

Antipsychotic-induced severe hypoglycemia

Hyperglycemia is more common in patients with antipsychotic treatment than in the general population. However, hypoglycemia is one of the idiosyncratic potentially life-threatening adverse effects of antipsychotics. While several cases of antipsychotic-induced hypoglycemia have been reported, the mechanisms responsible for hypoglycemia remain unclear.

The insulin/glucose ratio in patients with antipsychotic-induced hypoglycemia was high (>0.25), indicating the possibility of hyperinsulinemia. Hypersecretion of insulin by antipsychotics is thought to be a key mechanism of antipsychotic-induced severe hypoglycemia. Although several factors can cause hypoglycemia, including skipping a meal, exercising harder than usual, alcohol consumption, stress and infections, the underlying cause of hypoglycemia is a complex interaction between hyperinsulinemia and compromised physiologic and behavioral responses to falling glucose levels.

Hypotheses include these drugs' potential to cause insulin secretion, possibly through antagonism at the muscarinic receptors. However, antipsychotics with less affinity to the muscarinic receptors sometimes cause severe hypoglycemia. While several major chemical classes of antipsychotic drugs are developed, all antipsychotics are dopamine D2 antagonists. Dopamine and/or adrenaline may relate to insulin secretion.

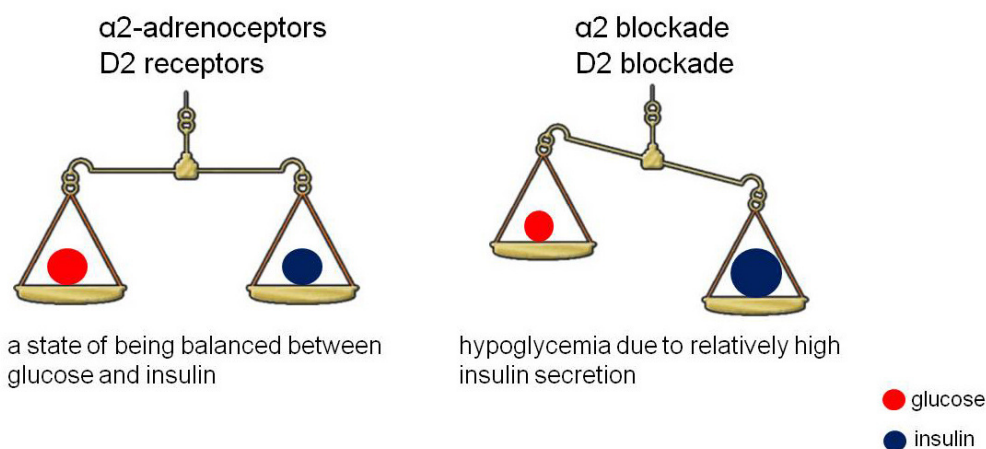


Fig. 1. The role of $\alpha 2$ -adrenoceptors and dopamine D2 receptors on pancreatic beta cells for blood glucose regulation

Whenever insulin is hypersecreted by antipsychotics, hypoglycemia seldom occurs, because glucose production and cellular glucose utilization are tightly regulated by glucose itself and hormones such as insulin, glucagon, adrenaline, glucocorticoids and incretins. Alterations in glucose result in rapid alteration of insulin to bring glucose back to normal range. Namely, while a fall in blood glucose is normally rapidly detected, counter-regulatory mechanisms are recruited to restore normoglycemia. The $\alpha 2$ -adrenoceptors and D2 receptors are expressed in pancreatic beta-cells, and seem to be important for the counter-regulation. The $\alpha 2$ -adrenoceptors on pancreatic β -cells inhibit insulin secretion, and $\alpha 2$ -adrenoceptor antagonists increase insulin secretion. Some in vivo studies suggested that stimulation of the pancreatic D2

receptors inhibits insulin release, which inhibitory effect on insulin secretion was reverted by the addition of D2 receptor antagonists. Moreover, mutant mice lacking D2 receptors have abnormal insulin secretion. When administering antipsychotic drug like risperidone, which possesses α_2 and D2 blocking effects, counter-regulatory mechanisms on glucose regulation might not have worked. Antipsychotics have a risk of mismatch between glucose levels and insulin secretion (Fig. 1).

Hypoglycemia is a condition known to disrupt many everyday activities and is associated with increased mortality. While many studies have reported that antipsychotics cause hyperglycemia, the link between hypoglycemia and antipsychotics has not been extensively studied. The importance of dopamine and adrenaline in central nervous system function is well known, but its effects on glucose homeostasis and pancreatic beta-cell function are not noticed. Further studies for the role of D2 receptors and α_2 -adrenoceptors on glucose regulation are needed.

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Publication

[Severe hypoglycemia associated with risperidone.](#)

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Psychiatry Clin Neurosci. 2016 Sep