Researchers discover process that may explain how type 2 diabetes develops

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A new study helps to explain the mechanism by which pancreatic cells secrete high levels of insulin during the early stages of diabetes.

A central question in diabetes research is why cells of the pancreas, known as beta cells, initially over-secrete insulin. The prevailing theory was that the body may be in the process of becoming "deaf" to insulin, so beta cells secrete more to compensate. But isolated beta cells still over-secrete insulin, which exposes a gap in that theory.

In the new study, researchers set out to understand what other mechanism beyond insulin resistance (that is, the body becoming "deaf" to insulin) and high glucose levels might explain why diabetes develops. The scientists found that a pathway independent of glucose, but sensitive to fatty acids, appears to drive insulin secretion in the early stages of diabetes.

The research team, led by Orian Shirihai, a professor of endocrinology and pharmacology at the David Geffen School of Medicine at UCLA and senior author of the study, used pre-diabetic mice to study the mechanisms by which insulin may be secreted in the absence of glucose.

The team found that in beta cells from obese, pre-diabetic animals, a protein known as Cyclophilin D, or CypD, induced a phenomenon known as "proton leak," and that this leak promoted insulin secretion in the absence of elevated glucose. The mechanism was dependent on fatty acids, which are normally incapable of stimulating insulin secretion in healthy animals.

Further, obese mice who lacked the gene for CypD did not secrete excess insulin. The team confirmed the same process was taking place in isolated human pancreas cells: In the presence of fatty acids at levels that would be typical in obese humans, the cells secreted insulin in the absence of elevated glucose.

The study was published in the American Diabetes Association's journal *Diabetes*.

The results suggest new ways to prevent the development of insulin resistance and to treat diabetes, including halting its progression by blocking the proton leak in the beta cell.

More information: Evan P. Taddeo et al. Mitochondrial Proton Leak Regulated by Cyclophilin D elevates Insulin Secretion in Islets at Non-Stimulatory Glucose Levels, *Diabetes* (2019). DOI: 10.2337/db19-0379