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Central Regulation of Glucose Metabolism in Humans: Fact or Fiction?

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In the past few years, insulin action in the central nervous system (CNS) has attracted a growing interest to better understand the association between neurodegenerative diseases and insulin resistance (IR). Rodent studies have indicated that insulin signaling in the CNS is critical for the suppression of endogenous glucose production (EGP) in the liver (1) and for the regulation of adipose tissue lipolysis (2). These central insulin effects likely depend on PI3K-mediated regulation of several proteins and transcription factors, among which are FoxO1 (3) and AMPK (4), and on the activation of K_{ATP} channels (5) in the hypothalamus (Fig. 1). Recent findings show that subsequent activation of hepatic Kupffer cells and an increase in hepatic interleukin-6 induce signal transducer and activator of transcription 3 (STAT3) phosphorylation to inhibit gluconeogenic gene expression (6). Suppression of lipolysis in adipose tissue by brain insulin signaling reduces the availability of gluconeogenic substrates for the liver, which will further decrease EGP (2). In contrast, studies in dogs did not support the concept of a physiological relevance of CNS insulin action for controlling EGP (7).

In humans, intranasal insulin (IN) application has been established as one approach to noninvasively examine brain insulin action in vivo. The IN spray application transiently increases the insulin concentration in liquor (8), likely due to bulk flow within the perivascular space of cerebral blood vessels (9). Using this technique, evidence for the central insulin regulation of systemic lipolysis (10), modulation of liver fat content and hepatic energy metabolism (11), and improvement in whole-body insulin sensitivity (12) has been provided. Interestingly, effects of IN on EGP seem to depend on the experimental conditions with no changes in the fasting state (11) but with reduction during pancreatic clamps (13). Modulation of energy-demanding processes might contribute to the rise in hepatic energy status after IN application. Of note, central insulin regulation of peripheral insulin sensitivity and hepatic energy metabolism was blunted in obese humans and patients with type 2 diabetes (11,12), suggesting that the presence of a combined central and peripheral IR and a dysregulation of a brain-liver cross talk in type 2 diabetes. Nevertheless, IN may have some limitations resulting from variable cerebral insulin delivery and/or peripheral insulin spillover.

Another approach to mimic brain insulin action in humans is the administration of the K_{ATP}-channel opener and sulfonylurea drug diazoxide. Dr. Hawkins' group showed that diazoxide treatment can suppress EGP in lean healthy humans, and complementary studies in rodents revealed increased hepatic STAT3 phosphorylation along with reduced hepatic gluconeogenic protein levels (14). The same group now presents a carefully planned and nicely performed follow-up study investigating the effects of diazoxide on EGP in patients with type 2 diabetes. Esterson et al. (15) combined diazoxide administration with euglycemic basal insulin and glucagon, growth hormone, and somatostatin clamps, allowing for the examination of glucose metabolism under carefully controlled conditions ruling out CNS effects on pancreatic insulin and glucagon secretion. By avoiding hepatic overinsulinization, this approach allows for the assessment of even minor changes in EGP over time. The possible limitation that the preceding overnight insulin infusion might suppress EGP and thereby attenuate the effect of diazoxide on EGP is discussed by the authors. Importantly, this study extends the group's previous observations by clearly demonstrating that diazoxide has no effect on EGP in patients with moderately to poorly controlled type 2 diabetes. Even more, the study confirms the effect of diazoxide on EGP in healthy humans. It has to be stated that the experimental groups were small and the effects of

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COMMENTARY

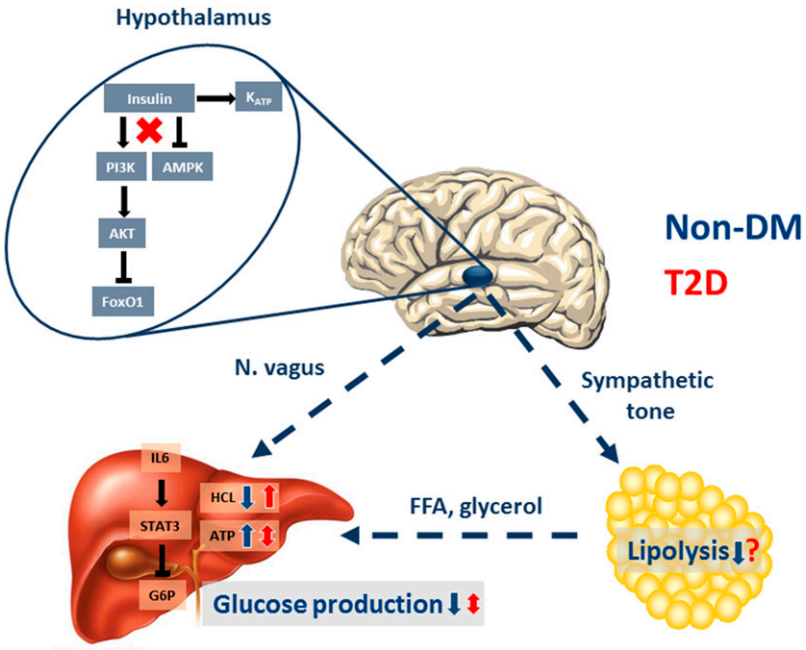

Figure 1—Brain insulin regulation of hepatic glucose production and adipose tissue lipolysis. The insulin-signaling pathway in the arcuate hypothalamus involves the activation of PI3K and AKT and the subsequent inactivation of FoxO1. Also, the inhibition of AMPK and opening of K_{ATP} channels are linked to brain insulin's peripheral metabolic effects. In addition to the reduction of lipolysis by modulation of sympathetic activity, brain insulin induces the suppression of hepatic glucose production, which is mediated by the vagus nerve–triggered hepatic interleukin (IL)-6 and STAT3 activation, leading to decreased hepatic gluconeogenic gene expression. Central insulin action also reduces liver fat content and increases hepatic energy status. This mechanism seems to be impaired in humans and rodents with type 2 diabetes. AKT, protein kinase B; FFA, free fatty acids; G6P, glucose 6-phosphate; HCL, liver fat content; Non-DM, nondiabetic; N. vagus, vagus nerve; T2D, type 2 diabetes.

longer-term treatment require further examination. Nevertheless, this study specifically benefits from the complementary studies in Zucker diabetic fatty rats, an established rodent model of type 2 diabetes, that support the findings in humans of a lack of effect of diazoxide on EGP and further probe the mechanism in greater detail by assessing molecular regulation of EGP.

In studies in humans with IR, IN or intravenous insulin application did not induce brain activity in the insulin-sensitive brain areas, i.e., the hippocampus, prefrontal cortex, fusiform gyrus, and hypothalamus, as measured by noninvasive brain imaging tools (16,17). Although such evidence for the activation of insulin-sensitive brain regions has not yet been demonstrated after diazoxide administration, the study by Esterson et al. (15) adds to the discussion on impaired central regulation of glucose and energy metabolism in type 2 diabetes (11). The question remains as to whether K_{ATP} channel activation and IN modulate peripheral insulin sensitivity by similar or different pathways. Specifically, it will be interesting to find out which and how brain-derived signals, induced either by IN or diazoxide, reach peripheral tissues to modulate glucose and energy metabolism. The autonomic nervous system is also a good candidate to mediate these effects in humans (5,12). Animal data revealed that CNS insulin-induced suppression of EGP depends on vagus nerve activation (6), whereas the sympathetic nervous system mediates for the reduction of adipose tissue lipolysis (2). However, it remains unclear how selective modulation of the autonomic nervous system tone could be used to improve glucose and lipid homeostasis. Finally, the observation that the sulfonylurea drug diazoxide fails to exert EGP-lowering effects in patients with diabetes contributes to a large body of evidence that does not raise the enthusiasm to use this drug class in type 2 diabetes.

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