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Letter to the Editor

Atypical Antipsychotic Drugs Directly Impair Insulin Action in Adipocytes: Effects on Glucose Transport, Lipogenesis, and Antilipolysis

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Sir

We like to comment on the study of Vestri *et al* (2006) that describes a direct effect of second-generation antipsychotics (SGAs) on glucose transport, lipogenesis, and antilipolysis in 3T3-L1 adipocytes and primary cultured rat adipocytes. The authors have studied the effects of the SGAs olanzapine, clozapine, risperidone, and quetiapine and the first-generation antipsychotics (FGAs) butyrophenone and trifluperazone on their effects on several important pathways in these adipocytes. They report that the SGAs clozapine and olanzapine—which bear the highest risk of weight gain and diabetes—but not risperidone decrease the insulin-stimulated glucose transport in 3T3-L1 adipocytes and that clozapine and risperidone are the most potent substances to decrease insulin-stimulated glucose transport in primary adipocytes. Both SGAs and FGAs increased glucose oxidation rates and lipogenesis was also increased by some of these substances. Finally, lipolysis in response to isoproterenol was reduced by SGAs but not by FGAs. The authors conclude that antipsychotic drugs can differentially affect insulin action and metabolism through direct cellular effects in adipocytes, and thereby induce insulin resistance and favor progressive lipid accumulation and adipocyte enlargement.

Studies from several groups have demonstrated an induction of insulin resistance mainly by clozapine and olanzapine, both in animal models and schizophrenia patients (Bergman and Ader, 2005).

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It remains unclear, however, which of the insulin-sensitive target organs play the major role in the induction of insulin resistance by these SGAs. Classically, white adipose tissue accounts for the disposal of approximately 5–15 percent of an oral glucose load. Thus, it might be, as Vestri *et al* conclude the abstract, that these effects could explain, at least in part, the association of SGAs with weight gain and diabetes.

Alternatively, glucose uptake in skeletal muscle accounts for the disposal of 70–90 percent of an oral glucose load. In line with the physiological importance of skeletal muscle, we analyzed whether olanzapine alters glycogen synthesis and the insulin-signaling cascade in L6 myotubes. Glycogen content was diminished in a time- and dose dependent manner. Within the insulin signaling cascade we have found diminished phosphorylation in different steps, such as the IRS-1 tyrosine phosphorylation, AKT, and GSK-3, whereas the phosphorylation of pGS was increased. Protein mass of IRS-1, AKT, GSK-3, and GS was unaltered after olanzapine incubation. IRS-1 associated PI3K activity was also diminished in a dose-dependent manner. Finally, we have compared olanzapine with amisulpride, as an SGA clinically not associated with induction of insulin resistance, and found no alteration of glycogen content in L6 myotubes following amisulpride addition (Engl *et al*, 2005).

Thus, these two major glucose uptaking organs are affected by some of the SGAs. To make the scenario even more complex, Ader *et al* (2005) have described marked hepatic insulin resistance and a failure of the beta-cells to compensate for hepatic insulin resistance. They conclude that their results may explain the diabetogenic effects of atypical antipsychotics and suggest that beta-cell compensation is under neural control (Ader *et al*, 2005). Insulin normally suppresses hepatic glucose production by more than 50 percent during a hyperinsulinemic–euglycemic clamp and the failure of beta-cell compensation that physiologically occurs in the state of insulin resistance

might be due to neural effects of the SGAs that induce insulin resistance.

As recently published in this Journal, olanzapine increases glucogenesis by multiple pathways in the brain. The chronic administration of olanzapine to rats for 21 days caused significant upregulation of 38 genes and downregulation of 31 genes in the frontal cortex (Fatemi *et al*, 2006). Some of the upregulated genes were insulin 2, pyruvate kinase, and muscle glycogen phosphorylase—all of them involved in energy production. The overall picture emerging from this study was that chronic administration of olanzapine in rats increased energy production in brain by greater provision of glucose for local use (Fatemi, 2006).

Thus, insulin resistance induced by SGAs is as complex as the 'common' insulin resistance syndrome that is caused not solely by defects in one organ but rather by dysfunctions of multiple organs, genes, and signaling pathways.

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