

Dale S. Edgerton and Alan D. Cherrington



Is Brain Insulin Action Relevant to the Control of Plasma Glucose in Humans?



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The notion that central nervous system (CNS) insulin action plays an important role in mediating the inhibition of endogenous glucose production (EGP) is becoming increasingly accepted (1–5). In the rodent, insulin's effect in the brain involves transport of insulin across the blood–brain barrier, activation of insulin signaling, opening of neuronal ATP-sensitive potassium (K_{ATP}) channels, signaling via vagal hepatic efferents, phosphorylation of liver STAT3, and suppression of gluconeogenic gene expression, with subsequent reduction of EGP due to inhibition of gluconeogenesis but not glycogenolysis (6–10). The effect was relatively slow in onset (requiring several hours to appear) and was evident under nonphysiological circumstances because infusion of insulin into a peripheral vein results in absolute or relative hepatic insulin deficiency (Fig. 1) (11,12). In addition, glucagon was not replaced, raising the possibility that insulin's brain–liver effect is only manifest when the liver is deprived of other normal regulatory inputs. Despite such limitations, these studies have led some to conclude that brain insulin action is “required,” “necessary,” or even “essential” for the suppression of EGP by insulin (2,5,7–10).

As in the rodent, the canine brain–liver insulin axis has been shown to involve CNS insulin signaling and K_{ATP} channel activation, a neurally mediated increase in hepatic STAT3 phosphorylation, and changes in glucoregulatory gene expression in the liver (13,14). In one study, a selective increase in brain insulin, brought about by insulin infusion into the carotid and vertebral arteries at a rate that raised insulin in the head but maintained basal insulin levels at the liver, decreased the transcription of gluconeogenic genes but did not suppress EGP under euglycemic clamp conditions (14). Lack of correlation between gluconeogenic gene expression and glucose flux is not surprising given the poor control strength of enzymes such as PEPCK across species

(15–17). After several hours, however, there was a modest increase in the ability of the liver to take up glucose. Notably, all of insulin's central effects were blocked by third ventricle infusion of a phosphatidylinositol 3-kinase (PI3K) inhibitor or a K_{ATP} channel blocker (14), the latter of which would block insulin's effects through both the PI3K and mitogen-activated protein kinase (MAPK) pathways (18).

As excess EGP contributes to hyperglycemia in humans with diabetes, it is imperative that regulation of the process be fully understood. In that regard it is necessary to determine whether a brain–liver insulin axis controlling EGP exists in the human, and if so, to what extent it is relevant. These are significant issues because targeting the brain–liver insulin axis may be of therapeutic value, especially if hypothalamic insulin resistance contributes to metabolic dysfunction (5). Although studying brain insulin action in the human is technically challenging, intranasal insulin administration is known to increase cerebrospinal fluid insulin concentrations and to affect cognitive performance, food intake, and satiety (19). Thus, it is a tool with which to address the above questions. Two articles, published in the current issue of *Diabetes* (20,21), describe the use of intranasal insulin to investigate the impact of brain insulin action on human glucose metabolism.

In the study by Dash et al. (20), insulin was administered intranasally (40 IU) on the background of a pancreatic clamp using somatostatin (insulin and glucagon were infused into a peripheral vein to clamp their levels at basal arterial values, meaning that the liver was deficient in both). After 3 h, a modest suppression of EGP became evident (36% reduction at 240 min and 15% during the last hour) in the test group relative to a control group in which insulin was infused peripherally to account for the leakage of intranasally delivered insulin into the bloodstream.

Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN

Corresponding author: Dale S. Edgerton, dale.edgerton@vanderbilt.edu.

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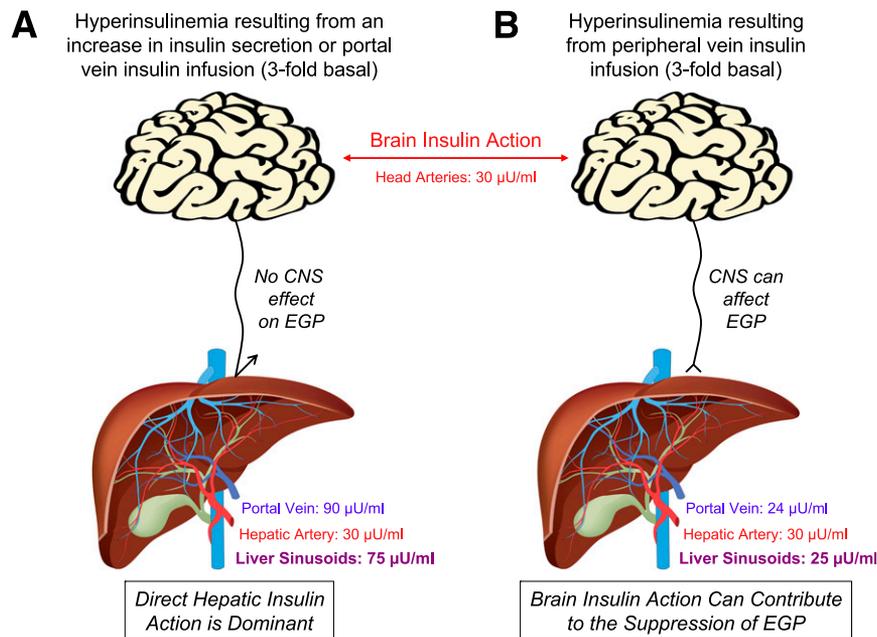


Figure 1—In the basal state, arterial and hepatic portal vein insulin concentrations are approximately 10 and 30 $\mu\text{U/mL}$, respectively, such that the concentration of insulin in blood entering the hepatic sinusoids is $\sim 25 \mu\text{U/mL}$. A threefold increase in basal insulin secretion or portal vein insulin infusion (A) increases both arterial (brain) and liver insulin concentrations by threefold. When insulin is acutely elevated in this way, insulin's direct hepatic effect drives the rapid suppression of EGP, and the CNS effects of insulin on the liver are masked. In response to a threefold rise in insulin brought about by infusion into a peripheral vein (B), arterial (brain) insulin concentrations are also elevated threefold, but in this case hepatic sinusoidal insulin levels remain at the basal level ($\sim 25 \mu\text{U/mL}$) because endogenous insulin secretion falls (exogenous insulin infusion inhibits insulin secretion in the human, dog, and rodent [12,40,41]) and the gut destroys 20% of the insulin in the blood perfusing it. Clearly, when insulin is administered intranasally, by direct infusion into the brain, or via a peripheral vein, the normal physiological insulin gradient between the brain and liver is lost. Thus, although brain insulin action can impact hepatic glucose production (albeit slowly) in the deficiency of insulin signaling at the liver, it cannot do so under circumstances in which the direct insulin signal is normal.

This observation indicates that a pharmacological dose of insulin given into the head can inhibit EGP in the human. Nevertheless, considering the slow onset of the effect (>3 h), Dash et al. (20) concluded that CNS insulin action cannot explain the rapid (minutes) suppression of EGP that is consistently seen during hyperinsulinemic clamps across species (11,12,22). Thus, even though these data support the existence of a brain–liver insulin axis in the human, they also clearly indicate that an acute increase in brain insulin action is not essential for the suppression of EGP by hyperinsulinemia.

Based on the observation that a large dose of intranasal insulin (160 IU) increased the glucose infusion rate required to maintain euglycemia during a hyperinsulinemic clamp, Heni et al. (23) recently concluded that brain insulin action rapidly (within 15 min) increases peripheral insulin sensitivity in the human. This finding disagrees with previous human, dog, and rodent studies, which have consistently shown that brain insulin action requires several hours to manifest effects on glucose metabolism (6–10,14,18,20). It should be noted that Dash et al. (20) measured significant peripheral spillover of insulin into the circulation after even a 10 IU intranasal dose of insulin. Unfortunately, this leakage was not

accounted for in the study of Heni et al. (23), and this most likely explains the increase in glucose infusion that was observed, rather than a brain insulin effect.

In an earlier attempt to identify a brain–liver insulin effect in the human, Kishore et al. (24) administered a K_{ATP} channel activator (diazoxide) orally to see if mimicking insulin action in the CNS would have any effect on EGP (diazoxide was given 3 h prior to a 4-h peripheral insulin clamp in which arterial insulin was increased threefold, with basal insulin levels at the liver). EGP did not change for 5 h, but decreased by 30% 6–7 h after dosing. Thus, although the studies of Dash et al. (20) and Kishore et al. (24) support the concept that brain insulin action can regulate EGP in the human, albeit slowly, both studies were pharmacological in nature and were carried out with the liver in a relatively insulin-deficient state, leaving open the question of the physiological relevance of brain insulin action in control of EGP in the human.

Unfortunately, the difficulty of hepatic portal vein access makes it challenging to create a normal insulin gradient between the liver and brain during a clamp in the human or rodent. It should be noted that the normal 3:1 ratio of insulin that exists between the liver and brain is

always eliminated when insulin is administered intranasally, by infusion directly into the brain, or via a peripheral vein. Studying the effect of neural input to the liver at a time when hepatic insulin and/or glucagon levels are inappropriately low, relative to those in the brain, complicates the interpretation of results regarding the physiological importance of the perturbation in question. A threefold rise in arterial insulin brought about by peripheral insulin infusion (6–10,24) is often considered hyperinsulinemic (Fig. 1), even though hepatic insulin levels are basal (11,12), and in such a case, it would be no surprise for the “hyperinsulinemic” effects of insulin to be entirely nonhepatic (25,26). Even a sixfold rise in the arterial (brain) insulin level produces only a twofold rise at the liver, again making interpretation of the results difficult. Thus, when determining the physiological relevance of brain insulin action on EGP, the appropriate hormonal gradient between the liver and brain must be preserved.

To our knowledge, only one study has examined the impact of acute brain insulin signaling on EGP during a normal physiological hyperinsulinemic clamp (i.e., when the same magnitude of rise in insulin occurred at all tissues) (13). In that dog study, we found that the non-central effects of insulin fully explained the suppression of EGP, such that there was no contribution of CNS insulin action to the rapid decrease in EGP. Likewise, when the normal brain–liver insulin gradient was maintained under basal insulin conditions, selectively increasing or blocking brain insulin signaling (via third ventricle infusion of insulin or PI3K/K_{ATP} channel inhibitors, respectively) had no effect on EGP (14). On the other hand, in another study a selective increase in insulin at the liver (but not brain) suppressed EGP within 15 min (22). While it has been postulated that insulin’s central and direct hepatic effects are redundant and equally sufficient for the inhibition of EGP in the rodent (4), the relevance of CNS insulin action in the response to physiological hyperinsulinemia (normal distribution of insulin and glucagon between the liver and brain) has never been measured in the rodent. The available data in the dog suggest that acute activation of brain insulin signaling does not have a meaningful impact on hepatic glucose metabolism under such conditions.

While the results of Dash et al. (20) provide hope that pharmacological activation of the brain–liver insulin axis may be useful clinically in the treatment of excess EGP in diabetes, the results of Ott et al. (21) question the efficacy of such an approach. In unclamped experiments, where neither somatostatin nor glucose were infused, Ott et al. created a prolonged elevation of central insulin by dosing healthy men with 10 or 20 IU of insulin intranasally every 15 min over 6 h (a total of 210 or 420 IU). Fasting plasma glucose levels decreased slightly (~5 mg/dL), but a similar drop occurred when intranasal insulin spillover was simulated by peripheral insulin infusion in a control group. Subtle alterations in endogenous insulin and glucagon

secretion could have masked small effects on the liver, although if EGP was suppressed by CNS insulin action (glucose kinetics were not determined), it had no net impact on basal glucose levels. Other studies in humans given intranasal insulin have shown either no change in arterial insulin, C-peptide, or glucose concentrations (27–30), or at most a 5% decrease in plasma glucose (31,32), probably resulting from insulin spillover, although those studies were only carried out for 3 h. Even chronic treatment with intranasal insulin (4 × 40 IU/day for 8 weeks) did not affect plasma insulin or glucose concentrations in healthy normal-weight subjects (33). Finally, hepatic denervation had little to no effect on hepatic insulin action in liver transplant patients despite complete lack of neural input to the liver (34–36). Thus, while it seems likely that brain insulin action can signal the liver across species, as of yet there are no studies demonstrating that it has a meaningful impact on EGP when the liver is receiving other direct signals normally.

In summary, *in vitro* (37), *ex vivo* (38), and *in vivo* (13,22) data across species clearly demonstrate that acute CNS insulin action is not essential for the rapid suppression (within minutes) of EGP by hyperinsulinemia. Nevertheless, findings in the rodent, dog, and now human suggest that brain insulin action has the potential to slowly alter hepatic glucose metabolism, leaving open the question of whether targeting brain insulin action could be of therapeutic value. It would appear that when proportional increases in insulin occur simultaneously at the liver and brain, as occurs normally, the direct effect of insulin on the liver is dominant and determines the rapid and predominantly antiglycogenolytic effect of the hormone (13,39). It remains to be seen, however, if chronic modulation of brain insulin action can alter the gluconeogenic tone of the liver such that the hepatic response to various factors, including the direct effects of insulin, might be altered. Further studies are required to determine when brain insulin action has physiological, pathophysiological, or therapeutic relevance in the regulation of hepatic glucose production.

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