The Inhibitory Effects of Insulin on Hepatic Glucose Production Are Both Direct and Indirect

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Previous studies suggest that insulin can inhibit hepatic glucose production by both direct and indirect actions. The indirect effects include inhibition of glucagon secretion, reduction in plasma nonesterified fatty acid levels, reduction of the amount of gluconeogenic precursor supplied to the liver, and change in neural input to the liver. There is a controversy concerning the fact that the dominant action of insulin on hepatic glucose production is direct, as suggested by studies in fed dogs, or indirect, via the hypothalamus, as suggested by studies in rodents. A possible explanation for this discrepancy will be proposed involving the relative importance of glycogenolysis and gluconeogenesis in hepatic glucose production in dogs and rodents. Finally, the relative importance of direct and/or indirect effects of insulin on hepatic glucose production for the treatment of diabetes will be discussed. *Diabetes* 55 (Suppl. 2):S65–S69, 2006

For a long time, it was believed that the inhibition of hepatic glucose production (HGP) by insulin resulted only from a direct effect of the hormone on the liver. This was logical since insulin is secreted in the portal vein and the liver is the first organ encountered by insulin. In addition, the liver is exposed to the highest insulin concentration among the insulin-sensitive organs. Finally, the liver capillaries are fenestrated (no endothelial barrier) and thus insulin can reach the liver immediately. However, several observations have challenged this view: *1*) whereas insulin is a potent inhibitor of HGP in vivo, the hormone is relatively ineffective in vitro in rodent liver (1,2) suggesting that insulin primarily acts on extrahepatic tissue; *2*) insulin infused peripherally in human and dogs is as effective in suppressing HGP as insulin infused intraportally (3–6), suggesting that insulin can inhibit HGP by both direct and indirect actions (rev. in 7); and *3*) HGP is suppressed slowly after exposition to insulin, suggesting that insulin acts first on tissues in which the transport of insulin is limited by the endothelial cell monolayer, as in muscle and adipose tissue (rev. in 8).

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INDIRECT ACTION OF INSULIN ON HEPATIC GLUCOSE PRODUCTION

The indirect effects of insulin on hepatic glucose production (HGP) could be explained by its actions on several tissues and cells (Fig. 1). Insulin inhibits glucagon secretion from pancreatic α-cells, thereby decreasing HGP. Adipose tissue and muscles are exquisitely sensitive to the inhibitory effect of insulin on lipolysis and proteolysis (9); thus, insulin induces a decrease in the release of nonesterified fatty acids and glycerol from adipose tissue and gluconeogenic precursors from skeletal muscles, thus causing a decrease in hepatic gluconeogenesis. More recently, insulin action in the brain has been demonstrated to play a role in the regulation of HGP (10) These different possibilities will be reviewed successively.

Indirect action via the inhibition of glucagon secretion. Blood flow in the islet reaches the β-cells before the α-cells; the insulin concentration at the α-cell affects to a greater extent glucagon secretion than do systemic insulin levels (11,12). Plasma glucagon falls during systemic insulin infusion (13,14), and in vitro, insulin inhibits glucagon secretion from pancreatic α-cells (15,16). Because glucagon is a crucial hormone for maintaining HGP (17), a decrease in glucagon secretion will be followed by an inhibition of HGP. Nevertheless, the role of glucagon in mediating the indirect effects of insulin on HGP is still controversial. Suppression of glucagon has been implicated as an important indirect mediator of the insulin-induced suppression of HGP (4,18,19). Moreover, the maintenance of plasma glucagon at a constant level during systemic insulin infusion diminished the ability of insulin to suppress HGP (4,6,19), suggesting that the indirect effect of insulin in suppressing HGP was lessened when plasma glucagon levels were maintained at a constant level. In contrast, recent data in liver-specific insulin receptor knockout (LIRKO) mice (20) suggest a minimal involvement of glucagon as a regulator of HGP. The failure of insulin to suppress glucagon secretion and HGP in LIRKO mice indicates that both indirect and direct effects of insulin require an intact insulin signaling pathway in the liver. Thus, the importance of inhibition of glucagon secretion for insulin-mediated suppression of HGP still remains to be experimentally demonstrated.

Indirect action via the inhibition of free fatty acid production by adipose tissue. Insulin induces a decrease in the release of nonesterified fatty acids (NEFAs) and glycerol from adipose tissue (21) and gluconeogenic precursors from skeletal muscles (22). Classically, hepatic fatty acid oxidation promotes gluconeogenesis via production of ATP, NADH, and acetyl-CoA (to activate pyruvate carboxylase) (1). Suppression of hepatic NEFA flux (Fig. 2), and presumably hepatic fatty acid oxidation, has consistently been shown to be the dominant mechanism by which actions of systemic insulin can indirectly suppress HGP (21,23–25). The recent finding that insulin suppressed

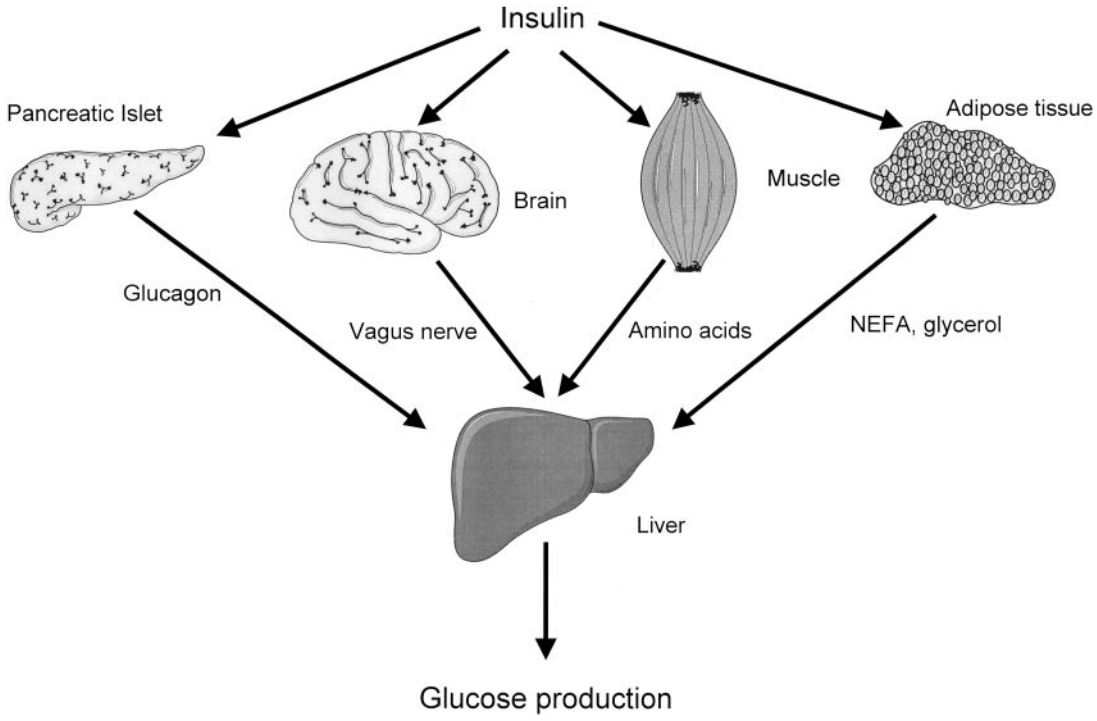

FIG. 1. Possible signals by which systemic insulin may regulate HGP.

NEFAs but failed to suppress glucose production in LIRKO mice (20) demonstrates the absence of an indirect effect of reduced NEFA flux in mediating HGP. If NEFA substrate flux to the liver is indeed a dominant extrahepatic regulator of HGP, these results suggest that this metabolic cross-talk requires the presence of an intact insulin-signaling network. These findings support a unifying hypothesis that NEFA-mediated insulin-induced suppression of HGP occurs via direct modulation of insulin signaling in the liver. NEFA infusion causes a reduction in insulin-stimulated insulin receptor substrate-1–associated phosphatidylinositol 3-kinase activity (26,27). Similarly, increased hepatic intracellular fatty acid–derived metabolites result in defects in insulin activation of insulin receptor substrate-2–associated phosphatidylinositol 3-kinase activity and an impaired ability of insulin to suppress endogenous glucose production in transgenic mice (28) and in rats fed high-fat diets (29).

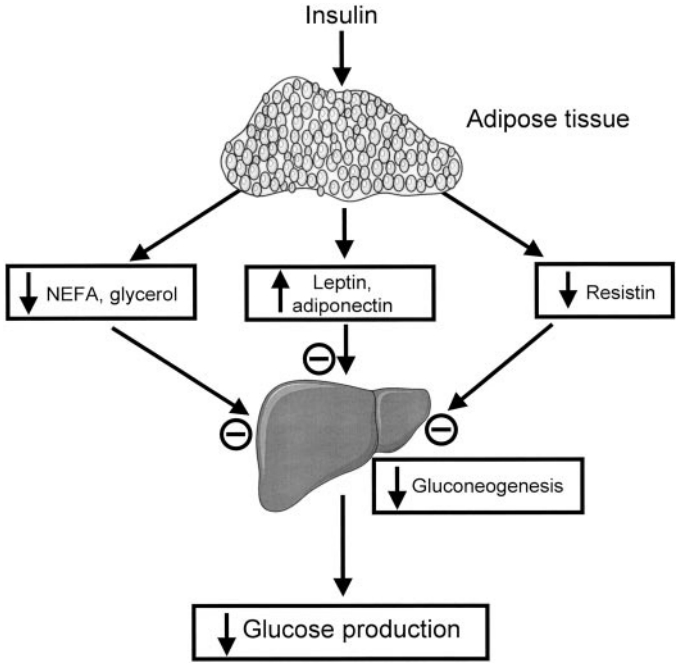

FIG. 2. Possible mechanisms by which insulin action on adipose tissue may regulate HGP.

Another possibility for an indirect action of insulin on HGP via the adipose tissue could be the modulation of adipokine secretion (Fig. 2). Adiponectin and, to a lesser degree, leptin, inhibit HGP and increase the ability of subphysiological levels of insulin to suppress HGP (30–32), suggesting that these adipokines are potent insulin enhancers linking adipose tissue and hepatic glucose metabolism. In contrast, resistin has been reported to increase glucose production (33,34). Because insulin has been shown to stimulate leptin and adiponectin expression (35,36) and to inhibit resistin expression (37), the indirect effects of insulin on HGP could be mediated in part by the modification of adipokine secretion by adipose tissue.

Indirect action via the hypothalamus. Several lines of evidence have revealed a new site of action of insulin on HGP in mice. The infusion of insulin in the third ventricle of rats reduces HGP independently of systemic levels of insulin and other contraregulatory hormones (including glucagon) (38). In addition, the blockade of insulin signaling pathways in the hypothalamus (downregulation of insulin receptor by injection of antisense oligonucleotides, phosphatidylinositol 3-kinase inhibitor) impairs the ability of insulin to inhibit HGP (38–40). Finally, the administration of inhibitors of ATP-sensitive potassium channels blunted the effect of insulin on HGP (38,41). Activation of ATP-sensitive potassium channels in the hypothalamus lowers blood glucose levels through inhibition of HGP and infusion of inhibitors of ATP-sensitive potassium chan-

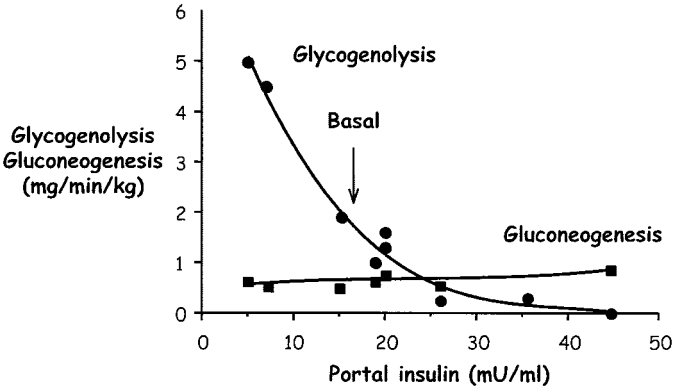

FIG. 3. The effects of rise in portal insulin on glycogenolysis and gluconeogenesis in overnight-fasted conscious dogs. From Burgess et al. (50).

nels, or the surgical resection of the hepatic branch of the vagus nerve reduces the effects of systemic insulin on HGP (41). In addition, mice lacking the SUR1 subunit of the ATP-sensitive potassium channel are resistant to the inhibitory action of insulin on gluconeogenesis (41). Another mechanism by which intracerebral ventricular insulin could inhibit HGP has been recently suggested (42). Insulin acted via the insulin receptor in the brain to induce interleukin-6 expression in hepatic Kupffer cells, which in turn, phosphorylates (activates) STAT3 in the liver and thus participates in the suppression of the hepatic PEPCK and G-6-Pase gene. These data suggest that there is a central nervous system (hypothalamus) liver axis contributing to HGP in response to insulin (43).

IS THE DOMINANT ACTION OF INSULIN ON HGP DIRECT OR INDIRECT?

The best in vivo demonstration of a direct effect of insulin on HGP comes from studies in overnight-fasted dogs in which changes in portal plasma insulin were made, in the absence of changes in plasma glucagon, NEFA, or gluconeogenic precursors, by using the pancreatic clamp technique. These data clearly show that the liver responds directly to insulin by inhibiting HGP (17). A recent article (44) confirms these data and demonstrates that insulin's direct effects on the liver dominate the control of HGP in overnight-fasted dogs. In addition, the authors show that a fourfold rise in head insulin does not enhance the inhibition of HGP in response to portal insulin (44). In perfused rat liver, it has been reported that pulsatile administration of insulin is more efficient than continuous insulin infusion to inhibit HGP (45), which could perhaps explain the incapacity to show an inhibition of HGP in early studies (1,2). Evidence that insulin can also directly inhibit HGP in humans has been obtained (46). An infusion of a small dose of tolbutamide, that does not result in an increase in peripheral insulin concentration, is associated with a rapid and significant decrease in HGP. Because C-peptide levels were higher in response to tolbutamide infusion, this suggested that portal insulin levels were higher despite absence of hyperinsulinemia. Thus, these data are consistent with the hypothesis that a small increase of portal insulin can directly inhibit HGP in humans. Another aspect that should be taken into account is the kinetics of insulin administration. The first phase of insulin secretion is more important for inhibition of HGP in dogs and overnight fasted humans than the second phase of insulin secretion (47). Because the first phase of insulin secretion is unlikely to significantly alter peripheral glucose utilization, this suggests that the direct effects of insulin are more important in restraining HGP than its indirect effects mediated by inhibition of lipolysis, secretion of glucagon, or action on the brain.

The importance of the insulin receptor for the direct and indirect actions of insulin on HGP was supported by the observation that, in LIRKO mice, high-dose insulin fails to suppress HGP (20), but these experiments have been questioned, since the long-term absence of insulin receptor may have induced an adaptive phenotype. Disruption of critical features of glucose metabolism may fail to yield the expected results. This was supported by the finding that even upon restoration of insulin receptors to the livers of LIRKO mice, insulin was not able to suppress HGP (48). This led to the conclusion that both the direct and indirect effects of insulin on HGP require an intact insulin signaling pathway in liver.

HOW CAN WE RECONCILE THE INVESTIGATIONS PERFORMED IN RODENTS AND DOGS?

It is now widely accepted that insulin inhibits HGP by both direct and indirect pathways (7), but controversy remains concerning which pathway exerts the dominant effect. Recently, convincing evidence was presented that the direct effects of insulin on HPG are dominant in overnight-fasted dogs and that the indirect effects of insulin on the brain are of minor importance (44). In contrast, Rossetti and coworkers (10,38) have provided robust evidence to support the existence of an indirect effect of insulin on HGP via the hypothalamus. Recently, a number of methodological and physiological considerations have been proposed to underlie the apparent complexity of insulin's observed actions on HGP (7). In particular, basal HGP in mice is 10–15 times greater (per kilogram of body weight) than in dogs, whereas plasma glucagon levels are similar (49). It is possible that in mice, the liver does have substantial neural input in the basal state and that the removal of hepatic insulin receptors leads to increased neural control of HGP as a protective response. Another possible explanation is that in overnight-fasted dogs, hepatic gluconeogenesis (as opposed to hepatic glycogenolysis) contributes to <50% of HGP, whereas it contributes to ~80–90% of HGP in rodents. In mice fasted for 4 and 24 h, hepatic glycogenolysis contributed to <10–20% of HGP (50). Hepatic gluconeogenesis is much less sensitive to inhibition by insulin than glycogenolysis, both in vivo (51,52) (Fig. 3) and in vitro. Using the perfused rat liver, insulin strikingly suppressed glucose production in liver of fed rats, but the inhibition was very small in liver of fasted rats. Glycogenolysis was the main process involved with a minor contribution from gluconeogenesis (2). Thus, it could be suggested that, in rodents, efficient inhibition of hepatic gluconeogenesis by insulin requires basal inputs from the central nervous system. Several lines of evidence suggest that an autonomic neural input to the liver can modulate liver metabolism (53,54). When insulin levels are increased via a systemic insulin infusion, the activation of central ATP-dependent potassium channels is required for the inhibition of HGP (38). It has been suggested that descending fibers within the hepatic branch of the vagus nerve could vehiculate autonomic neural input to the liver to modulate liver metabolism (Fig. 4). Indeed, the inhibition of central fat oxidation, which like insulin infusion

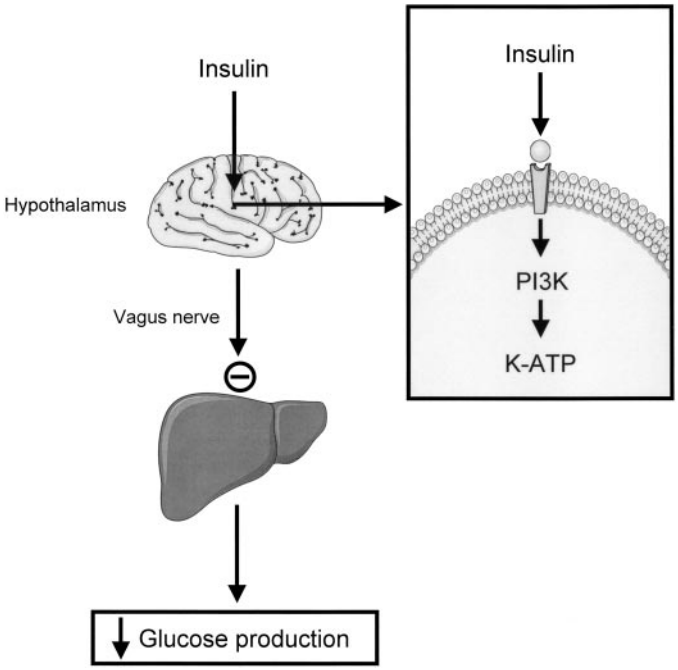

FIG. 4. Possible mechanisms by which insulin action on hypothalamus may regulate HGP. PI3K, phosphatidylinositol 3-kinase.

inhibits HGP, is largely accounted for by a marked inhibition of gluconeogenesis (43). Furthermore, hepatic vagotomy abolishes the effects of inhibition of central fat oxidation on HGP (41,43). It could be of interest to investigate whether the inhibition of HGP in response to insulin infusion is due to an inhibition of gluconeogenesis and whether hepatic vagotomy abolishes this effect (49). Lastly, it is possible that in overnight fasted dogs acute changes in plasma insulin have a predominant direct effect on glycogenolysis, whereas at a later time point, insulin inhibits gluconeogenesis by a predominant indirect effect (secondarily to an inhibition of lipolysis in adipose tissue and proteolysis in skeletal muscle, thus reducing the amount of free fatty acid, glycerol, and amino acids reaching the liver [17]).

RELATIVE IMPORTANCE OF DIRECT AND/OR INDIRECT EFFECTS OF INSULIN ON HGP FOR THE TREATMENT OF DIABETES

The relative importance of direct and/or indirect effects of insulin on HGP could have implications for diabetes treatment. Indeed, the enhanced HGP observed in type 2 diabetes is primarily due to an increased gluconeogenesis (55). Because gluconeogenesis is much less sensitive than glycogenolysis to inhibition by insulin, hepatic insulin resistance observed in type 2 diabetes could be simply due to the enhanced gluconeogenesis and not necessarily to a defect in insulin signaling. If this is true, a rational therapeutic approach for the correction of hepatic glucose overproduction in type 2 diabetes would be an inhibition of gluconeogenesis. Plasma glucagon is increased throughout the day in type 2 diabetic patients despite hyperglycemia (56), and glucagon stimulates gluconeogenic enzyme gene expression (57). This could explain the predominance of this pathway in the liver of type 2 diabetic patients. Recently, it was shown that GLP-1, in addition to its well-known effect on the stimulation of insulin secretion, was able to inhibit glucagon secretion (58). This molecule could have promising effects for the treatment of increased HGP seen in type 2 diabetes.

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