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Atypical antipsychotics and the neural regulation of food intake and peripheral metabolism

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Abstract

The atypical antipsychotics (AAPs) are associated with weight gain and an increased incidence of metabolic disease including type 2 diabetes mellitus. Epidemiological, cross-sectional and prospective studies suggest that two of the AAPs, olanzapine and clozapine, cause the most dramatic weight gain and metabolic impairments including increased fasting glucose, insulin and triglycerides. Relative to the other AAPs, both olanzapine and clozapine exhibit a particularly high antagonistic affinity for histamine and muscarinic receptors which have been hypothesized as mediators of the reported increase in weight and glucose abnormalities. In this article, we review the current evidence for the AAP associated weight gain and abnormal glucose metabolism. We postulate that the effects of the AAPs on food intake and peripheral metabolism are initially independently regulated but with increasing body adiposity, the early AAP-induced impairments in peripheral metabolism will be exacerbated, thereby establishing a vicious cycle such that the effects of the AAP are magnified by the known pathophysiological consequences of obesity. Furthermore, we examine how inhibition of the histaminergic pathway may mediate increases in food intake and the potential role of the vagus nerve in the reported peripheral metabolic effects.

Keywords

histamine; vagus; insulin; glucose; weight gain; obesity

1. Introduction

Within the last 20 years, there has been a striking increase in the incidence of metabolic disease in the schizophrenic population. The number of studies reporting anti-psychotic induced weight gain rose from less than 20 before 1970 to over 250 since 1990 (1). In addition to weight gain, there are numerous reports of significant increases in fasting insulin and glucose levels (2–6). Markers of lipid abnormalities and predictors of cardiovascular disease are also consistently altered with patients presenting with low HDL, high triglycerides (7–10) and elevated free fatty acids (11). Based on the large NIH funded CATIE trials (Clinical Antipsychotic Trials of Intervention Effectiveness), the prevalence of

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metabolic syndrome, as indicated by 3 or more of 5 clinical symptoms (increased waist girth, hyperglycemia, hypertension, hypertriglyceridemia and low HDL-cholesterol) is twice to three times greater in schizophrenic patients on atypical anti-psychotics than in age, sex and race matched controls from the NHANES III database (12;13). As the metabolic syndrome is predictive of CVD, the long-term health consequences for schizophrenic patients are significant (14;15).

The increase in obesity and metabolic disease appears to coincide with the development of a new class of drugs designed to treat schizophrenia, termed the second generation anti-psychotics or atypical anti-psychotics (AAPs). While there is still ongoing discussion as to whether the weight gain and metabolic disease are part of the natural etiology of schizophrenia, the premise of this article is that although we acknowledge the genetic and lifestyle factors associated with schizophrenia that may contribute to weight gain and metabolic disease, we believe that there is ample evidence for treatment-emergent effects. In vitro studies (16;17), animal models (18) (19), studies conducted in children with first-time use of AAPs (20) and evidence of similar side effects in other psychiatric disorders (21;22) provide support of AAP-induced adverse effects.

The AAPs influence multiple neurotransmitter systems exerting antagonistic actions on dopaminergic, adrenergic, serotonergic, histaminergic and muscarinic receptor subtypes. These neurotransmitters have all been implicated directly or indirectly in pathways associated with food intake regulation and/or metabolism. In this article, we will give a brief overview of the evidence for AAP-induced weight gain and metabolic dysregulation. We postulate that the effects of the AAPs on food intake and peripheral metabolism are initially independently regulated but with increasing body adiposity, the early AAP-induced impairments in peripheral metabolism will be exacerbated, thereby establishing a vicious cycle such that the effects of the AAP are magnified by the known pathophysiological consequences of obesity. We focus on two exemplary neurotransmitter/neuronal systems: the central histaminergic pathway, mediating increases in food intake and the vagus nerve, hypothesized to mediate some of the peripheral metabolic side effects. We focus on these two neurotransmitter systems because olanzapine and clozapine, the two agents associated with the greatest weight gain and most impaired metabolic profile, exhibit a particularly high antagonistic affinity for histamine and muscarinic receptors. Other mechanisms may be equally important but we are using these to illustrate the potential complexity of action of the AAPs on both behavior and metabolic processes.

2.0 Atypical Antipsychotics (AAP): Effects on Weight gain and Food Intake

2.1 Human Studies

In the late 1990's reports started to emerge stating that weight gain must be considered a side effect of the new second generation antipsychotics (23;24). Isolated reports also indicated that the AAPs may be associated with metabolic consequences such as increases in plasma insulin which were correlated with circulating levels of clozapine (25). Allison et al. (26) published a review of the literature providing support for AAP-induced weight gain and suggesting that the weight gain may contribute to metabolic dysregulation in patients with schizophrenia. The CATIE trials later indicated that significant weight gain was associated with AAP treatment and that some of the AAPs appeared to cause greater weight gain than others (for example ziprasidone was the only agent not associated with weight gain) but the data were confounded by the patient's previous exposure to multiple medications and a varying length of treatment duration (27). A recent post-hoc database analysis of weight effects across treatments compared short term (4–12 weeks) to long term (1 year) effects and found that after short-term administration, haloperidol (a first generation antipsychotic) and ziprasidone (a second generation anti-psychotic) did not cause significantly greater weight

gain than placebo (28). In contrast, amisulpride, risperidone and olanzapine had significantly increased incidence of weight gain. Weight change following olanzapine treatment was the greatest compared to the other drugs, with an average 11.1 lb gained and 55% of patients exhibiting weight gain greater than 7%. Thus, over half of the subjects treated with olanzapine gained more than 7% of their body weight. These effects were essentially paralleled after 1 year of treatment, with risperidone and olanzapine being associated with the greatest weight gain while ziprasidone and aripiprazole were not different from placebo. Overall, the data show that olanzapine and clozapine are consistently associated with the greatest weight gain although because clozapine is less frequently prescribed due to the associated agranulocytosis, recent attention has focused on olanzapine.

Despite the recognized increases in weight with AAP treatment, relatively little is known about changes in food intake and appetitive behavior. Significant increases in food intake were reported in healthy male volunteers after 15 days of olanzapine administration which resulted in a modest increase in body weight coupled with an 18% increase in food intake, independent of changes in energy expenditure or insulin sensitivity relative to placebo (29). Other studies using a test meal challenge have reported no increase in energy intake or changes in macronutrient consumption in either patients or control subjects (30;31). Increases in hunger coupled with decreases in satiety have been reported consistently following olanzapine administration. Kluge et al. (32) found that both clozapine and olanzapine were associated with an increase in self-reported binge eating and a significant increase in food craving as well. However, the study was conducted on an inpatient population and there was no placebo control group so it is difficult to interpret whether the food craving was a function of the limitations of a hospital diet or a direct consequence of the drug administration. In healthy control subjects, a small non-significant increase in the breakfast hunger curve coupled with modest weight gain was observed after olanzapine was administered on an outpatient basis for 15 days (31). In another study, appetite ratings from 4 separate studies in which olanzapine was administered for 12–24 weeks were analyzed. Appetite was assessed with 5 different scales, some developed by Lilly, the company which manufactures olanzapine as well as a couple of other validated scales. Using their in-house “Eating Behavior Assessment”, they also found an increase in craved fatty foods and craved sweet foods, and an increase in self-reported overeating (33). Eating behaviors have also been evaluated as predictors of weight gain following AAP administration. Post-hoc analysis of 3 clinical studies conducted by Lilly suggested that significant predictors of weight gain included decreases in cognitive restraint as measured by the Three Factor Eating Inventory (34), increases in hunger and overeating at baseline (35). Overall, the same methodological issues which limit the evaluation and measurement of human eating behavior in general, plague this area as well. The validity of laboratory versus real-world evaluation of eating behavior and the lack of accuracy with dietary recall measurements are two primary hurdles.

2.2 Animal Studies

Animal models provide one strategy to investigate the potential mechanisms involved in AAPs-mediated food intake and weight gain. However, the results from the animal experiments are inconsistent. For example, while multiple studies utilizing female rodents demonstrate that AAP administration via various methods such as drinking water, minipump, intraperitoneal injection, over both the long and short term, increases food intake and body weight (18;36–40;40;41;41) a recent report by Cooper et al. (42) failed to demonstrate that chronic administration of clozapine had any effects on food intake in female rats despite evidence that clozapine is one of the AAPs associated with the greatest weight gain in humans. In one study with male rats, there was enhanced adiposity in the absence of hyperphagia, weight gain or metabolic abnormalities (43) suggesting that AAPs

may have direct peripheral effects which bypass central nervous system-mediated food intake regulation. Pouzet et al. showed that haloperidol, which does not cause noticeable weight gain in patients, led to weight gain in a rat model (36). However, it has been argued that the minimal response of chronic administration of olanzapine is due to its degradation in solution (44) which may explain the discrepancies in the animal models. In addition, there is no clinical evidence showing that AAP-mediated weight gain or metabolic impairments are sex-specific. Since food intake, weight gain and metabolic phenotype in rodent models can be influenced by various factors such as strain, sex, food choice and environmental context, it is crucial to refine and identify the methods needed to establish a valid animal model. However, despite their current limitations, animal models can still provide valuable insights into underlying signal transduction and neural circuit pathways modulating AAP-mediated weight gain and food intake.

3.0 AAP Effects on Peripheral Glucose Metabolism

3.1 Human Studies

Consistent with the findings on weight gain, epidemiological studies consistently demonstrate that the two AAPs with the metabolic profiles most predictive of T2DM are olanzapine and clozapine (45–48) while ziprasidone has been shown to improve metabolic parameters. A recent meta-analysis reviewed data from 48 randomized blinded studies comparing the AAPs and found that olanzapine produced greater weight gain and higher glucose and cholesterol levels than any of the other drugs including clozapine (49). Cross-sectional clinical studies also provide evidence of abnormal glucose metabolism and insulin resistance in schizophrenic patients on olanzapine and clozapine (3;50–52). Olanzapine has been shown to induce higher levels of glucose and/or insulin at baseline (53;54) and during oral glucose tolerance tests (53;55) although some studies report no effects (56). Homeostatic model assessment-insulin resistance (HOMA-R) measurements can be derived from fasting glucose and insulin concentrations and are used as an index of insulin resistance. Schizophrenic patients on both olanzapine and clozapine exhibit higher HOMA-IR levels compared to control subjects or patients on other antipsychotic agents (57). In addition, prospective studies demonstrate that olanzapine increases HOMA-IR relative to an age and sex matched control group (58). Studies utilizing more sophisticated measures of insulin sensitivity such as the frequently sampled intravenous glucose tolerance test (FSIGT) report either significantly reduced insulin sensitivity and glucose effectiveness in patients on olanzapine and clozapine relative to risperidone (59) or no significant differences (60). The reported increases in fasting glucose and insulin concentrations are indicative of hepatic insulin resistance but only one study has directly measured endogenous glucose production or hepatic insulin resistance in a patient population (61). Consistent with the more indirect assessments, an increased rate of endogenous glucose production was observed in first episode antipsychotic-naïve schizophrenic patients relative to weight matched controls. Overall, the studies vary widely in that some evaluate first-episode schizophrenic patients, while others examine patients that have been on multiple treatment regimens making comparison between studies difficult. Furthermore, because the AAPs increase weight (62;63) it is difficult to ascertain the extent to which the metabolic consequences of the AAPs are due to increased body adiposity or are a direct effect of the drugs on tissue function and metabolism. Thus, untangling the etiology of metabolic disease in schizophrenic populations is fraught with confounding issues.

One approach to teasing out the effects of disease or prior exposure to other drugs from direct treatment-related consequences is to investigate the effect of the AAPs in normal, healthy control subjects. Sowell and co-workers conducted two studies examining the effect of AAP administration on insulin secretion and insulin sensitivity in healthy controls: one study utilized a hyperglycemic clamp (64), and the other, a hyperinsulinemic, euglycemic

clamp (65). Both studies administered 10 mg/d of olanzapine for a 15–21 day period, compared the results to risperidone and placebo and reported no significant effects on insulin secretion or insulin resistance although modest effects on weight gain were found. In addition, Hardy et al. published a study (66) which re-analyzed data from the hyperglycemic clamp study and found an increase in the acute insulin response to glucose (first ten minutes of insulin secretion) and a decrease in insulin sensitivity after olanzapine administration. However, due to a lack of significant difference in the disposition indexes, the authors concluded that olanzapine had no effect on glucose metabolism. In contrast, a significant decrease in insulin sensitivity as measured by the euglycemic, hyperinsulinemic clamp was reported after olanzapine administration to normal healthy subjects for a 10 day period compared to ziprasidone (67). In these studies, subjects still gain some weight during the acute olanzapine administration and therefore, the effects on metabolism could have been secondary to weight gain. Only one study has reported on significant effects of olanzapine on insulin sensitivity independent of weight gain and they found modest decreases in insulin sensitivity during a euglycemic, hyperinsulinemic clamp with no change in endogenous glucose production (68).

In addition to the reported effects on glucose metabolism, olanzapine and clozapine have been associated with increased fasting triglyceride (TG) concentrations (69–72) and low density lipoproteins. Interestingly, metabolomics were used to examine lipid profiles in schizophrenics treated with either olanzapine, risperidone or aripiprazole and no effects were found in patients on aripiprazole, but 50 lipids and lipid metabolites were increased with the other two drugs (73). The effects of olanzapine on plasma free fatty acid (FFAs) levels are inconsistent. One study reported an increase in free fatty acid levels in patients on chronic treatment with AAPs (11) but when olanzapine was administered to healthy subjects, a decrease in fasting FFA levels and a blunted suppression of FFA levels during a euglycemic, hyperinsulinemic clamp (68) was observed. The authors speculated that olanzapine inhibits lipoprotein lipase (LPL) in the muscle but impairs the action of insulin on LPL in adipose tissue. Increases in triglycerides may be due to a decrease in the metabolic clearance of TG or alternatively, an increase in hepatic de novo lipogenesis as suggested by the animal studies.

3.2 Animal Studies

It is generally assumed that the increased incidence of diabetes and cardiovascular disease associated with AAP treatment is secondary to weight gain. However, *in vitro* and acute animal studies provide evidence for direct effects of olanzapine on glucose or lipid metabolism independent of disease or weight gain. Using 3T3-L1 adipocytes and primary cultured rat adipocytes, AAPs were shown to impair insulin-induced glucose transport and increase lipogenesis (16). Similar effects on lipogenesis were reported by Yang et al. (17) who also demonstrated an induction of sterol regulatory element binding protein (SREBP-1), the upstream regulator of fatty acid synthase. Increases in gene expression of fatty acid synthase and stearoyl-CoA desaturase, two lipid biosynthetic genes, were also observed in isolated peripheral blood cells from patients on olanzapine (74). Moreover, our group also found that sub-nM range of olanzapine and clozapine can specifically enhance fatty acid synthesis and TG in HeLa cells without affecting cholesterol levels while the same doses of ziprasidone have no effect on any lipogenesis (unpublished observation). The effects on adipocytes are not completely consistent as one study found no changes in basal or insulin-stimulated glucose transport at therapeutic concentrations of olanzapine in 3T3-L1 cells (75).

Acute administration of the AAPs in whole animal models also provides evidence of direct effects of the drugs on glucose and lipid metabolism. Chintoh et al. (76) conducted both euglycemic and hyperglycemic clamps after acute olanzapine administration and found

increases in endogenous glucose production and decreases in insulin secretion, respectively. Houseknecht et al. administered acute subcutaneous doses of olanzapine and clozapine to rats, and found an increase in hepatic glucose production and a decrease in insulin sensitivity during a euglycemic, hyperinsulinemic clamp (77). Chronic administration using osmotic mini-pumps has no effect on weight gain or food intake but was shown to cause increases in visceral fat, decreases in locomotor activity and increases in endogenous glucose production (78). Recently, some animal studies have started to shed light on potential mechanisms. Albaugh et al. (79) found that chronic administration of olanzapine to rats decreased FFA and triglyceride levels coincident with increases in glucose and insulin suggesting that the drug uncouples the known relationship between elevated FFA concentrations and insulin resistance. They also reported a decrease in nocturnal resting energy expenditure as well as citric acid cycle precursors of malonyl-CoA synthesis which regulate fat oxidation. Interestingly, the accelerated fat oxidation was associated with increased lipid storage and decreased lipolysis which potentially could be associated with increased hepatic lipid accumulation. This would support data by Oh et al. (19) who showed increased expression of SREBP and decreased AMPK activity in the liver which could contribute to hepatic lipid accumulation. However, Martins et al. (80) showed that both peripheral and central administration of olanzapine induces hepatic insulin resistance and peripheral administration increases hypothalamic AMPK. Thus, whether the effects of olanzapine on hepatic glucose and lipid metabolism are peripherally or centrally-mediated or both, are still not known.

4. 0 Atypical Antipsychotic Binding Profile: overview

The atypical antipsychotics (AAPs) were the second generation of drugs developed to treat psychosis. The first generation anti-psychotic drugs were primarily dopaminergic antagonists and were associated with a high incidence of tardive dyskinesia. In contrast, the AAPs act on multiple receptors sub-types with a range of affinity for dopamine, serotonin, histamine, muscarinic and adrenergic receptors (81–84). The decreased specificity for dopamine receptors of the AAPs has lessened the motor disorders associated with previous agents such as haloperidol but the lack of specificity may be responsible for the wide spread metabolic side effects associated with the drugs. As discussed above, the clinical data indicate that some AAPs such as clozapine and olanzapine induce the most significant weight gain and metabolic disturbances while risperidone and aripiprazole may have modest effects and others such as ziprasidone appear to be weight-neutral. These data suggest that subtle differences in receptor binding and affinity may have profound effects on food intake, weight gain and ultimately metabolism.

One common and unique characteristic of olanzapine and clozapine, the two AAPs associated with the greatest weight gain and metabolic impairments is their high affinity for both muscarinic and histaminergic receptors. Olanzapine and clozapine exhibit binding affinities for muscarinic receptors of at least two orders of magnitude higher than the other AAPs (Table 1) and (83). Similarly, both these drugs exhibit a high antagonist affinity for H1 receptors (85). The differential binding affinity of olanzapine and clozapine to muscarinic and histaminergic receptors has lead to hypotheses that these receptors play a primary role in the abnormal metabolic and orexigenic properties of these drugs. A number of review articles have reported positive correlations between histamine binding and increased weight gain as well as muscarinic binding and metabolic impairment (84;86;87). Below we discuss the potential role of these two systems as mechanisms for the effects of the AAPs on food intake and metabolism

5.0 AAP administration: Central histaminergic antagonism as a potential mediator of increased food intake

Energy homeostasis is a balancing act between energy intake (food intake) and energy expenditure (basal metabolism and physical activity) and is orchestrated by both the brain and periphery. One of the key regions in regulating this process is the hypothalamus in the brain (88;89). A set of systemic lesion experiments identified the specific hypothalamic structures that are directly involved in energy homeostasis such as hypothalamic ventromedial (VMH), the paraventricular (PVN) and dorsal medial (DMH) nuclei as satiety centers and the lateral hypothalamus (LH) as the hunger center (90;91). Genetic deletion studies have enabled us to identify a large number of peptides as well as signaling cascades within the hypothalamus responsible for these feeding behaviors. Hence, food intake is now believed to be controlled by a neural circuit with specific peptides such as leptin, melanocyte-stimulating hormone- α (α -MSH), neuropeptide Y (NPY), agouti-related hormone (AgRP) and many other neuropeptides regulating energy homeostasis instead of specific hypothalamic nuclei (89).

Non-homeostatic eating behavior, often driven by the hedonic and rewarding properties of food also contributes to energy intake (92;93). Palatable food enhances mood and stimulates the reward system (94). Specifically, the mesoaccumbens dopamine system is activated by palatable food and appetite controlling hormones such as leptin and ghrelin (95). Interestingly, patients with Parkinson's disease, a condition associated with loss of dopamine containing neurons, exhibit reduced food intake, which is ameliorated with treatment of dopamine agonists (96;97). Moreover, dopamine agonists can trigger compulsive eating behavior in non-affected controls implying that the dopamine pathway in the midbrain is involved in food intake control (98). Further, a genetic deletion of tyrosine hydroxylase, a rate limiting enzyme for dopamine synthesis reduces sucrose consumption over water compared to wild type mice suggesting that the mesoaccumbens dopamine system modulates motivational aspects of food intake (99).

The monoamine histamine is another important chemical messenger that regulates a wide variety of physiologic responses in the brain and peripheral organs including food intake (100). Four metabotropic histamine receptor types (H1R-H4R) have been cloned so far (101). H1R-H3R are expressed in abundance in the brain and H4R mainly occurs in peripheral tissues (102). Histamine-containing neurons and histamine H1 receptors are distributed within the brain and peripheral tissues. Particularly, histaminergic neurons in the mammalian brain are located exclusively in tuberomammillary nucleus of the posterior hypothalamus and send their axons throughout the central nervous system (100). The signal transduction of H1R is similar to that of other $G_{\alpha q/11}$ protein-coupled receptor. Histamine binding to H1R results in the cellular accumulation of $\text{Ins}(1,4,5)\text{P}_3$ and DAG via hydrolysis of the membrane bound lipid inositol, $\text{PtdIns}(4,5)\text{P}_2$, by phosphoinositide-specific phospholipase C (PLC). DAG goes on to activate protein kinase C (PKC) while $\text{Ins}(1,4,5)\text{P}_3$ binds the $\text{Ins}(1,4,5)\text{P}_3$ -receptor/channel and allosterically mediates the release of Ca^{2+} from intracellular pools within the endoplasmic reticulum (103).

Several studies showed that histamine can suppress the mesolimbic dopamine pathway which controls palatable food consumption via the H3 autoreceptor and yet activate it through the histamine H1 receptor (104), perhaps suggesting that the effect of H3 deletion is mediated by its ability to inhibit the histamine H1 pathway (105). Histamine or H1R agonists injected centrally decrease the level of food intake and enhance *c-fos*-like immunoactivity in the PVN in mice (106–108) while blockade as well as genetic deletion of H1R elicits an increased daily food intake (109) indicating the H1R is important for regulation of energy balance. In addition to the effect on food intake, it has been shown that brain histamine

might regulate body weight and adiposity by modulating peripheral energy metabolism in rodents (110). The central administration of H1R agonists increase the expression of uncoupling protein 1 in brown adipose tissue which is a marker for energy expenditure, and enhances the lipolytic response in white adipose tissue of rats (111;112). Several studies examining drug-binding profiles to various receptors showed that the AAPs binding affinity for histamine H1 receptor is a good predictor of AAP-mediated weight gain (82). Also, our group's recent studies further corroborate drug-receptor binding profiles by showing that orexigenic AAPs specifically activate hypothalamic AMP-activated kinase, which is a key enzyme in the regulation of appetite and is mediated by histamine H1 receptor (85).

6. AAP administration: Muscarinic antagonism as a potential mediator of impaired peripheral metabolism

The vagus nerve, part of the parasympathetic nervous system, is a mixed nerve composed of both sensory afferents and motor efferents. Vagal afferents relay information from peripheral tissues such as the stomach and intestine to the nucleus of the solitary tract (NTS). Neurons from the NTS descend in a topographical manner into the dorsal motor nucleus of the vagus (DMV). At the onset of, and during food ingestion, descending pre-ganglionic vagal efferent neurons from the DMV are activated and stimulate post-ganglionic neurons which release acetylcholine on target tissues including the pancreas and liver, two tissues critically involved in the regulation of blood glucose (Figure 1). In the pancreas, the vagal efferents terminate on intrapancreatic neurons which release acetylcholine as well as other peptides such as vasointestinal peptide. To elicit insulin secretion (113), acetylcholine binds to M₃ muscarinic receptors and activates phospholipase C resulting in hydrolysis of phosphoinositides (114;115). This intracellular pathway is activated by acetylcholine and carbachol, a muscarinic agonist and inhibited by atropine, the muscarinic antagonist. Acetylcholine enhances insulin secretion to glucose (113) and conditions leading to desensitization of insulin release to glucose have been associated with increased sensitivity to acetylcholine in pancreatic islets (116;117). Conversely, elevated free fatty acids postulated in the etiology of insulin resistance, can inhibit the stimulatory effect of acetylcholine on insulin release from pancreatic islets (118). Olanzapine and clozapine have been shown to inhibit inositol phosphate accumulation and insulin secretion to carbachol in pancreatic islets, demonstrating functionally significant consequences of M₃ binding by the AAPs (119).

In healthy humans, vagal efferent activation only takes place during food ingestion as the sensory properties of food stimulate receptors in the oral cavity. The sensory properties of food can elicit a small insulin response, termed the cephalic phase insulin response, that is dependent on vagal efferent activation, and occurs prior to nutrient absorption in the first 10 minutes of food ingestion or just by tasting and chewing food (120;121). Increases in cephalic phase insulin release (CPIR) indicate that vagal efferent activation has occurred. When glucose is administered directly into the stomach via a nasogastric tube, there is no CPIR since vagal efferent stimulation of insulin release does not take place (122). Under these conditions, post-prandial glucose levels are 30% greater than when food is tasted simultaneously to gastric administration alone. Similarly, when glucose is administered intravenously (IV), there is no vagal efferent contribution to insulin secretion as demonstrated by a lack of effect of administration of the muscarinic antagonist atropine on insulin secretion (123;124). Understanding the conditions by which vagal efferent activation takes place, is crucial for interpreting the results of experiments assessing the vagal contribution to various physiological responses. For example, trying to reveal the effect of an intervention (i.e. AAP administration) on a vagally-mediated response such as insulin release will be ineffective using the established methodologies for assessing insulin secretion and insulin sensitivity which involve IV glucose administration. A vagal efferent

contribution to insulin secretion after IV glucose only takes place during conditions requiring compensatory insulin secretion such as would occur during over-feeding or as we have shown during prolonged stimulation of the pancreatic β -cell with a 48-h glucose infusion (123). Under these conditions, there is an induction of vagal efferent activity which contributes to the increase in insulin required to maintain glucose homeostasis.

The vagus nerve also plays a role in the regulation of hepatic glucose production. In studies published more than 30 years ago, Shimazu demonstrated that electrical stimulation of the vagus inhibits glycogenolysis (125) and increases activity of enzymes involved in glycogen synthesis (126). When acetylcholine is administered directly into the portal vein of dogs (127) and streptozotocin-diabetic rats, net hepatic glucose uptake is increased (128). Furthermore, both vagotomy and atropine increase hepatic glucose output (129). The importance of vagal mediation of hepatic glucose production has been elegantly verified by the demonstration that activation of ATP-dependent potassium channels in the hypothalamus lowers peripheral blood glucose levels by inhibition of hepatic glucose output (130). This effect can be blocked by surgical resection of the hepatic branch of the vagus nerve, resulting in an increase in hepatic glucose production. In humans, administration of the muscarinic agonist, bethanechol decreases hepatic glucose production, confirming the functionality of muscarinic activation in mediating hepatic glucose production (131). While these many physiological experiments support an important role for vagal innervation of the liver, it is still not clear where the neurons terminate and which receptors mediate the reported effects.

Inhibition of vagally-mediated responses such as the enhancement of insulin secretion and inhibition of endogenous glucose production by an AAP with a high muscarinic antagonism would contribute to a pre-diabetic profile of impaired post-prandial insulin release and increased endogenous glucose production, two hallmarks of diabetes. While these outcomes may be the ultimate consequence of chronic AAP administration on a background of increased weight gain and body adiposity as well as increased levels of circulating lipids, we postulate that short-term administration of some of the AAPs, such as olanzapine may initially result in an increase in vagally-mediated insulin release due to two factors: 1) increased food intake which would repetitively stimulate vagal efferent activity and 2) a compensatory increase in central vagal efferent activity due to peripheral blockade of muscarinic receptors (Figure 2). Preliminary data from our laboratory indicates that short-term administration of olanzapine to healthy men results in significant increases in cephalic phase insulin release as well as post-prandial hyperinsulinemia. The hyperinsulinemia occurs independent of weight gain and accompanied by only very modest insulin resistance such has been reported previously (132). To date, only two studies have examined the effect of olanzapine or other AAPs such as risperidone on post-prandial hormonal release. In one study, blood sampling only took place every 2 hours which was insufficient to document changes in post-prandial responses (65) while in another, where short and long-acting olanzapine were compared, the effects of the drugs on insulin were not reported although no significant differences in other hormones such as glucagon-like peptide were found (133). As discussed above, only meal ingestion could reveal whether there was an enhancement or deficit in vagally-mediated responses. We postulate that the increase in post-prandial insulin will drive the deposition of nutrients thereby contributing to weight gain. In addition to a direct effect on the pancreatic β -cell, the AAPs may target hepatic lipid synthesis and storage. Early changes in plasma lipids and modest insulin resistance have been reported after short periods of AAP administration, primarily olanzapine, to healthy individuals (68). The magnitude of decrease in insulin sensitivity is relatively small after a 9–14 day period of administration and it is unlikely that this is mediated through muscle insulin resistance. A more plausible hypothesis is that there are direct effects of the AAPs on hepatic glucose and lipid metabolism as well as on the pancreas.

As body adiposity accumulates, the known effects of weight gain are manifested: elevated triglycerides, increased free fatty acids, elevated levels of plasma glucose and insulin. Thus, chronic AAP treatment is now being administered on a background of the metabolic syndrome phenotype. Many of the diagnostic components of the metabolic syndrome overlap with those potentially induced by AAP administration. Thus, weight gain will exacerbate the acute AAP-induced metabolic impairments and in some individuals, may eventually result in overt diabetes. Long term administration of the AAP may eventually result in down-regulation of receptors or desensitization to the antagonist effects of the drugs. It is not known whether the stimulatory effect of food intake is maintained over long term treatment. Clinical data seems to suggest that rapid weight gain occurs primarily at the onset of treatment. We would postulate that the compensatory vagally-mediated responses such as the increase in post-prandial insulin release and suppression of endogenous glucose production may be down-regulated or in the case of insulin secretion, may be inhibited by the presence of elevated free fatty acids binding to muscarinic receptors as has been demonstrated *in vitro* (118). Loss of the compensatory responses would contribute to impaired glucose tolerance (3).

7. 0 Conclusions

In this article we have highlighted two neurotransmitter systems which could potentially contribute to the observed increases in food intake and metabolic impairments following AAP treatment, the histaminergic and muscarinic pathways, respectively. We postulate that the increased antagonistic affinity of olanzapine and clozapine for muscarinic and histaminergic receptors may be responsible for the increased weight gain and metabolic impairments that are specifically associated with these two antipsychotics. Furthermore, we would speculate that the initial administration of an AAP like olanzapine results in peripheral muscarinic blockade with compensatory increases in centrally-mediated vagal efferent activity, possibly via the hypothalamus through repetitive and increased food ingestion, resulting in increased post-prandial insulin release (Figure 2). Over time, the increase in centrally-mediated vagal efferent activity may be down-regulated or the effects of muscarinic stimulation further blocked by increases in circulating free fatty acids (Figure 3). However, the observed clinical and experimental effects of the AAPs are not solely mediated through these two systems. As mentioned in the introduction, all the neurotransmitters potentially influenced by the AAPs: dopamine, serotonin, noradrenaline as well as acetylcholine and histamine have been implicated in the regulation of food intake, insulin release and glucose metabolism. Both dopamine and serotonin are involved in the motivational (134–136) and regulational aspects of food intake and therefore, it is not surprising that these drugs may be associated with weight gain (137–139). In addition, decreased sympathetic nervous system activity would contribute to increased lipid storage and an inhibition of lipolysis. Thus, what we highlight illustrates how two systems could be contributing to the adverse metabolic profile associated with some of the AAPs. We believe that teasing out the specific pathways responsible for the detrimental side effects will be difficult because of the large redundancy in the mechanisms regulating food intake and the overlap in the mechanisms induced by AAP treatment and those in the etiology of diabetes. However, in the process of understanding how the AAPs contribute to weight gain and metabolic disease, we are likely to advance our understanding of food intake regulation and the etiology of diabetes and cardiovascular disease.

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Reference List

1. Baptista T, Zarate J, Joobor R, Colasante C, Beaulieu S, et al. Drug induced weight gain, an impediment to successful pharmacotherapy: focus on antipsychotics. *Curr Drug Targets*. 2004; 5(3): 279–299. Review. [PubMed: 15058313]
2. Henderson D, Cagliero E, Gray C, Nasrallah R, Hayden D, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five year naturalistic study. *Am J Psychiatry*. 2000; 157:975–981. [PubMed: 10831479]
3. Newcomer J, Haupt D, Fucetola R, Melson A, Schweiger J, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002; 59(4):337–345. [PubMed: 11926934]
4. Lambert M. Olanzapine is associated with more rapid weight gain than haloperidol in people with first episode psychosis. *Evid Based Ment Health*. 2006; 9(3):72. [PubMed: 16868191]
5. Duncan E, Dunlop BW, Boshoven W, Woolson SL, Hamer RM, Phillips LS. Relative risk of glucose elevation during antipsychotic exposure in a Veterans Administration population. *Int Clin Psychopharmacol*. 2007; 22(1):1–11. [PubMed: 17159454]
6. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003; 160(2):290–296. [PubMed: 12562575]
7. Rettenbacher MA, Ebenbichler C, Hofer A, Kemmler G, Baumgartner S, et al. Early changes of plasma lipids during treatment with atypical antipsychotics. *Int Clin Psychopharmacol*. 2006; 21(6): 369–372. [PubMed: 17012984]
8. Hardy T, Marquez E, Kryzhanovskaya L, Taylor C, Cavazzoni P. Cross-sectional Comparison of Fasting Lipids in Normoglycemic Patients With Schizophrenia During Chronic Treatment With Olanzapine, Risperidone, or Typical Antipsychotics. *J Clin Psychopharmacol*. 2006; 26(4):405–408. [PubMed: 16855460]
9. Huang TL, Chen JF. Serum lipid profiles and schizophrenia: effects of conventional or atypical antipsychotic drugs in Taiwan. *Schizophr Res*. 2005; 80(1):55–59. [PubMed: 15964176]
10. Ried LD, Renner BT, McConkey JR, Bengtson MA, Lopez LM. Increased cardiovascular risk with second-generation antipsychotic agent switches. *J Am Pharm Assoc (2003)*. 2006; 46(4):491–498. [PubMed: 16913393]
11. Wang CJ, Zhang ZJ, Sun J, Zhang XB, Mou XD, et al. Serum free Fatty acids and glucose metabolism, insulin resistance in schizophrenia with chronic antipsychotics. *Biol Psychiatry*. 2006; 60(12):1309–1313. [PubMed: 16650386]
12. Nasrallah HA. Metabolic findings from the CATIE trial and their relation to tolerability. *CNS Spectr*. 2006; 11(7 Suppl 7):32–39. [PubMed: 16816798]
13. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry*. 2007; 68 (Suppl 1):20–27. [PubMed: 17286524]
14. Eberly L, Prineas R, Cohen J, Vazquez G, Zhi X, et al. Metabolic syndrome: risk factor distribution and 18-year mortality in the multiple risk factor intervention trial. *Diabetes Care*. 2006; 29(1):123–130. [PubMed: 16373907]
15. Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah HA, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*. 2005; 80(1):45–53. [PubMed: 16198088]
16. Vestri H, Maianu L, Moellering D, Garvey W. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. *Neuropsychopharmacology*. 2007; 32(4):765–772. [PubMed: 16823387]
17. Yang LH, Chen TM, Yu ST, Chen YH. Olanzapine induces SREBP-1-related adipogenesis in 3T3-L1 cells. *Pharmacol Res*. 2007; 56(3):202–208. [PubMed: 17651982]
18. Cope MB, Nagy TR, Fernandez JR, Geary N, Casey DE, Allison DB. Antipsychotic drug-induced weight gain: development of an animal model. *Int J Obes (Lond)*. 2005; 29(6):607–614. [PubMed: 15795750]
19. Oh KJ, Park J, Lee SY, Hwang I, Kim JB, et al. Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. *Am J Physiol Endocrinol Metab*. 2011

20. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009; 302(16):1765–1773. [PubMed: 19861668]
21. Lipkovich I, Citrome L, Perlis R, Deberdt W, Houston J, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol*. 2006; 26(3):316–320. [PubMed: 16702898]
22. Lieberman DZ, Goodwin FK. Use of olanzapine in the treatment of bipolar I disorder. *Expert Rev Neurother*. 2004; 4(5):759–767. [PubMed: 15853503]
23. Fulton B, Goa KL. Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. *Drugs*. 1997; 53(2):281–298. [PubMed: 9028746]
24. Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? *J Clin Psychopharmacol*. 1999; 19(4):316–321. [PubMed: 10440458]
25. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry*. 1999; 60(11):783–791. [PubMed: 10584769]
26. Allison D, Mentore J, Heo M, Chandler L, Cappelleri JC, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999; 156:1686–1696. [PubMed: 10553730]
27. Meyer J, Nasrallah H, McEvoy J, Goff D, Davis S, et al. The clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial: Clinical comparison of subgroups with and without the metabolic syndrome. *Schizophrenia Res*. 2005; 80:9–18.
28. Parsons B, Allison DB, Loebel A, Williams K, Giller E, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. *Schizophr Res*. 2009; 110(1–3):103–110. [PubMed: 19321312]
29. Fountaine RJ, Taylor AE, Mancuso JP, Greenway FL, Byerley LO, et al. Increased food intake and energy expenditure following administration of olanzapine to healthy men. *Obesity (Silver Spring)*. 2010; 18(8):1646–1651. [PubMed: 20134408]
30. Blouin M, Tremblay A, Jalbert ME, Venables H, Bouchard RH, et al. Adiposity and eating behaviors in patients under second generation antipsychotics. *Obesity (Silver Spring)*. 2008; 16(8):1780–1787. [PubMed: 18535555]
31. Roerig JL, Mitchell JE, de Zwaan M, Crosby RD, Gosnell BA, et al. A comparison of the effects of olanzapine and risperidone versus placebo on eating behaviors. *J Clin Psychopharmacol*. 2005; 25(5):413–418. [PubMed: 16160615]
32. Kluge M, Schuld A, Himmerich H, Dalal M, Schacht A, et al. Clozapine and olanzapine are associated with food craving and binge eating: results from a randomized double-blind study. *J Clin Psychopharmacol*. 2007; 27(6):662–666. [PubMed: 18004133]
33. Case M, Treuer T, Karagianis J, Hoffmann VP. The potential role of appetite in predicting weight changes during treatment with olanzapine. *BMC Psychiatry*. 2010; 10:72. [PubMed: 20840778]
34. Stunkard AJ, Messick S. The three factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res*. 1985; 29:71–83. [PubMed: 3981480]
35. Stauffer VL, Lipkovich I, Hoffmann VP, Heinloth AN, McGregor HS, Kinon BJ. Predictors and correlates for weight changes in patients co-treated with olanzapine and weight mitigating agents: a post-hoc analysis. *BMC Psychiatry*. 2009; 9:12. [PubMed: 19327167]
36. Pouzet B, Mow T, Kreilgaard M, Velschow S. Chronic treatment with antipsychotics in rats as a model for antipsychotic-induced weight gain in human. *Pharmacol Biochem Behav*. 2003; 75(1):133–140. [PubMed: 12759121]
37. Dwyer DS, Donohoe D. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. *Pharmacol Biochem Behav*. 2003; 75(2):255–260. [PubMed: 12873613]
38. Zarate JM, Boksa P, Baptista T, Joobor R. Effects of clozapine on behavioral and metabolic traits relevant for schizophrenia in two mouse strains. *Psychopharmacology (Berl)*. 2004; 171(2):162–172. [PubMed: 14615871]

39. Kaur G, Kulkarni SK. Studies on modulation of feeding behavior by atypical antipsychotics in female mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002; 26(2):277–285. [PubMed: 11817504]
40. Coccurello R, Caprioli A, Ghirardi O, Conti R, Ciani B, 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(4):561–571. [PubMed: 16758241]
41. 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(4):693–702. [PubMed: 19052729]
42. Cooper GD, Pickavance LC, Wilding JP, Harrold JA, Halford JC, Goudie AJ. Effects of olanzapine in male rats: enhanced adiposity in the absence of hyperphagia, weight gain or metabolic abnormalities. *J Psychopharmacol*. 2007; 21(4):405–413. [PubMed: 17050655]
43. Cooper GD, Harrold JA, Halford JC, Goudie AJ. Chronic clozapine treatment in female rats does not induce weight gain or metabolic abnormalities but enhances adiposity: implications for animal models of antipsychotic-induced weight gain. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32(2):428–436. [PubMed: 17933447]
44. van der Zwaal EM, Luijendijk MC, Adan RA, La Fleur SE. Olanzapine-induced weight gain: chronic infusion using osmotic minipumps does not result in stable plasma levels due to degradation of olanzapine in solution. *Eur J Pharmacol*. 2008; 585(1):130–136. [PubMed: 18378227]
45. Ashim S, Warrington S, Anderson IM. Management of diabetes mellitus occurring during treatment with olanzapine: report of six cases and clinical implications. *J Psychopharmacol*. 2004; 18(1):128–132. [PubMed: 15107197]
46. 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(5 Suppl 1):S7–14. [PubMed: 15356415]
47. Cohen D. Atypical antipsychotics and new onset diabetes mellitus. An overview of the literature. *Pharmacopsychiatry*. 2004; 37(1):1–11. [PubMed: 14750042]
48. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs*. 2004; 64(7):701–723. [PubMed: 15025545]
49. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2010; 123(2–3):225–233. [PubMed: 20692814]
50. L'Italiani GJ, Casey DE, Kan HJ, Carson WH, Marcus RN. Comparison of metabolic syndrome incidence among schizophrenia patients treated with aripiprazole versus olanzapine or placebo. *J Clin Psychiatry*. 2007; 68(10):1510–1516. [PubMed: 17960964]
51. Scheen AJ, De Hert MA. Abnormal glucose metabolism in patients treated with antipsychotics. *Diabetes Metab*. 2007; 33(3):169–175. [PubMed: 17412628]
52. van Winkel R, De Hert M, Wampers M, Van Eyck D, Hanssens L, 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(3):472–479. [PubMed: 18348593]
53. Wu RR, Zhao JP, Liu ZN, Zhai JG, Guo XF, et al. Effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia. *Psychopharmacology (Berl)*. 2006; 186(4):572–578. [PubMed: 16601995]
54. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003; 160(2):290–296. [PubMed: 12562575]
55. Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia - a randomized double-blind controlled, short-term prospective study. *Schizophr Res*. 2008; 101(1–3):266–272. [PubMed: 18262771]

56. Newcomer J. Abnormalities of glucose metabolism associated with atypical antipsychotic drugs. *J Clin Psychiatry*. 2004; 65(Suppl 18):36–46. [PubMed: 15600383]
57. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003; 160(2):290–296. [PubMed: 12562575]
58. Ebenbichler C, Laimer M, Eder U, Mangweth B, Weiss E, et al. Olanzapine induces insulin resistance: results from a prospective study. *J Clin Psychiatry*. 2003; 64(12):1436–1439. [PubMed: 14728104]
59. Henderson D, Cagliero E, Copeland P, Borba C, Evins E, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry*. 2005; 62(1):19–28. [PubMed: 15630069]
60. Haupt DW, Fahnestock PA, Flavin KA, Schweiger JA, Stevens A, et al. Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. *Neuropsychopharmacology*. 2007; 32(12):2561–2569. [PubMed: 17375138]
61. van Nimwegen LJ, Storosum JG, Blumer RM, Allick G, Venema HW, et al. Hepatic insulin resistance in antipsychotic naive schizophrenic patients: stable isotope studies of glucose metabolism. *J Clin Endocrinol metab*. 2008; 93(2):572–577. [PubMed: 18029467]
62. Kinon B, Basson B, Gilmore J, Tollefson G. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry*. 2001; 62(2):92–100. [PubMed: 11247108]
63. Baptista T, Kin NMKNY, Beaulieu S, De Baptista EA. Obesity and related metabolic abnormalities during antipsychotic drug administration: Mechanisms, management and research perspectives. *Pharmacopsychiatry*. 2002; 35:205–219. [PubMed: 12518268]
64. Sowell M, Mukhopadhyay N, Cavazzoni P, Shankar S, Steinberg H, et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo. *J Clin Endocrinol Metab*. 2002; 87(6):2918–2923. [PubMed: 12050274]
65. Sowell M, Mukhopadhyay N, Cavazzoni P, Carlson C, Mudaliar S, et al. Evaluation of insulin sensitivity in healthy volunteers treated with olanzapine, risperidone, or placebo: a prospective, randomized study using the two-step hyperinsulinemic, euglycemic clamp. *J Clin Endocrinol Metab*. 2003; 88(12):5875–5880. [PubMed: 14671184]
66. Hardy TA, Meyers AL, Yu J, Shankar SS, Steinberg HO, Porsken NK. Acute insulin response and beta-cell compensation in normal subjects treated with olanzapine or risperidone for 2 weeks. *Diabetes Care*. 2007; 30(1):157–158. [PubMed: 17192353]
67. Sacher J, Mossaheb N, Spindelegger C, Klein N, Geiss-Granadia T, et al. Effects of olanzapine and ziprasidone on glucose tolerance in healthy volunteers. *Neuropsychopharmacology*. 2008; 33(7):1633–1641. [PubMed: 17712347]
68. Vidarsdottir S, de Leeuw van Weenen JE, Frolich M, Roelfsema F, Romijn JA, Pijl H. Effects of olanzapine and haloperidol on the metabolic status of healthy men. *J Clin Endocrinol metab*. 2010; 95(1):118–125. [PubMed: 19906788]
69. Chiu C, Chen K, Liu H, Lu ML. The early effect of olanzapine and risperidone on insulin secretion in atypical-naive schizophrenic patients. *J Clin Psychopharmacol*. 2006; 26(5):504–507. [PubMed: 16974193]
70. 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(5):425–433. [PubMed: 12019668]
71. Rettenbacher MA, Ebenbichler C, Hofer A, Kemmler G, Baumgartner S, et al. Early changes of plasma lipids during treatment with atypical antipsychotics. *Int Clin Psychopharmacol*. 2006; 21(6):369–372. [PubMed: 17012984]
72. Koro CE, Meyer JM. Atypical antipsychotic therapy and hyperlipidemia: a review. *Essent Psychopharmacol*. 2005; 6(3):148–157. [PubMed: 15869022]
73. Kaddurah-Daouk R, McEvoy J, Baillie RA, Lee D, Yao JK, et al. Metabolomic mapping of atypical antipsychotic effects in schizophrenia. *Mol Psychiatry*. 2007; 12(10):934–945. [PubMed: 17440431]

74. Vik-Mo AO, Birkenaes AB, Ferno J, Jonsdottir H, Andreassen OA, Steen VM. Increased expression of lipid biosynthesis genes in peripheral blood cells of olanzapine-treated patients. *Int J Neuropsychopharmacol*. 2008; 11(5):679–684. [PubMed: 18241359]
75. Robinson K, Yacoub S, Buse M. At therapeutic concentrations, olanzapine does not affect basal or insulin-stimulated glucose transport in 3T3-L1 adipocytes. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30:93–98. [PubMed: 16019120]
76. Chintoh AF, Mann SW, Lam L, Lam C, Cohn TA, et al. Insulin resistance and decreased glucose-stimulated insulin secretion after acute olanzapine administration. *J Clin Psychopharmacol*. 2008; 28(5):494–499. [PubMed: 18794643]
77. Houseknecht K, Robertson AS, Zavadoski W, Gibbs EM, Johnson DE, Rollema H. Acute effects of atypical antipsychotics on whole body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology*. 2006; Online:1–29.
78. Chintoh AF, Mann SW, Lam TK, Giacca A, Remington G. Insulin resistance following continuous, chronic olanzapine treatment: an animal model. *Schizophr Res*. 2008; 104(1–3):23–30. [PubMed: 18675538]
79. Albaugh VL, Vary TC, Ilkayeva O, Wenner BR, Maresca KP, et al. Atypical Antipsychotics Rapidly and Inappropriately Switch Peripheral Fuel Utilization to Lipids, Impairing Metabolic Flexibility in Rodents. *Schizophr Bull*. 2010
80. Martins PJ, Haas M, Obici S. Central nervous system delivery of the antipsychotic olanzapine induces hepatic insulin resistance. *Diabetes*. 2010; 59(10):2418–2425. [PubMed: 20682682]
81. Markowitz J, Brown C, Moore T. Atypical antipsychotics. Part I: Pharmacology, pharmacokinetics, and efficacy. *Ann Pharmacother*. 1999; 33(1):73–85. Review. [PubMed: 9972387]
82. Kroeze W, Hufeisen S, Popadak B, Renock S, Steinberg S, et al. H1-Histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology*. 2003; 28:519–526. [PubMed: 12629531]
83. Bymaster F, Felder C, Tzavara E, Nomikos G, Calligaro D, Mckinzie D. Muscarinic mechanisms of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; 27(7):1125–1143. Review. [PubMed: 14642972]
84. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry*. 2008; 13(1):27–35. [PubMed: 17848919]
85. 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(9):3456–3459. [PubMed: 17360666]
86. Starrenburg FC, Bogers JP. How can antipsychotics cause Diabetes Mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. *Eur Psychiatry*. 2009; 24(3):164–170. [PubMed: 19285836]
87. Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatr Scand*. 2009; 119(3):171–179. [PubMed: 19178394]
88. Gao Q, Horvath TL. Neurobiology of feeding and energy expenditure. *Annu Rev Neurosci*. 2007; 30:367–398. [PubMed: 17506645]
89. Wynne K, Stanley S, McGowan B, Bloom S. Appetite control. *J Endocrinol*. 2005; 184(2):291–318. [PubMed: 15684339]
90. Sandoval D, Cota D, Seeley RJ. The integrative role of CNS fuel-sensing mechanisms in energy balance and glucose regulation. *Annu Rev Physiol*. 2008; 70:513–535. [PubMed: 17988209]
91. Berthoud HR, Morrison C. The brain, appetite, and obesity. *Annu Rev Psychol*. 2008; 59:55–92. [PubMed: 18154499]
92. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr*. 2009; 139(3):629–632. [PubMed: 19176746]
93. Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, et al. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron*. 2006; 51(6):801–810. [PubMed: 16982424]
94. Macht M, Mueller J. Immediate effects of chocolate on experimentally induced mood states. *Appetite*. 2007; 49(3):667–674. [PubMed: 17597253]

95. Pandit R, de Jong JW, Vanderschuren LJ, Adan RA. Neurobiology of overeating and obesity: The role of melanocortins and beyond. *Eur J Pharmacol.* 2011; 660(1):28–42. [PubMed: 21295024]
96. Nirenberg MJ, Waters C. Compulsive eating and weight gain related to dopamine agonist use. *Mov Disord.* 2006; 21(4):524–529. [PubMed: 16261618]
97. Dagher A, Robbins TW. Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron.* 2009; 61(4):502–510. [PubMed: 19249271]
98. Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. *Sleep.* 2010; 33(1):81–87. [PubMed: 20120624]
99. Cannon CM, Palmiter RD. Reward without dopamine. *J Neurosci.* 2003; 23(34):10827–10831. [PubMed: 14645475]
100. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. *Physiol Rev.* 2008; 88(3):1183–1241. [PubMed: 18626069]
101. Martinez-Mir MI, Pollard H, Moreau J, Arrang JM, Ruat M, et al. Three histamine receptors (H1, H2 and H3) visualized in the brain of human and non-human primates. *Brain Res.* 1990; 526(2):322–327. [PubMed: 1979518]
102. Nguyen T, Shapiro DA, George SR, Setola V, Lee DK, et al. Discovery of a novel member of the histamine receptor family. *Mol Pharmacol.* 2001; 59(3):427–433. [PubMed: 11179435]
103. Panula P, Yang HY, Costa E. Histamine-containing neurons in the rat hypothalamus. *Proc Natl Acad Sci U S A.* 1984; 81(8):2572–2576. [PubMed: 6371818]
104. 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(3):421–441. [PubMed: 20638439]
105. Yoshimatsu H. Hypothalamic neuronal histamine regulates body weight through the modulation of diurnal feeding rhythm. *Nutrition.* 2008; 24(9):827–831. [PubMed: 18725079]
106. 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(1–2):279–288. [PubMed: 9630675]
107. Masaki T, Chiba S, Yasuda T, Noguchi H, Kakuma T, et al. Involvement of hypothalamic histamine H1 receptor in the regulation of feeding rhythm and obesity. *Diabetes.* 2004; 53(9):2250–2260. [PubMed: 15331534]
108. Orthen-Gambill N. Antihistaminic drugs increase feeding, while histidine suppresses feeding in rats. *Pharmacol Biochem Behav.* 1988; 31(1):81–86. [PubMed: 2908065]
109. Sakata T, Ookuma K, Fukagawa K, Fujimoto K, Yoshimatsu H, et al. Blockade of the histamine H1-receptor in the rat ventromedial hypothalamus and feeding elicitation. *Brain Res.* 1988; 441(1–2):403–407. [PubMed: 3359243]
110. Masaki T, Yoshimatsu H. The hypothalamic H1 receptor: a novel therapeutic target for disrupting diurnal feeding rhythm and obesity. *Trends Pharmacol Sci.* 2006; 27(5):279–284. [PubMed: 16584790]
111. Tsuda K, Yoshimatsu H, Nijima A, Chiba S, Okeda T, Sakata T. Hypothalamic histamine neurons activate lipolysis in rat adipose tissue. *Exp Biol Med (Maywood).* 2002; 227(3):208–213. [PubMed: 11856820]
112. Masaki T, Yoshimatsu H, Chiba S, Watanabe T, Sakata T. Central infusion of histamine reduces fat accumulation and upregulates UCP family in leptin-resistant obese mice. *Diabetes.* 2001; 50(2):376–384. [PubMed: 11272150]
113. Zawulich WS, Zawulich KC, Rasmussen H. Cholinergic agonists prime the B-cell to glucose stimulation. *Endocrinology.* 1989; 125:2400–2406. [PubMed: 2676484]
114. Zawulich WS, Zawulich KC, Shulman GI, Rossetti L. Chronic in vivo hyperglycemia impairs phosphoinositide hydrolysis and insulin release in isolated perfused rat islets. *Endocrinology.* 1990; 126:253–260.
115. Zawulich W, Zawulich K, Kelley G. Time-dependent effects of cholinergic stimulation on beta cell responsiveness. *Pflugers Arch.* 1996; 432(4):589–596. [PubMed: 8764958]

116. Doliba NM, Qin W, Vatamaniuk MZ, Buettger CW, Collins HW, et al. Cholinergic regulation of fuel-induced hormone secretion and respiration of SUR1^{-/-} mouse islets. *Am J Physiol Endocrinol Metab.* 2006; 291(3):E525–E535. [PubMed: 16638820]
117. Doliba NM, Qin W, Vatamaniuk MZ, Li C, Zelent D, et al. Restitution of defective glucose-stimulated insulin release of sulfonylurea type 1 receptor knockout mice by acetylcholine. *Am J Physiol Endocrinol Metab.* 2004; 286(5):E834–E843. [PubMed: 14736703]
118. 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(3):E475–E485. [PubMed: 20606076]
119. Johnson DE, Yamazaki H, Ward KM, Schmidt AW, Lebel WS, et al. Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perfused rat islets: role of muscarinic antagonism in antipsychotic-induced diabetes and hyperglycemia. *Diabetes.* 2005; 54(5):1552–1558. [PubMed: 15855345]
120. Teff KL, Mattes RD, Engelman K. Cephalic phase insulin release in normal weight males: verification and reliability. *Am J Physiol.* 1991; 261(24):E430–E436. [PubMed: 1928335]
121. Teff, KL. Cephalic Phase Insulin Release in Humans: mechanism and function. In: Fernstrom, JD.; Miller, GD., editors. *Appetite and Body Weight Regulation: sugar, fat and macronutrient substitutes.* Boca Raton: CRC Press; 1994. p. 37-50.
122. Teff KL, Engelman K. Oral sensory stimulation improves glucose tolerance: effects on post-prandial glucose, insulin, C-peptide and glucagon. *Am J Physiol.* 1996; 270:R1371–R1379. [PubMed: 8764306]
123. Teff KL, Townsend RR. Prolonged mild hyperglycemia induces vagally mediated compensatory increase in C-peptide secretion in humans. *J Clin Endo Metab.* 2004; 89:5606–5613.
124. Henderson JR, Jeffreys DB, Jones RH, Stanley D. The effect of atropine on the insulin release caused by oral and intravenous glucose in human subjects. *Acta Endocrinologica.* 1976; 83:772–780. [PubMed: 1036650]
125. Shimazu T. Regulation of glycogen metabolism in liver by the autonomic nervous system vs activation of glycogen synthetase by vagal stimulation. *Biochimica et Biophysica Acta.* 1971; 252:28–38. [PubMed: 5141826]
126. Shimazu T. Glycogen synthetase activity in liver: regulation by the autonomic nerves. *Science.* 1967; 156:1256–1257. [PubMed: 6025550]
127. Shiota M, Jackson P, Galassetti P, Scott M, Neal DW, Cherrington AD. Combined intraportal infusion of acetylcholine and adrenergic blockers augments net hepatic glucose uptake. *Am J Physiol Endocrinol Metab.* 2000; 278(3):E544–E552. [PubMed: 10710510]
128. Stumpel F, Jungermann K. Sensing by intrahepatic muscarinic nerves of a portal-arterial glucose concentration gradient as a signal for insulin-dependent glucose uptake in the perfused rat liver. *FEBS lett.* 1997; 406:119–122. [PubMed: 9109399]
129. Chap Z, Ishida T, Chou J, Lewis R, Hartley C, et al. Effects of Atropine and gastric inhibitory polypeptide on hepatic glucose uptake and insulin extraction in conscious dogs. *J Clin Invest.* 1985; 76:1174–1181. [PubMed: 3900134]
130. Pocai A, Obici S, Schwartz GJ, Rossetti L. A brain-liver circuit regulates glucose homeostasis. *Cell Metabolism.* 2005; 1:53–61. [PubMed: 16054044]
131. Boyle JG, Liggett SB, Shah SD, Cryer PE. Direct muscarinic cholinergic inhibition of hepatic glucose production in humans. *J Clin Invest.* 1988; 82:445–449. [PubMed: 2900252]
132. Teff KL, Rickels MR, Grudziak J, Rickels K. Short-term administration of olanzapine induces insulin resistance in healthy subjects, independent of weight gain. *Endocrine Reviews.* 2010; 31(3):S2541.
133. Vidarsdottir S, Roelfsema F, Streefland T, Holst JJ, Rehfeld JF, Pijl H. Short-term treatment with olanzapine does not modulate gut hormone secretion: olanzapine disintegrating versus standard tablets. *Eur J Endocrinol.* 2010; 162(1):75–83. [PubMed: 19779025]
134. Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, et al. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron.* 2006; 51(6):801–810. [PubMed: 16982424]

135. Davis C, Patte K, Levitan R, Reid C, Tweed S, Curtis C. From motivation to behaviour: A model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. *Appetite*. 2006
136. Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am J Physiol*. 2003; 284(4):R882–R892.
137. Blundell J. Serotonin and Appetite. *Neuropharmacology*. 1984; 23(12B):1537–1551. [PubMed: 6152027]
138. Carrub M, Mantegazza P, Memo M, Missale C, Spano P. Peripheral and central mechanisms of action of serotonergic anorectic drugs. *Appetite*. 1986; 7:105–113. [PubMed: 3740835]
139. Piji H, Koppeschaar H, Willekens F, Veldhuia H, Meinders A. Effect of serotonin re-uptake inhibition by fluoxetine on body weight and spontaneous food choice in obesity. *Inter J of Obesity*. 1991; 15:237–242.

Research Highlights

- The atypical antipsychotics, particularly olanzapine and clozapine, are associated with weight gain and an increased incidence of metabolic disease
- Antipsychotic-induced glucose and lipid abnormalities may be drug-dependent and independent of weight gain and psychiatric disease
- Blockade of histamine receptors may promote food intake and changes in vagal mediation of insulin secretion and hepatic glucose production may contribute to impaired glucose tolerance

Figure 1.

Role of the Vagus Nerve in Glucose Homeostasis.

Vagal afferents relay sensory information from peripheral tissues such as the stomach and intestine to the brain which may initiate vagal efferent activation. Food ingestion is required to activate pre-ganglionic vagal efferent fibers terminating on post-ganglionic intrapancreatic neurons which release acetylcholine. Acetylcholine enhances insulin release to glucose and other nutrients. Physiological studies suggest that the vagal efferents may inhibit hepatic glucose production although the site of hepatic innervation has not been identified. Muscarinic receptors have been shown to mediate vagally-mediated insulin secretion. Hepatic responses may be mediated by either nicotinic or muscarinic receptors.

Figure 2.

Acute Effects of Atypical Antipsychotic Administration to Humans

Initial administration of some atypical antipsychotics increases food intake and decreases the rewarding experience of food ingestion potentially through blockade of histaminergic, dopaminergic and serotonergic receptors in the central nervous system. The increase in food intake results in repetitive stimulation of vagal efferent activity, eliciting cephalic phase insulin release and post-prandial hyperinsulinemia which overcomes peripheral muscarinic blockade by the AAPs. The post-prandial hyperinsulinemia would then promote nutrient storage and weight gain, exacerbating the effects of increased food intake.

Figure 3.

Chronic Effects of Atypical Antipsychotic Administration to Humans

Chronic administration of the AAPs to individuals who already have increased body adiposity and hyperlipidemia will result in a decrease in vagally-mediated responses, possibly due to blockade of muscarinic receptors by elevations in circulating free fatty acids (FFAs). The decrease in acetylcholine-mediated responses will result in impaired post-prandial insulin release and lack of suppression of endogenous glucose production, leading to impaired glucose tolerance. Some individuals may ultimately develop type 2 diabetes mellitus.

Table 1

Atypical antipsychotics and their receptor subtype affinities

Receptor	Aripiprazole	Clozapine	Olanzapine	Risperidone	Ziprasidone
M ₃	pK _i <6	7<pK _i <8	7<pK _i <8	pK _i <6	pK _i <6
H ₁	7<pK _i <8	8<pK _i <9	8<pK _i <9	7<pK _i <8	6<pK _i <7
D ₂	pK _i >9	6<pK _i <7	7<pK _i <8	8<pK _i <9	8<pK _i <9
5-HT _{1A}	8<pK _i <9	6<pK _i <7	pK _i <6	6<pK _i <7	7<pK _i <8
α-2A	7<pK _i <8	6<pK _i <7	6<pK _i <7	6<pK _i <7	6<pK _i <7

Abbreviations: M, muscarinic receptor; H, histamine receptor; D, dopamine receptor; 5-HT, serotonin receptor; α, α-adrenoreceptor;
Adapted from Nasrallah (2008).