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Low dose of serotonin-acting chemical improves blood sugar tolerance

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An appetite-suppressing chemical also improves glucose tolerance and lowers insulin levels in obese and diabetic mice, researchers report in the November issue of *Cell Metabolism*, a publication of Cell Press. Importantly, the researchers found, those effects of the drug occurred at a low dose that had no influence on feeding behavior, body weight, activity level, or energy expenditure.

The decades-old drug compound, known as m-chlorophenylpiperazine (mCPP), triggers serotonin receptors in the brain. The findings suggest a new strategy for treating the rising tide of people with type 2 diabetes via targeting the so-called serotonin 2C (5-HT2C) receptors.

“Though just a first step, this work provides a new direction in the search for novel pathways and molecules in the brain to target for the treatment of type 2 diabetes,” said Lora Heisler of the University of Cambridge. “The challenge now is to come up with drugs that selectively target 5-HT2C receptors safely and effectively.”

mCPP has primarily been used in scientific studies of the serotonin pathway and may not itself be appropriate for type 2 diabetes treatment due to its other known effects, Heisler added. Heisler’s collaborators included Joel Elmquist of the University of Texas Southwestern Medical Center and Andrew Butler of Louisiana State University System.

Serotonin is a chemical nerve messenger with effects on physiology and behavior, including mood, sleep, and appetite, that are mediated by

multiple serotonin receptors clustered into seven distinct families that are widely expressed in the central and/or peripheral nervous systems, the researchers explained. Earlier studies had explored serotonin-acting drugs in treating obesity, but the possibility of a direct role for serotonin in the development and treatment of type 2 diabetes has received little attention, they said.

Earlier studies revealed that mice lacking the 5-HT2C receptor develop insulin resistance and type 2 diabetes and later overeat and become obese. In the current study, the researchers examined whether a drug that acts on 5-HT2C receptors could improve glucose tolerance. They show in mouse models of obesity and insulin resistance that the drug does improve blood sugar levels. Moreover, it does so even at concentrations that do not lead to reductions in food intake or body weight.

The researchers further report evidence that the serotonin-acting drug may work by stimulating “a-melanocyte-stimulating hormone” (a-MSH) in the brain’s arcuate nucleus, a portion of the hypothalamus important for appetite control. They show that the primary effect of the drug on glucose balance requires activation of one type of a-MSH receptor, called melanocortin-4 receptors (MC4R).

“Our findings add to emerging evidence that the brain may have important influences on glucose metabolism and insulin action,” Heisler added.

While the findings do link serotonin pathways to improved blood sugar tolerance, serotonin supplements would not produce this effect, Heisler noted. That’s because serotonin taken in through the diet cannot cross the blood-brain barrier to reach the critical receptors.

“The identification of new classes of antidiabetic agents is a clinical imperative,” the researchers concluded. “The findings presented here

identify a novel therapeutic application for a class of pharmacological compounds developed more than two decades ago. We demonstrate that 5-HT2C receptor agonists significantly improve glucose tolerance and [lower insulin levels in mouse] models of obesity and type 2 diabetes via an MC4R-dependent mechanism. These findings not only delineate specific neuronal pathways of relevance to a highly prevalent metabolic disease but also suggest that 5-HT2C receptor agonists may prove an effective and mechanistically novel treatment for type 2 diabetes."

Source: Cell Press

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