Illuminating the molecular basis for some antipsychotic drug-induced metabolic burden

Herbert Y. Meltzer*

Departments of Psychiatry and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37212

The atypical antipsychotic drugs (AAPDs), especially olanzapine (OLZ), quetiapine, and risperidone, are the most widely used treatments for schizophrenia (SCH) and other psychotic illnesses, having, in the last decade, displaced the typical antipsychotic drugs (TAPDs), such as haloperidol, chlorpromazine, and others of that class. However, as a group, the AAPDs are currently receiving an unprecedented level of scrutiny in the scientific literature and public forums because some recent well publicized studies have not confirmed some key aspects of their reputed advantages for efficacy, cost-effectiveness, and tolerability (1, 2). The propensity of OLZ, once the most widely used AAPD, to cause weight gain, glucose dysregulation, lipid increases, especially triglycerides, and diabetes mellitus (DM), including diabetic ketoacidosis, has been linked to the very high rate of ischemic cardiovascular disease and a 20- to 25-year- shorter life span of people with SCH in the United States. Clozapine (CLZ), which is much less widely used than OLZ because of its risk for agranulocytosis, produces weight gain similar to that of OLZ. In this issue of PNAS, Kim *et al.* (3) show for the first time that these two AAPDs stimulate hypothalamic AMP-protein kinase (AMPK) through histamine$_1$ receptor (H1R) antagonism, a likely molecular basis for their metabolic liability. They demonstrate that activation of hypothalamic AMPK was abolished in H1R knockout mice. Other AAPDs that produce less weight gain than CLZ and OLZ were less effective at activating AMPK in intact animals.

AMPK: A Histamine$_1$ Receptor-Mediated Metabolic Regulator

Kim *et al.* also show that CLZ treatment blocked the ability of the anorexigenic peptide, leptin, as well as insulin, to reduce hypothalamic phosphorylated AMPK, a clear demonstration of central insulin resistance, which is believed to be the core pathophysiology of the metabolic syndrome, a well established cluster of symptoms and signs associated with increased risk for ischemic cardiovascular disease (4). Activation of AMPK functions as a fuel sensor and has been shown to stimulate ATP-forming (catabolic) pathways and inhibit ATP-using (anabolic) pathways at the cellular level, which also serves to regulate energy balance at the whole body level (5). It may mediate the action of antidiabetic drugs such as metformin and peroxisome proliferator-activated receptor γ agonists (5). The findings of Kim *et al.* are also consistent with previous research from Masaki and Yoshimatsu (6), who showed that H1R knockout mice gradually developed late-onset obesity, which is caused by hyperphagia, and that younger nonobese knockout mice exhibited impaired leptin responsiveness and disruption of the diurnal rhythm of feeding. Importantly, central administration of an H1R agonist affected feeding behavior, body weight, and c-*fos*-like immunoreactivity in the hypothalamus, suggesting that the H1R may be a novel therapeutic target for the treatment of obesity (6).

Typical vs. Atypical Antipsychotic Drugs

Before further discussion of the results of Kim *et al.* (3), it is important to understand current concepts of the differences between TAPDs and AAPDs. AAPDs are distinguished from the TAPDs by their greatly diminished liability to cause extrapyramidal (parkinsonian) side effects. At least three AAPDs, CLZ, quetiapine, and melperone, but no TAPDs, have been found to be tolerable to patients with Parkinson's disease who develop L-dopa-induced psychosis (7). Interest in the AAPDs was further stimulated by the evidence from the prototypical AAPD, CLZ, that it was more effective for treating psychosis in patients with SCH who had failed to respond to TAPDs and had advantages for negative symptoms, suicidality, and cognition (8, 9). However, these advantages have been challenged in two recent government-sponsored clinical trials (1, 2) that failed to demonstrate the expected efficacy advantages for the AAPDs, other than CLZ, over TAPDs. The discrepancies between these results and the preponderance of evidence supporting the view that the AAPDs have genuine advantages over the TAPDs requires extensive further study (International Psychopharmacology Algorithm Project, www.ipap.org).

Metabolic Side Effects of Antipsychotic Drugs

Most AAPDs, including aripiprazole, paliperidone, quetiapine, risperidone, and ziprasidone, produce, on average, little or no weight gain (1, 11, 12). It should be noted that some TAPDs produce weight gain that may be comparable with CLZ and OLZ (11). However, since the introduction of the AAPDs, there has been a 0.7% per year higher rate of increase in type II DM in patients with SCH compared with the general population, which itself has experienced a steadily increasing rate of DM (13). For sure, some of the increases in weight and DM in patients with SCH during the last decade are caused, in part, by diet and exercise changes that have caused the entire population to do the same. However, it is clear that OLZ and CLZ produce rapid or delayed, but sustained, weight gain that is drug-related (11, 12, 14). Together, all of these factors have contributed to the large increase in morbidity and mortality caused by DM and ischemic cardiovascular disease in the seriously mentally ill population. Thus, identification of the H1R as an important target for minimizing weight gain raises the possibility of using this information to guide therapeutic attempts to alleviate the metabolic side effects and develop novel AAPDs, lacking H1R antagonism, that should cause fewer metabolic side effects (15).

There is other evidence that blockade of the H1R may be the major reason for weight gain of at least some AAPDs, some of which points toward other pharmacologic bases for weight gain produced by other APDs, as well as CLZ and OLZ. Thus, Kroeze *et al.* (16) correlated the weight gain reported for 17 antipsychotic drugs (11) with their affinities for 12 G protein-coupled receptors and found that the most important predictor was H1R affinity. Further evidence regarding histamine and weight gain is that betahistine, an H1R agonist/H3 antagonist, attenuated the weight gain due to OLZ in first episode patients with SCH (17).

In support of the relationship between AMPK and OLZ-induced weight gain, Dwyer *et al.* (17), in their review of the mechanistic connections between glucose/lipid distrubances and weight gain induced

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*E-mail: herbert.meltzer@vanderbilt.edu.

by antipsychotic drugs, mentioned, but did not present the actual data then or since, their finding that both 5-aminoimidazole-4-carboxamide riboside, which activates AMPK in the hypothalamus, and OLZ activated AMPK in PC12 cells. They then suggested that the ability of OLZ to activate glucose-sensing neurons in the hypothalamus could increase appetite, weight gain, and mobilization of glucose from peripheral stores of glycogen and that AMPK activation was a likely possibility to explain both glucose and lipid abnormalities, as well as weight gain, attributable to OLZ. Kim *et al.* (3) have now provided the first experimental evidence to support this hypothesis.

Multiple Factors Contribute to Antipsychotic-Drug-Induced Metabolic Side Effects

There is marked variability in weight gain among patients treated with CLZ and OLZ, which could be caused by differences in H1R structure or expression, as well as a variety of other risk factors. Some individuals treated with other AAPDs that have no effect on AMPK, e.g., risperidone and aripiprazole (3), are associated with marked weight gain in a small proportion of patients. In addition to HIR affinity, and after adjustment for D_2 receptor affinity, which, along with 5-HT_{2A} receptor antagonism plays a key role in their mechanism of action (19), eight other G protein-coupled receptors were found to correlate with weight gain produced by 17 APDs. In rank order, these were affinities for 5-HT_{2C}, α_{1A}, 5-HT_6, α_{2A}, α_{2B}, M_3, 5-HT_{2A}, and α_{2B} receptors (16). Much additional evidence supports the role of 5-HT_{2C} receptor antagonism as the most important (16). Further research on the molecular mechanisms by which these receptors mediate metabolic side effects is needed. They may well act via AMPK or downstream from it. AAPDs have been suggested to cause appetite stimulation and weight gain because of a variety of other factors, including glucose transporters, cytochrome P450 enzymes, aryl hydrocarbon, receptors, K^+ channels, and glucose-sensing systems (18). It is highly likely that pharmacogenomic studies will lead to clinically useful predictors of tolerability and efficacy to guide choice of atypicals or their successors.

In addition to weight gain, CLZ and OLZ produce marked increases in lipids, especially triglycerides, and other signs of insulin resistance (12, 20). This finding would suggest that the activation of AMPK should also contribute to the increase in lipids produced by CLZ and OLZ. However, there is inconsistent evidence that the increase in lipids produced by CLZ or OLZ is significantly correlated with weight gain. Further, H1R knockout mice show no significant increases in the levels of serum triglycerides, free fatty acid of glucose (6). Other mechanisms as noted above may be more responsible for the lipid-raising effects of the AAPDs.

Relationship Between Weight Gain and Clinical Response

Kim *et al.* (3) found that CLZ had no effect on AMPK activation in mouse cortex or cerebellum, but they did not report on its effects on limbic system AMPK activity, which would be most relevant to its ability to improve psychopathology. However, there is extensive evidence demonstrating a correlation between improvement in psychopathology with CLZ and OLZ and weight gain (21–23). Further study to determine whether there is a common neurochemical mechanism linking clinical response and weight gain is indicated. CLZ and OLZ are the two antipsychotic drugs for which there is the best evidence that they are effective in patients who fail to respond to other antipsychotic drugs. It could be that a relationship between 5-HT_{2C} affinities, or some other pharmacologic characteristic of the AAPDs, which is the basis for the ability of weight gain to predict improvement in psychotic symptoms.

A number of key issues remain to be investigated. Metformin and thiazolidinedione, both extensively used to treat type II DM, like OLZ and CLZ, have also been reported to increase skeletal muscle and hepatocyte AMPK activity (24). Recently, the effectiveness of metformin was shown to attenuate further weight gain and decrease a surrogate marker of insulin sensitivity in 39 adolescents whose weight had increased by >10% during <1 year of OLZ, risperidone, or quetiapine treatment (25). Regardless of whether these clinical results are replicable, additional research is needed to further study the importance of the effects of metformin and OLZ on hypothalamic AMPK activation with regard to type II DM and metabolic burden and to clarify the interactions between these two agents.

It is interesting to note that chlorpromazine, the first antipsychotic drug of the modern era, was originally developed in the search for a better antihistamine (26). We have now come full circle. With the accumulating evidence for the role of HIR antagonism in causing the metabolic effects of OLZ and CLZ, it is clearly of interest to develop agents that minimally affect H1R activity or specific agents that reverse the effects of CLZ and OLZ on H1R directly or can otherwise attenuate their ability to activate AMPK. The search for a more effective H1R agonist should now be a high priority, not only to counteract the adverse metabolic effects of CLZ and OLZ but also to inhibit the appetite for all of those who need assistance in reducing caloric intake (10).

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