Title: Crosstalk Between Insulin and Dopamine Signaling: A Basis for the Metabolic Effects of Antipsychotic Drugs

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Highlights

Dopamine and insulin signaling systems have a reciprocal regulatory relationship.

Schizophrenia and its treatment impart a high risk for obesity and hyperinsulinemia

Short-term antagonism of dopamine D2 receptors increases insulin secretion.

Insulin increases dopamine reuptake acutely but downregulates it chronically.

Altered dopamine signaling may contribute to the pathogenesis of metabolic syndrome.

Abstract

In the setting of rising rates of obesity and metabolic syndrome, characterized in part by hyperinsulinemia, it is increasingly important to understand the mechanisms that contribute to insulin dysregulation. The higher risk for metabolic syndrome imparted by antipsychotic medication use highlights one such mechanism. Though there is great variation in the number and types of signaling pathways targeted by these medications, the one common mechanism of action is through dopamine. Dopamine's effects on insulin signaling begin at the level of insulin secretion from the pancreas and continue through the central nervous system. In a reciprocal fashion, insulin also affects dopamine signaling, with specific effects on dopamine reuptake from the synapse. This review probes the dopamine-insulin connection to provide a comprehensive examination of how antipsychotics may contribute towards insulin resistance.

Abbreviations Used: D2R, dopamine receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; DARPP-32, dopamine and cAMP-regulated phosphoprotein; PP1, protein phosphatase 1; MEK, mitogen-activated protein kinase/ERK kinase; ERK, extracellular-signal regulated kinase; DAT, dopamine transporter; GIRK, G-protein-gated inwardly-rectifying potassium channel; CAMKII, calcium/calmodulin-dependent kinase II; Akt, protein kinase B; PP2A, protein phosphatase 2A; GSK-3, glycogen synthase kinase-3; DA, dopamine; IRS, insulin receptor substrate protein; PI3K, phosphoinositol-kinase; PDK1, phosphoinositide-dependent kinase 1; Grb2, growth factor receptor-bound protein 2; Sos, son of sevenless.