Exp Ther. 2002;301:229-33.
92 Poyurovsky M, Isaacs I, Fuchs C, Schneidman M, Faragian S, Weizman R, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. Am J Psychiatry. 2003;160:297-302.
93 Matsui-Sakata A, Ohtani H, Sawada Y. Receptor occupancy-based analysis of the contributions of various receptors to antipsychotics-induced weight gain and diabetes mellitus. Drug Metab Pharmacokinet. 2005;20:368-78.
94 Ujike H, Nomura A, Morita Y, Morio A, Okahisa Y, Kotaka T, et al. Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study. J Clin Psychiatry. 2008;69:1416-22.
95 Basile VS, Masellis M, McIntyre RS, Meltzer HY, Lieberman JA, Kennedy JL. Genetic dissection of atypical antipsychotic-induced weight gain: novel preliminary data on the pharmacogenetic puzzle. J Clin Psychiatry. 2001;62:45-66.
96 Emorine L, Blin N, Strosberg AD. The human beta 3-adrenoceptor: the search for a physiological function. Trends Pharmacol Sci. 1994;15:3-7.
97 Nahmias C, Blin N, Elalouf JM, Mattei MG, Strosberg AD, Emorine LJ. Molecular characterization of the mouse beta 3-adrenergic receptor: relationship with the atypical receptor of adipocytes. EMBO J. 1991;10:3721-7.
98 Krief S, Lonnqvist F, Raimbault S, Baude B, Van Spronsen A, Arner P, et al. Tissue distribution of beta 3-adrenergic receptor mRNA in man. J Clin Invest. 1993;91:344-9.
99 Ahren B. Autonomic regulation of islet hormone secretion--implications for health and disease. Diabetologia. 2000;43:393-410.
100 Gilon P, Henquin JC. Mechanisms and physiological significance of the cholinergic control of pancreatic beta-cell function. Endocr Rev. 2001;22:565-604.
101 Satin LS, Kinard TA. Neurotransmitters and their receptors in the islets of Langerhans of the pancreas: what messages do acetylcholine, glutamate, and GABA transmit? Endocrine. 1998;8:213-23.
102 Verspohl EJ, Tacke R, Mutschler E, Lambrecht G. Muscarinic receptor subtypes in rat pancreatic islets: binding and functional studies. Eur J Pharmacol. 1990;178:303-11.
103 Brunicardi FC, Shavelle DM, Andersen DK. Neural regulation of the endocrine pancreas. Int J Pancreatol. 1995;18:177-95.
104 Wess J. Molecular biology of muscarinic acetylcholine receptors. Crit Rev Neurobiol. 1996;10:69-99.
105 Boschero AC, Szpak-Glasman M, Carneiro EM, Bordin S, Paul I, Rojas E, et al. Oxotremorine-m potentiation of glucose-induced insulin release from rat islets involves M3 muscarinic receptors. Am J Physiol. 1995;268:E336-42.
106 Tang SH, Sharp GW. Identification of muscarinic receptor subtypes in RINm5F cells by means of polymerase chain reaction, subcloning, and DNA sequencing. Diabetes. 1997;46:1419-23.
107 Iismaa TP, Kerr EA, Wilson JR, Carpenter L, Sims N, Biden TJ. Quantitative and functional characterization of muscarinic receptor subtypes in insulin-secreting cell lines and rat pancreatic islets. Diabetes. 2000;49:392-8.
108 Duttaroy A, Zimliki CL, Gautam D, Cui Y, Mears D, Wess J. Muscarinic stimulation of pancreatic insulin and glucagon release is abolished in m3 muscarinic acetylcholine receptor-deficient mice. Diabetes. 2004;53:1714-20.
109 Gautam D, Han SJ, Hamdan FF, Jeon J, Li B, Li JH, et al. A critical role for beta cell M3 muscarinic acetylcholine receptors in regulating insulin release and blood glucose homeostasis in vivo. Cell Metab. 2006;3:449-61.
110 Doliba NM, Qin W, Vinogradov SA, Wilson DF, Matschinsky FM. Palmitic acid acutely inhibits acetylcholine- but not GLP-1-stimulated insulin secretion in mouse pancreatic islets. Am J Physiol Endocrinol Metab. 2010;299:E475-85.
111 Johnson DE, Yamazaki H, Ward KM, Schmidt AW, Lebel WS, Treadway JL, et al. Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perifused rat islets: role of muscarinic antagonism in antipsychotic-induced diabetes and hyperglycemia. Diabetes. 2005;54:1552-8.
112 Coccurello R, Caprioli A, Ghirardi O, Conti R, Ciani B, Daniele S, et al. Chronic administration of olanzapine induces metabolic and food intake alterations: a mouse model of the atypical antipsychotic-associated adverse effects. Psychopharmacology (Berl). 2006;186:561-71.
113 Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res. 2004;66:51-7.