Targeting glucagon pathway may offer a new approach to treating diabetes

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Maintaining the right level of sugar in the blood is the responsibility not only of insulin, which removes glucose, but also of a hormone called glucagon, which adds glucose.

For decades, treatments for type II diabetes have taken aim at insulin, but a new study suggests that a better approach may be to target glucagon's sweetening effect.

The findings were published today in the online edition of Cell Metabolism.

"What we've found is a way to reduce glucagon's influence on blood sugar without the side effects of global glucagon repression," said Ira Tabas, MD, PhD, Richard J. Stock Professor and Vice Chair of Research in the Department of Medicine and professor of Anatomy & Cell Biology (in Physiology and Cellular Biophysics), who led the study with Lale Ozcan, PhD, associate research scientist.

Though glucagon was discovered at the same time as insulin, research on it has languished compared with that of its cousin, and treatments have almost exclusively targeted the latter.

In the last decade, the success of incretins, a new class of drugs for type II diabetes, has sparked a renaissance in glucagon research. When they were first introduced, incretins were known to stimulate insulin secretion. But recent studies show that a significant part of their clinical

success can be attributed to previously unsuspected inhibiting effects on glucagon secretion.

The experience with incretin has led to a renewed search for other drugs that act against glucagon, including compounds that block glucagon in the liver, where it acts to free glucose. Drugs that block the glucagon receptor in the liver have been tested, but glucagon has multiple roles, and recent early clinical trials show that it can raise cholesterol and lead to fat accumulation in the liver.

The new study shows how glucagon's effect on glucose could be disrupted without disturbing glucagon's other duties, raising prospects for a safer anti-glucagon diabetes treatment.

Drs. Tabas and Ozcan found that once glucagon binds to its receptor, glucose is fully released only after an enzyme called CaMKII is activated. When activated, CaMKII sends a protein called FoxO1 into the cell nucleus, where it turns on the genes needed for glucose secretion. A related pathway, working in parallel to this one, sends a FoxO1 helper protein into the cell nucleus, as reported in a paper on which Dr. Tabas is a co-author, published online on April 8 in Nature (embargoed until that time).

"Even when their disease is well controlled, most patients with type II diabetes have excess glucagon action, so blocking CaMKII could potentially be a new way to lower blood sugar and better treat the disease," said Dr. Tabas.

When the researchers blocked CaMKII in obese, diabetic mice, the animals' blood sugar went down, with no negative side effects. Instead, cholesterol declined, insulin sensitivity improved, and the liver became less fatty.

"Until now, it has been difficult to block glucagon's effect on blood sugar without interfering with glucagon's other functions," said Dr. Tabas, "but we think CaMKII is different."

Dr. Tabas is now working on the possibility of developing a CaMKII inhibitor to treat diabetes.

More information: Drs. Ozcan's and Tabas' paper is titled, "Calcium signaling through CaMKII regulates hepatic glucose production in fasting and obesity."

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