Unraveling the Mechanisms Underlying Olanzapine-Induced Insulin Resistance

Nigel Irwin[1] and Victor Alan Gault[2]

Atypical antipsychotics (AAPs) are widely prescribed agents for treatment of schizophrenia and other related psychiatric disorders. Although AAPs were a major development in psychopharmacology, so-called second-generation agents such as olanzapine have exhibited unexpected and unfavorable metabolic side effects. These side effects include weight gain, glucose intolerance, and insulin resistance, all of which increase the likelihood of developing diabetes and cardiovascular disease (1). Nonetheless, how these adverse metabolic effects arise following AAP treatment remains unclear. A key question is whether AAP-associated metabolic impairments are because of the psychiatric illness itself or if they are merely secondary to weight gain.

In this issue, Teff et al. (2) examine the direct effects of second-generation AAPs on insulin resistance and postprandial gut hormone profiles following a mixed meal. The antipsychotic drugs used in these experiments—olanzapine and aripiprazole—were administered to healthy volunteers for 9 consecutive days to exclude potential confounding issues associated with psychiatric disease or potential weight gain. In the clinic, olanzapine therapy tends to result in weight gain and metabolic dysregulation (3), whereas aripiprazole is considered metabolically neutral (4). Thus, Teff et al. logically hypothesized that detrimental effects on meal-related metabolism would be limited to olanzapine. Consistent with this hypothesis, the authors showed that aripiprazole had no effect on body weight, blood pressure, and circulating levels of key blood parameters over the 9-day treatment period. Aripiprazole also did not result in significant changes in postprandial metabolism following a mixed meal. In contrast, olanzapine increased fasting plasma insulin by day 9. This corresponded with postprandial hyperinsulinemia, suggesting that olanzapine had detrimental effects on insulin sensitivity. Indeed, hyperinsulinemic-euglycemic clamps supported this theory. However, aripiprazole also induced insulin resistance despite it generally being considered lacking in metabolic effects.

A unique aspect to the study by Teff et al. (2) was participant ingestion of a mixed meal that elicited both incretin responses (5) and neurally mediated insulin release (6), both of which could be critical for the metabolic effects of centrally acting drugs. Surprisingly, olanzapine administration increased postprandial glucagon-like peptide-1 (GLP-1) secretion and circulating glucagon levels. These responses were unexpected for two reasons. First, GLP-1 is believed to improve insulin sensitivity and reduce weight gain. Second, it directly inhibits glucagon release (7). The authors speculate that other unknown factors, such as glucose-dependent insulinotropic polypeptide (GIP) secretion or cholinergic vagally mediated actions, may mediate the altered postprandial metabolic profile following olanzapine administration. In this regard, it has recently been shown that biologic action of GIP can be potentiated by xenin-25, a peptide cosecreted with GIP from intestinal K cells, which is thought to indirectly activate muscarinic receptors (8). Olanzapine is a well-characterized muscarinic receptor antagonist (9). Thus, interactions between GIP and other vagal inputs could be of importance for the postprandial metabolic effects of AAPs (Fig. 1).

The new data are interesting but need to be corroborated in studies with larger sample sizes to increase power and also to be verified in psychiatric patients. A previous study has shown no effect of olanzapine on gut hormone secretion (10). The direct effect of AAPs on GIP secretion and action certainly needs to be considered. Although weight gain did not affect data interpretation, Teff et al. (2) clearly acknowledge that adiposity could be a confounding factor. In addition, the nutrient composition of the mixed meal could have important implications on GIP and GLP-1 secretion. Both incretin hormones are strongly released in response to carbohydrates, but GIP is released much more powerfully than GLP-1 in response to fat (11).

Taken together, the data illustrate that olanzapine can induce insulin resistance and postprandial hormonal dysregulation independently of weight gain. Although the regulatory mechanisms involved remain to be fully elucidated, the well-characterized weight gain following prolonged olanzapine administration would likely exacerbate these effects. Thus, interventions to inhibit weight gain in patients receiving AAP therapy may only be partially effective in preventing metabolic disease. The report by Teff et al. (2) should stimulate continued efforts aimed at resolving the direct detrimental metabolic effects of AAPs that may ultimately lead to improved treatment options for these patients.

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From the [1]School of Pharmacy and Pharmaceutical Sciences, The SAAD Centre for Pharmacy and Diabetes, University of Ulster, Coleraine, Northern Ireland, U.K.; and the [2]School of Biomedical Sciences, The SAAD Centre for Pharmacy and Diabetes, University of Ulster, Coleraine, Northern Ireland, U.K.

Corresponding author: Victor Alan Gault, va.gault@ulster.ac.uk.

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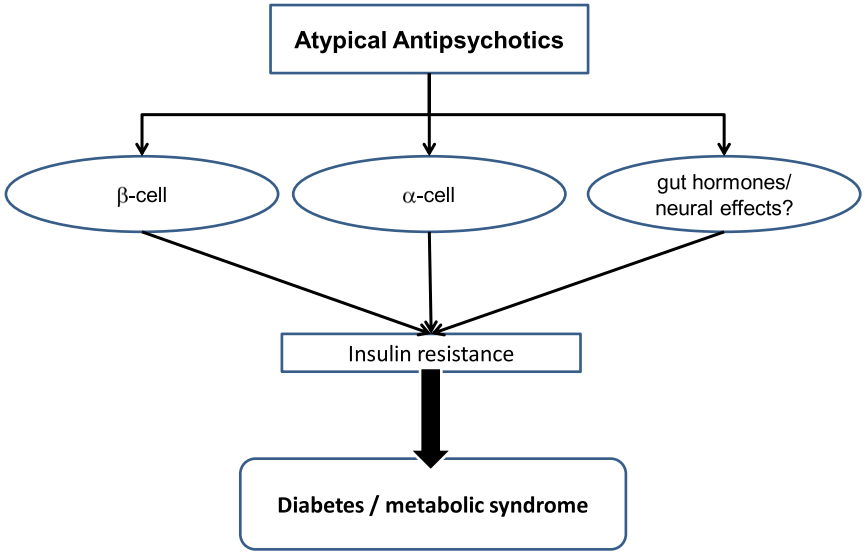

FIG. 1. Direct effects of AAPs on insulin resistance independent of weight gain. Teff et al. (2) report that olanzapine induces insulin resistance concomitant with postprandial hormonal dysregulation in healthy humans.

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