Dopamine D₂ receptors in the CNS regulate blood glucose levels through the sympathetic and parasympathetic nerves

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BACKGROUND: The blood glucose levels are known to be regulated by the balance between glucose metabolism and hepatic glucose production. Recently, the possibility that the central nervous system (CNS) also regulates blood glucose levels is pointed out, but those mechanisms are unknown. To investigate the mechanisms how the CNS regulates blood glucose levels, we focused on dopamine neurons in the CNS, and examined how central dopamine neurons regulate blood glucose levels. **METHODS:** Male ICR mice (6-7 weeks old) were used. Blood glucose levels were measured by the glucose oxidase method. The mRNA levels of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), which are the key enzymes for hepatic glucose production, were measured by RT-PCR. **RESULTS:** The i.c.v. injections of neither dopamine D₁ receptor agonist SKF 38393 nor antagonist SCH 23390 changed the blood glucose levels. In contrast, the i.c.v. injections of both dopamine D₂ receptor agonist quinpirole and antagonist l-sulpiride significantly increased the blood glucose levels. The increase in the blood glucose levels induced by l-sulpiride, but not quinpirole was significantly inhibited by α_2 and β_3 adrenergic receptor antagonists, yohimbine and ICI 118,551, respectively. The increase in the blood glucose levels induced by quinpirole, but not l-sulpiride, was significantly inhibited by hepatic vagotomy. These results suggest that the stimulation of dopamine D₂ receptors increases blood glucose levels through parasympathetic nerves whereas the inhibition of dopamine D₂ receptors increases blood glucose levels through sympathetic nerves. Both quinpirole and l-sulpiride significantly increased the mRNA levels of G6Pase and PEPCK, suggesting that glucose production in the liver is increased by the stimulation or inhibition of dopamine D₂ receptors in the CNS. **CONCLUSION:** The present study has shown that dopamine D₂ receptors, but not dopamine D₁ receptors, in the CNS regulate the blood glucose levels. Moreover, these results indicated that the stimulation of dopamine D₂ receptors in the CNS increases blood glucose level by increasing hepatic glucose production through parasympathetic nerves whereas the inhibition of dopamine D₂ receptors in the CNS increases blood glucose level by increasing hepatic glucose production through sympathetic nerves.