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PANCREAS

FGF21 gets the juices flowing

Fibroblast growth factor 21 (FGF21) stimulates the secretion of digestive enzymes from acinar cells in the exocrine pancreas and the flow of pancreatic juices, according to a new study published in *Cell Metabolism*.

The researchers, led by David Mangelsdorf and Steven Kliewer, were interested in understanding the physiologic role of FGF21 in the exocrine pancreas, where the hormone is expressed at levels 100-fold higher than in the liver.

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Pancreata from *Fgf21*-knockout mice had more zymogen granules and higher levels of digestive enzymes than wild-type mice, effects that were reversed by administration of exogenous FGF21. Zymogen granules also accumulated in mice carrying an acinar-cell-specific deletion of *Klb* (which encodes β-klotho, a component of the FGF21 signalling complex); however, FGF21-induced secretion of digestive enzymes was absent in these mice, and the pancreatic juice flow rate was markedly reduced. The findings suggest that FGF21 acts directly on acinar cells to stimulate both digestive enzyme secretion and pancreatic juice flow.

As overloading of acinar cells with digestive enzymes causes endoplasmic reticulum (ER) stress that can lead to pancreatitis, the team next investigated whether FGF21 could alleviate this condition by reducing protein load and concomitant ER stress. Markers of ER stress were induced in pancreata of both wild-type and *Fgf21*-knockout mice by cerulein-induced pancreatitis (CIP), albeit more so in the *Fgf21*-knockout mice. Conversely, induction of ER stress markers by CIP was suppressed in mice overexpressing an *Fgf21* transgene. Furthermore, FGF21 administration doubled digestive enzyme secretion and the pancreatic juice flow rate in wild-type mice without stimulating pancreatic protein synthesis. Overall, the data show that FGF21 is a potent secretagogue that can mitigate ER stress in the pancreas by flushing proteins out of acinar cells and stimulating juice flow through the pancreatic ducts.

"Our findings provide a mechanistic basis for earlier observations showing that FGF21 protects against pancreatitis and reveal an unexpected physiologic role for FGF21 that is distinct from its endocrine and pharmacologic effects on metabolism," explains Mangelsdorf. "A key question now is whether FGF21 might be effective in treating pancreatitis," he adds. As few effective treatments for pancreatitis are currently available, further investigation of the therapeutic potential of FGF21 is warranted.

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