last year marked the ninetieth anniversary of the discovery of insulin by Nobel Laureates Frederick Banting and John Macleod, as well as Charles Best and James Bertram Collip. The initial success of insulin’s ability to lower glucose levels in type 1 diabetes is now shadowed by the urgent need to characterize insulin resistance and secretion defects in type 2 diabetes and obesity. Insulin triggers signaling pathways in liver, muscle, and fat that inhibit glucose production and increase glucose uptake (1). However, it has only been in recent years that the brain has received attention for being an insulin-sensitive organ that regulates food intake (2) and glucose (3) and lipid (4) homeostasis in animals (Fig. 1).

Circulating insulin crosses the blood-brain barrier and acts on its receptor in the hypothalamus to lower food intake and body weight (2). Infusion of insulin into the central nervous system (CNS) lowers food intake in rats (5), mice (6), and baboons (7), whereas hyperphagia is detected in neuronal insulin receptor knockout mice (8). Further, high-fat feeding induces hypothalamic insulin resistance in rodents (9). Although these animal studies expand the role of insulin to regulate appetite and suggest that characterizing insulin signaling pathways may reveal novel targets that reverse brain insulin resistance in obesity, a central question remains, Is insulin action in the brain clinically relevant?

To address this question, an intranasal peptide delivery method was developed in humans (10). This method enables selective elevation of peptide levels in the cerebrospinal fluid without altering plasma peptide levels (10). Using this method, intranasal injection of insulin was found to inhibit food intake in normal fasting men but not women (11). This is consistent with the fact that central insulin lowers food intake in male but not female rats (5); however, hyperphagia is detected in neuronal insulin receptor knockout female but not male mice (8). Further, high-fat feeding induces hypothalamic insulin resistance in rodents (9). Although these animal studies expand the role of insulin to regulate appetite and suggest that characterizing insulin signaling pathways may reveal novel targets that reverse brain insulin resistance in obesity, it remains to be tested.

Another important finding made by the authors was that within ~30–40 min of intranasal insulin injection (i.e., time 1345 h), while appetite was yet to be affected, plasma glucose level was lowered by ~1 mmol/L in the postprandial women. Importantly, this significant reduction in plasma glucose occurred independently of changes in circulating plasma insulin, C-peptide, leptin, and ghrelin levels at this time point. It is not known whether a change in plasma glucagon level was detected. Nonetheless, given that intranasal insulin delivery in 30 min is sufficient to elevate insulin levels in cerebrospinal fluid (10), these findings are in line with previous reports in rats (3) and dogs (16,17), suggesting that direct brain insulin infusion lowers plasma glucose levels independently of changes in food intake.

Only when the liver is removed does central insulin fail to lower glucose levels in dogs (17), suggesting that brain insulin action lowers glucose levels through a modulation of hepatic glucose metabolism. In fact, insulin triggers signaling cascades and activates ATP-sensitive potassium (K\textsubscript{ATP}) channels in the hypothalamus to inhibit glucose production in rodents (3), while activation of hypothalamic
**FIG. 1. A working hypothesis for insulin action in the brain.** Insulin triggers signaling cascades in the brain to regulate food intake and modulate the reward-related hedonic food response. In addition, brain insulin action alters glucose and lipid metabolism. The hypothalamus (blue) is the main effector of the metabolic changes induced by insulin and can coordinate the prefrontal cortex (green) to regulate the hedonic assessment of appetite. WAT, white adipose tissue.

$K_{ATP}$ channels in humans is implicated to inhibit glucose production (18). Although accumulating evidence indicates that insulin action in the brain of humans and animals reduces plasma glucose levels, it remains to be assessed whether changes in hepatic glucose production induced by CNS lead to the drop in plasma glucose levels. This is due to the fact that insulin action in the brain fails to inhibit hepatic glucose production in dogs while inhibiting net hepatic glucose output and increasing hepatic glycogen synthesis (19). Future comparative studies are warranted in humans, dogs, and rodents to evaluate the ability of insulin action in the brain to regulate hepatic glucose metabolism and glucose homeostasis in various experimental conditions.

Although the drop in plasma glucose induced by intranasal insulin delivery was rapid, the effect was transient and disappeared before a change in appetite was detected. Could a continuous delivery of intranasal insulin sustain the drop in plasma glucose levels and consequently reduce appetite at an earlier time point? Is it because intranasal insulin delivery first delivers insulin to brain regions that are important for glucose regulation and then to other regions for food reward regulation that a drop in plasma glucose levels is first detected? The current study would have benefited from the use of neuroimaging to assess whether different regions of the brain are affected at the time when intranasal insulin delivery reduced appetite and intake of highly palatable snack but not glucose levels and vice versa. In addition, use of a glucose-kinetics clamp technique (18) would be crucial to evaluate whether intranasal insulin delivery inhibits glucose production.

The impact of intranasal insulin delivery on the regulation of lipid homeostasis in humans warrants future investigations. In addition, it has been observed that an enhancement of hypothalamic endoplasmic reticulum stress causes hypothalamic insulin resistance in rodents (6). Given that brain insulin resistance is also detected (20) and delivery of chemical chaperones that reduce endoplasmic reticulum stress improves peripheral insulin sensitivity (21) in obese humans, could the delivery of chemical chaperones enhance brain insulin action?

In summary, although future studies are needed to clarify and evaluate the clinical and metabolic impact of brain insulin action, mounting evidence is beginning to suggest that insulin action in the brain of both animals and humans regulates energy and glucose homeostasis.

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