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Liver hormone is a cause of insulin resistance

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Researchers have identified a hormone produced and secreted by the liver as a previously unknown cause of insulin resistance. The findings, in the November issue of *Cell Metabolism*, suggest a new target for the treatment of insulin resistance and type 2 diabetes, the researchers say.

"The current study sheds light on a previously underexplored function of the liver; the liver participates in the pathogenesis of insulin resistance through hormone secretion," said Hirofumi Misu of Kanazawa University Graduate School of Medical Science in Japan.

The researchers had discovered earlier that genes encoding secretory proteins are abundantly expressed in the livers of people with type 2 diabetes. On the basis of those findings, Misu and colleagues began to suspect that, similar to the role of fat tissue, the liver might contribute to the development of type 2 diabetes and insulin resistance via secretory proteins they call "hepatokines."

Now, the researchers report the results of comprehensive gene expression analyses, revealing that the liver expresses higher levels of the gene encoding selenoprotein P (SeP) in people with type 2 diabetes who are more insulin resistant. Blood levels of SeP are also increased in people with diabetes compared to healthy people.

Further studies in mice added support to the notion that the connection between SeP and insulin resistance is causal. When the researchers gave normal mice SeP, they became insulin resistant and their blood sugar levels rose. A treatment that blocked the activity of SeP in the livers of

diabetic and obese mice improved their sensitivity to insulin and lowered blood sugar levels.

Misu said that SeP was known previously as a protein produced mainly in the liver, where it transports the essential trace element selenium from the liver to other parts of the body. But the protein's clinical significance and, more specifically, its role in glucose homeostasis weren't known.

In the development of insulin resistance, the researchers don't think SeP acts on its own. It is well known, they explain, that fat tissue is a main contributor to the development of insulin resistance by producing fat-derived hormones called adipokines. But they say they have preliminary evidence for a connection between SeP and adipokine production, which will be the subject of further investigation.

The new findings suggest that there may be other hormones derived from the liver with important and varied roles in the body, Misu and his colleague Toshinari Takamura add. "Our study raises the possibility that the liver functions as an endocrine organ by producing a variety of hepatokines and that the dysregulation or impairment of hepatokine production might contribute to the development of various diseases."

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