Insulin’s effect on the liver: “Direct or indirect?” continues to be the question

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Previous studies suggest that insulin can inhibit hepatic glucose production (HGP) 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. A study in this issue of the JCI demonstrates that, in overnight-fasted dogs, an acute, selective increase of portal insulin induces a rapid inhibition of HGP, and a 4-fold rise in head insulin level does not enhance the inhibition of HGP in response to portal insulin infusion (see the related article beginning on page 521). This study demonstrates that insulin’s direct effects on the liver dominate the control of HGP. These data balance previous studies in mice that suggested that indirect effects of insulin via the hypothalamus are the primary determinant of HGP.

Introduction

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. However, 2 observations challenged this view: (a) whereas insulin is a potent inhibitor of HGP in vivo, the hormone is relatively ineffective in vitro in rodent liver (1), suggesting that insulin primarily acts on an extrahepatic tissue; and (b) peripheral insulin infusion in humans and dogs is just as effective as intraportal insulin infusion in suppressing HGP (2–4), suggesting that insulin can inhibit HGP by both direct and indirect actions (reviewed in ref. 5).

Indirect action of insulin on HGP

The indirect effects of insulin on HGP could be explained by its actions on pancreatic α cells, adipose tissue, and skeletal muscles. Insulin inhibits glucagon secretion from pancreatic α cells, thereby decreasing HGP (6, 7). Adipose tissue and muscles are exquisitely sensitive to the inhibitory effect of insulin on lipolysis and proteolysis. Insulin induces a decrease in the release of nonesterified fatty acids and glycerol from adipose tissue (8) and gluconeogenic precursors from skeletal muscles (9), thus causing a decrease in hepatic gluconeogenesis. More recently, insulin action on the brain has been demonstrated to play a role in the regulation of HGP (10): infusion of insulin in the third cerebral ventricle of rats reduces HGP. The blockade of insulin receptors in the rodent hypothalamus (by injection of antisense oligonucleotides that
inhibit insulin receptor expression) impairs the ability of insulin to inhibit HGP (11).

Direct and dominant action of insulin on HGP

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, in the absence of changes in plasma glucagon, nonesterified fatty acid, or gluconeogenic precursors, effectively inhibit HGP (12). The study reported by Edgerton et al. in this issue of the JCI confirms these data and demonstrates that insulin’s direct effects on the liver dominate the control of HGP in overnight-fasted dogs (13). In addition, the authors show that a 4-fold rise in head insulin level does not enhance the inhibition of HGP in response to portal insulin infusion. The importance of the insulin receptor for the direct actions of insulin on HGP was supported by the observation that, in liver-specific insulin receptor knockout (LIRKO) mice, high-dose insulin fails to suppress HGP (14), but these results have been questioned, since the long-term absence of the insulin receptor may have induced an adaptive phenotype. This was supported by the finding that even upon restoration of insulin receptors to the liver of LIRKO mice, insulin was not able to suppress HGP (15). This led to the conclusion that both the direct and the indirect effects of insulin on HGP require an intact insulin-signaling pathway in liver.

How do we reconcile the investigations performed in rodents and in dogs?

It is now widely accepted that insulin inhibits HGP by both direct and indirect pathways (5), but controversy remains concerning which pathway exerts the dominant effect. In this issue of the JCI, Edgerton and colleagues provide convincing evidence that the direct effects of insulin on HGP are dominant in overnight-fasted dogs and that the indirect effects of insulin on the brain are of minor importance (13). In contrast, Rossetti and coworkers (10, 16) have provided robust evidence to support the existence of an indirect effect of insulin on HGP via the hypothalamic axis. Recently, a number of methodological and physiological considerations have been proposed to underlie the apparent complexity of insulin’s observed actions on HGP (5). In particular, basal HGP is 10–15 times greater (per kilogram of body weight) in mice than in dogs, while plasma glucagon levels are similar. It is possible that, in mice, the liver does have substantial neural input in the basal state and 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 glycolysis) contributes to less than 50% of HGP, whereas it contributes to approximately 80–90% of HGP in rodents. In mice fasted for 4 hours and 24 hours, hepatic glycolysis contributed to less than 10–20% of HGP (17). As hepatic gluconeogenesis is much less sensitive to inhibition by insulin than glycolysis (18), it could be suggested that, in mice, efficient inhibition of hepatic gluconeogenesis by insulin requires basal inputs from the CNS. Several lines of evidence suggest that an autonomic neural input to the liver can modulate liver metabolism (19, 20). 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 (16). 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. Indeed, the inhibition of central fat oxidation, which, like insulin infusion, inhibits HGP, is largely accounted for by a marked inhibition of gluconeogenesis (21). Furthermore, hepatic vagotomy abolishes the effects of inhibition of central fat oxidation on HGP (21). 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 aboliishes this effect.

It is possible that in overnight-fasted dogs, acute changes in plasma insulin have a predominantly direct effect on glyco-

Concluding remarks

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 patients is primarily due to an increase in gluconeogenesis (22). As gluconeogenesis is much less sensitive than glycolysis to the inhibition by insulin, hepatic insulin resistance observed in type 2 diabetics could be due simply 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 HGP in type 2 diabetes would be an inhibition of gluconeogenesis. Plasma glucagon levels are increased throughout the day in type 2 diabetic patients despite hyperglycemia (23), and glucagon stimulates gluconeogenic enzyme gene expression (24). This could explain the predominance of this pathway in the liver of type 2 diabetics. Recently, it has been shown that glucagon-like peptide-1, in addition to its well-known effect on the stimulation of insulin secretion, was able to inhibit glucagon secretion (25). This molecule could have promising effects for the treatment of increased HGP seen in type 2 diabetes.
Thus, this work establishes a feedback loop whereby Fcγ phagocytes. The 2 most important opsonins in blood are Ig and complement (C). Specifically, IgG and C3b bind to a target where they serve as ligands for Fcγ and C receptors, respectively. This reaction can be conveniently split into 2 sequential steps; namely, immune adherence followed by internalization. Early on, it was recognized that C3b and C receptors most effectively mediated the adherence step, while Fcγ receptors (FcγRs) most effectively mediated the internalization step. This combination of “talents” ensures efficient phagocytosis of an infectious particle. As the humoral immune response rapidly matures, it deposits more and more IgG on particles, which subsequently elicits complement activation.

Many types of in vivo and in vitro experiments have demonstrated how much more proficient C3b and IgG are as partners than either is alone in promoting phagocytosis. C3b can mediate internalization but requires a relatively large ligand load and activated monocytes/macrophages. IgG can mediate adherence, but again, a heavy dose of ligand is necessary. However, a combination of C3b and IgG is synergistic in mediating the phagocytic process. Thus, this cooperation between the receptors for these 2 ligands enhances this time-honored immune phenomenon that is critical to survival. In this issue of the JCI, Kumar, Gessner, and colleagues provide further evidence for another remarkable interaction among complement-derived ligands, Igs, and their receptors (1).

Cross-talk between C5a and FcγRs
Kumar et al. (1) report a clear demonstration of cross-talk between the C and Ig receptors (Figure 1 and Table 1). In a mouse model of a so-called antibody-dependent, type II autoimmune reaction, the authors convincingly demonstrate the following interesting sequence of events: (a) upon injection of an autoantibody to mouse rbc, immune complexes form that bind to FcγRs on liver macrophages (Kupffer cells); (b) these cells in turn secrete C5 and possibly a protease (yet to be clearly defined) that cleaves C5 into the anaphylatoxin C5a and the initiator of membrane attack complex, C5b; (c) C5a binds to its receptor (C5AR) on Kupffer cells, which upregulates FcγR mRNA expression; and then (d) the increased number of FcγRs on these macrophages facilitates elimination of the antibody-coated rbc, thereby leading to a more severe hemolytic anemia. While this

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Opsonization: helping phagocytes to eat
Opsonins attach to invading microorganisms and other antigens in order to enhance the uptake of foreign particles by phagocytes. The 2 most important opsonins in blood are Ig and complement (C). Specifically, IgG and C3b bind to a target where they serve as ligands for Fcγ and C receptors, respectively. This reaction can be conveniently split into 2 sequential steps; namely, immune adherence followed by internalization. Early on, it was

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Citation for this article: J Clin Invest. 116:304–306 (2006). doi:10.1172/JCI27759.

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