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Unraveling the Paradox of Selective Insulin Resistance in the Liver: the Brain–Liver Connection

The insulin receptor (IR) is expressed widely throughout the brain (1); however, unlike insulin in peripheral tissues whose major function is regulation of glucose metabolism, the actions of insulin in the brain are less glucocentric. Glucose enters neurons and glia of the brain primarily through the facilitative glucose transporters GLUT1 and GLUT3 (2), which are not insulin dependent. Despite being dispensable for glucose entry into the brain, early work by Woods et al. (3) and others (reviewed in ref. 1) demonstrated that intracerebroventricular (ICV) delivery of insulin into the brain could produce a multitude of effects, including suppression of feeding behavior and hepatic glucose production, activation of thermogenesis in brown adipose tissue, and stimulation of lipogenesis in white adipose tissue, all without significantly altering systemic insulin levels. Using a conditional knockout of the IR in the brain, Brüning and colleagues (4,5) demonstrated that the actions of insulin in the brain require IRs and can produce a range of phenotypes including mild obesity, decreased counterregulatory responsiveness to hypoglycemia, and hypothalamic hypogonadism. This has been confirmed and refined by region-specific IR knockouts and knockdowns of the IR using antisense technology (6,7). Studies using animal models and in vitro systems have uncovered many other roles for brain insulin signaling, including insulin-dependent uptake of glucose in the hippocampus for memory formation (8), stimulation of brain cholesterol synthesis (9), and increased astrocyte glycogen storage (10), to name a few.

In normal physiology, a major function of insulin is to suppress hepatic gluconeogenesis while stimulating hepatic cholesterol and triglyceride synthesis (Fig. 1A) and glucose uptake into muscle and fat. Mice with hepatic insulin resistance created by knockout of the IR in the liver (LIRKO mice) demonstrate increased hepatic gluconeogenesis and decreased hepatic lipogenesis, consistent with insulin resistance in both pathways (11). In type 2 diabetes, however, the liver exhibits higher levels of gluconeogenesis, consistent with insulin resistance, but also has high levels of cholesterol and triglyceride synthesis, suggesting that these pathways remain insulin sensitive (Fig. 1B) (12,13). This paradox has been termed selective insulin resistance (12). One factor contributing to the increased triglyceride synthesis in diabetes has been shown to be substrate availability (14). Thus in diabetes, increased lipolysis from insulin-resistant fat can provide substrate for the liver to form additional triglycerides, whereas in the LIRKO mouse the high insulin levels act on insulin-sensitive fat to suppress lipolysis.

In this issue of *Diabetes*, Scherer et al. (15) propose a different hypothesis for selective hepatic insulin resistance by examining the brain–liver connection. Insulin resistance and diabetes can lead to the pathologic accumulation of lipids in the liver due to increased hepatic synthesis or reduced secretion by the liver. By using fasting animals and tyloxapol to block plasma lipolytic activity, the authors were able to specifically isolate the secretion of triglyceride-rich VLDL particles, uncoupling them from de novo lipogenesis or absorption of triglycerides from the diet. Interestingly, they found that ICV insulin increased hepatic VLDL secretion, in contrast to systemic insulin, which decreased secretion. Indeed, chronic ICV insulin significantly decreased the hepatic lipid load. When they knocked out the IR from the brain, hepatic triglyceride secretion decreased, whereas loss of IRs from the periphery produced the opposite effect. Thus, Scherer et al. (15) hypothesize that insulin signaling in the brain acts to counter the signals generated by hyperglycemia in the brain, which others have shown results in decreased hepatic triglyceride secretion (16). This hypothesis helps explain the fatty liver in type 2 diabetes, where the presence of hyperglycemia and impaired insulin signaling could act together to increase retention of lipids in the liver, thus promoting steatosis (Fig. 1B). At the

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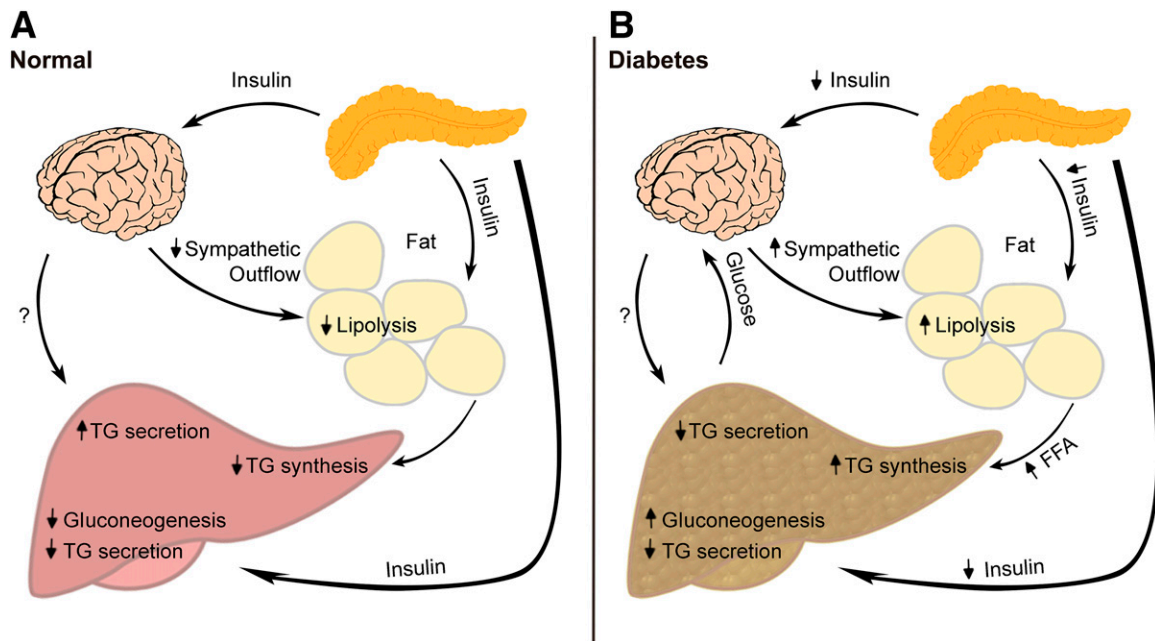Corresponding author: C. Ronald Kahn, c.ronald.kahn@joslin.harvard.edu.

Figure 1—*A*: Insulin secreted from the pancreas suppresses fat lipolysis, hepatic triglyceride (TG) secretion, and gluconeogenesis. Insulin also acts on the brain, which independently suppresses lipolysis by suppression of sympathetic outflow and increases TG secretion from the liver through an unknown mechanism. *B*: In diabetes, decreased insulin action on the brain and fat results in increased lipolysis. This increases the delivery of free fatty acids (FFAs) to the liver, increasing TG synthesis. Impaired insulin action at the liver results in increased gluconeogenesis. Increased blood glucose and decreased insulin action at the brain suppress TG secretion from the liver.

same time, the insulin-resistant fat and brain are unable to mount signals to suppress lipolysis, thereby flooding the liver with fatty acids and increasing triglyceride synthesis.

It is interesting to speculate about the potential impact of this brain–liver pathway when insulin is given therapeutically by intranasal administration (as is being tested for Alzheimer disease and diabetes), although this was not part of the study by Scherer et al. In a small trial of intranasal insulin in control subjects and subjects with type 2 diabetes (17), the subjects without diabetes showed a decrease in hepatic lipid content following a single large dose of intranasal insulin, whereas there was no change in subjects with diabetes. This suggests that either longer-term administration of intranasal insulin or intranasal insulin in combination with an insulin sensitizer may be required to show beneficial metabolic effects on the diabetic liver.

The work by Scherer et al. (15) is the most recent example that some components of insulin resistance in the liver may not actually reside in the liver but rather be the summation of signals received by the liver from multiple organs in the body. It also is another demonstration that the brain is an important organ in control of metabolism and not just a regulator of feeding behavior. Going forward, it will be important to define the specific brain regions involved and determine the relative roles of neurons and astroglial cells in the brain insulin response. Mapping the neural circuits responsible for the many effects of insulin in the brain in more detail may allow

development of brain-targeted therapies for specific metabolic disorders.

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