

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

Jean Girard

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).

From the Département Endocrinologie, Métabolisme, and Cancer, Institut Cochin, Paris, France; the Institut National de la Santé et de la Recherche Médicale, Paris, France; the Centre National de la Recherche Scientifique, Paris, France; and the Faculté de Médecine René Descartes, Université Paris, Paris, France.

Address correspondence and reprint requests to Jean Girard, Département Endocrinologie, Métabolisme, and Cancer, Institut Cochin, 24 rue du Fbg Saint-Jacques, F-75014 Paris, France. E-mail: girard@cochin.inserm.fr.

Received for publication 27 March 2006 and accepted in revised form 12 May 2006.

This article is based on a presentation at a symposium. The symposium and the publication of this article were made possible by an unrestricted educational grant from Servier.

HGP, hepatic glucose production; NEFA, nonesterified fatty acid.

DOI: 10.2337/db06-S009

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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

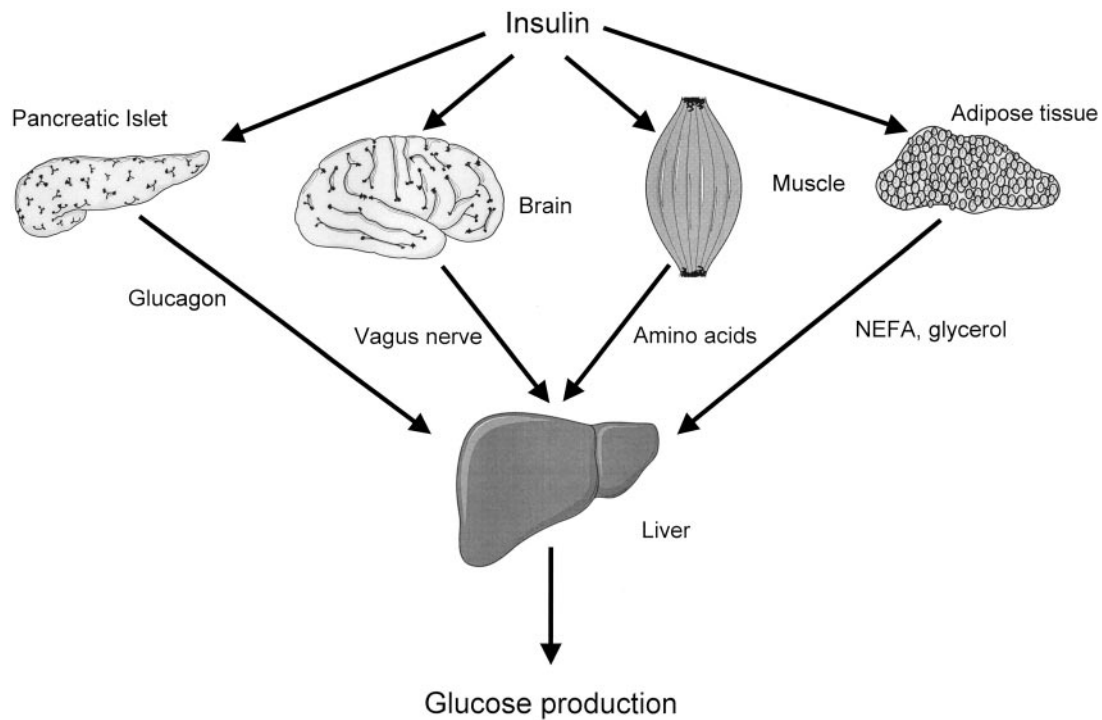


FIG. 1. Possible signals by which systemic insulin may regulate HGP.

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-stimu-

lated 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).

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-

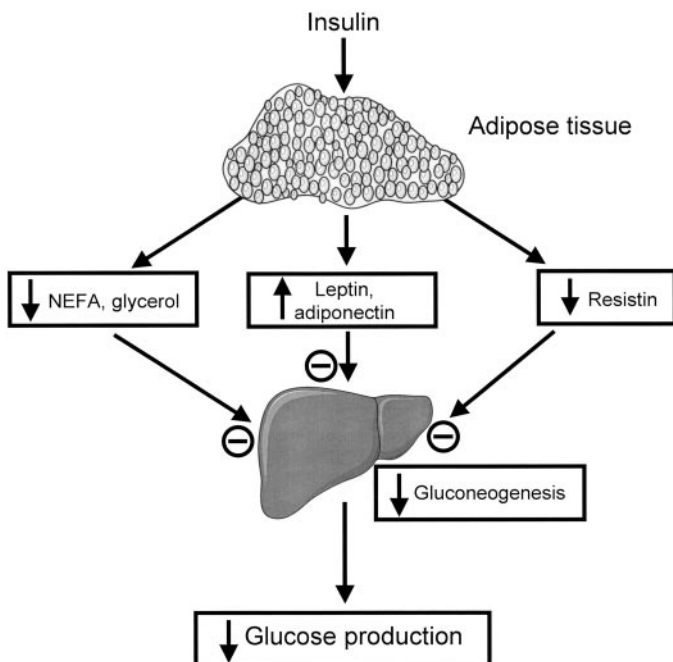


FIG. 2. Possible mechanisms by which insulin action on adipose tissue may regulate HGP.

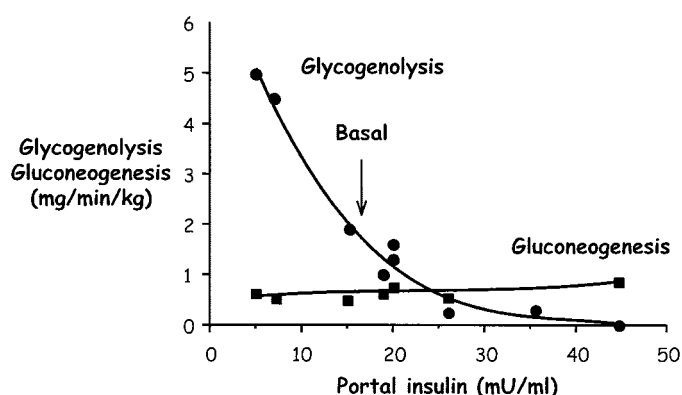


FIG. 3. The effects of rise in portal insulin on glycogenolysis and gluconeogenesis in overnight-fasted conscious dogs. From Burgess et al. (50).

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 HGP 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

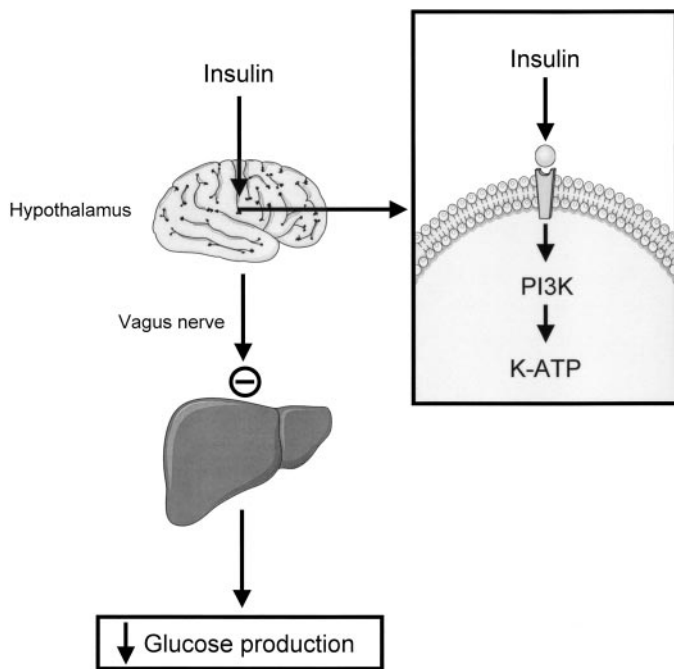


FIG. 4. Possible mechanisms by which insulin action on hypothalamus may regulate HGP. PI3K, phosphatidylinositol 3-kinase.

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.

REFERENCES

- Williamson J, Wright P, Malaisse W, Ashmore J: Control of gluconeogenesis by acetyl CoA in rats treated with glucagon and anti-insulin serum. *Biochem Biophys Res Commun* 22:765–770, 1966
- Mortimore G: Effect of insulin on release of glucose and urea by isolated rat liver. *Am J Physiol* 204:399–704, 1961
- Ader M, Bergman R: Peripheral effects of insulin dominate suppression of fasting hepatic glucose production. *Am J Physiol* 258:E1020–E1032, 1990
- Giacca A, Fisher SJ, Shi ZQ, Gupta R, Lickley HLA, Vranic M: Importance of insulin levels for insulin-induced suppression of glucose production in depancreatized dogs. *J Clin Invest* 90:1769–1777, 1992
- Rebrin K, Steil GM, Getty L, Bergman RN: Free fatty acid as a link in the regulation of hepatic glucose output by peripheral insulin. *Diabetes* 44:1038–1045, 1995
- Lewis GF, Zinman B, Groenewoud Y, Vranic M, Giacca A: Hepatic glucose production is regulated both by direct hepatic and extrahepatic effects of insulin in humans. *Diabetes* 45:454–462, 1996
- Cherrington AD: The role of hepatic insulin receptors in the regulation of glucose production. *J Clin Invest* 115:1136–1139, 2005
- Bergman RN: Pathogenesis and prediction of diabetes mellitus: lessons from integrative physiology. *Mt Sinai J Med* 69:280–290, 2002
- Cahill GJ: Physiology of insulin in man. *Diabetes* 20:785–799, 1971
- Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L: Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nat Neurosci* 5:566–572, 2002
- Maruyama H, Hisatomi A, Orci L, Grodsky G, Unger R: Insulin within islets is a physiological glucagon release inhibitor. *J Clin Invest* 74:2296–2229, 1984
- Samols E, Stagner J, Ewart R, Marks V: The order of islet microvascular cellular perfusion is B to A to D in the perfused rat pancreas. *J Clin Invest* 82:350–353, 1988
- Raskin P, Fujita Y, Unger R: Effect of insulin-glucose infusions on plasma glucagon levels in fasting diabetics and nondiabetics. *J Clin Invest* 56:1132–1138, 1975
- Asplin C, Paquette T, Palmer J: In vivo inhibition of glucagon secretion by paracrine beta cell activity in man. *J Clin Invest* 68:314–318, 1981
- Ishihara H, Maechler P, Gjinovci A, Herrera PL, Wollheim CB: Islet β -cell secretion determines glucagon release from neighbouring alpha-cells. *Nat Cell Biol* 5:330–335, 2003
- Diao J, Asghar Z, Chan CB, Wheeler MB: Glucose-regulated glucagon secretion requires insulin receptor expression in pancreatic alpha-cells. *J Biol Chem* 280:33487–33496, 2005
- Cherrington A: Control of glucose uptake and release by the liver in vivo. *Diabetes* 48:1198–1214, 1999
- Giacca A, Fisher SJ, McCall RH, Shi ZQ, Vranic M: Direct and indirect effects of insulin in suppressing glucose production in depancreatized dogs: role of glucagon. *Endocrinology* 138:999–1007, 1997
- Lewis GF, Vranic M, Giacca A: Glucagon enhances the direct suppressive effect of insulin on hepatic glucose production in humans. *Am J Physiol* 271:E371–E378, 1997
- Fisher SJ, Kahn CR: Insulin signaling is required for insulin's direct and indirect action on hepatic glucose production. *J Clin Invest* 111:463–468, 2003
- Sindelar DK, Chu CA, Rohlie M, Neal DW, Swift LL, Cherrington AD: The role of fatty acids in mediating the effects of peripheral insulin on hepatic glucose production in the conscious dog. *Diabetes* 46:187–196, 1997
- Sindelar DK, Balcom JH, Chu CA, Neal DW, Cherrington AD: A comparison of the effects of selective increases in peripheral or portal insulin on hepatic glucose production in the conscious dog. *Diabetes* 45:1594–1604, 1996
- Rebrin K, Steil GM, Mittelman SD, Bergman RN: Causal linkage between insulin suppression of lipolysis and suppression of liver glucose output in dogs. *J Clin Invest* 98:741–749, 1996
- Lewis GF, Vranic M, Harley P, Giacca A: Fatty acids mediate the acute extrahepatic effects of insulin on hepatic glucose production in humans. *Diabetes* 46:1111–1119, 1997
- Mittelman SD, Bergman RN: Inhibition of lipolysis causes suppression of endogenous glucose production independent of changes in insulin. *Am J Physiol* 279:E630–E637, 2000
- Griffin ME, Marcucci MJ, Cline GW, Bell K, Barucci N, Lee D, Goodyear LJ, Kraegen EW, White MF, Shulman GI: Free fatty acid-induced insulin resistance is associated with activation of protein kinase C θ and alterations in the insulin signaling cascade. *Diabetes* 48:1270–1274, 1999
- Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, Slezak

- LA, Andersen DK, Hundal RS, Rothman DL, Petersen KF, Shulman GI: Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. *J Clin Invest* 103:253–259, 1999
28. Kim J, Fillmore J, Chen Y, Yu C, Moore I, Pypaert M, Lutz E, Kako Y, Velez-Carrasco W, Goldberg I, Breslow J, Shulman G: Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proc Natl Acad Sci U S A* 98:7522–7527, 2001
 29. Samuel V, Liu Z, Qu X, Elder B, Bilz S, Befroy D, Romanelli A, Shulman G: Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *J Biol Chem* 279:32345–32353, 2004
 30. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L: Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J Clin Invest* 108:1875–1881, 2001
 31. Berg A, Combs TP, Du X, Brownlee M, Scherer PE: The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 7:947–953, 2001
 32. Lam NT, Lewis JT, Cheung AT, Luk CT, Tse J, Wang J, Bryer-Ash M, Kolls JK, Kieffer TJ: Leptin increases hepatic insulin sensitivity and protein tyrosine phosphatase 1B expression. *Mol Endocrinol* 18:1333–1345, 2004
 33. Banerjee R, Rangwala S, Shapiro J, Rich A, Rhoades B, Qi Y, Wang J, Rajala M, Pocai A, Scherer P, Steppan C, Ahima R, Obici S, Rossetti L, Lazar M: Regulation of fasted blood glucose by resistin. *Science* 303:1195–1198, 2004
 34. Muse ED, Obici S, Bhanot S, Monia BP, McKay RA, Rajala MW, Scherer PE, Rossetti L: Role of resistin in diet-induced hepatic insulin resistance. *J Clin Invest* 114:232–239, 2004
 35. Saladin R, De Vos P, Guerre-Millo M, Leturque A, Girard J, Staels B, Auwerx J: Insulin mediates the transient increase in ob gene expression after food intake. *Nature* 377:527–529, 1995
 36. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ: Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 87:5662–5667, 2002
 37. Haugen F, Jorgensen A, Drevon CA, Trayhurn P: Inhibition by insulin of resistin gene expression in 3T3-L1 adipocytes. *FEBS Lett* 507:105–108, 2001
 38. Obici S, Zhang BB, Karkanas G, Rossetti L: Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat Med* 8:1376–1382, 2002
 39. Buettner C, Patel R, Muse ED, Bhanot S, Monia BP, McKay R, Obici S, Rossetti L: Severe impairment in liver insulin signaling fails to alter hepatic insulin action in conscious mice. *J Clin Invest* 115:1306–1313, 2005
 40. Gelling RW, Morton GJ, Morrison CD, Niswender KD, Myers MGJ, Rhodes CJ, Schwartz MW: Insulin action in the brain contributes to glucose lowering during insulin treatment of diabetes. *Cell Metab* 3:67–73, 2006
 41. Pocai A, Lam TKT, Gutierrez-Juarez R, Obici S, Schwartz GJ, Bryan J, Aguilar-Bryan L, Rossetti L: Hypothalamic K-ATP channels control hepatic glucose production. *Nature* 43:1026–1031, 2005
 42. Inoue H, Ogawa W, Asakawa A, Okamoto Y, Nishizawa A, Matsumoto M, Teshigawara K, Matsuki Y, Watanabe E, Hiramatsu R, Notohara K, Katayose K, Okamura H, Kahn CR, Noda T, Takeda K, Akira S, Inui A, Kasuga M: Role of hepatic STAT3 in brain-insulin action on hepatic glucose production. *Cell Metab* 3:267–275, 2006
 43. Pocai A, Obici S, Schwartz G, Rossetti L: A brain-liver circuit regulates glucose homeostasis. *Cell Metab* 1:53–61, 2005
 44. Edgerton DS, Lautz M, Scott M, Everett CA, Stettler KM, Neal DW, Chu CA, Cherrington AD: Insulin's direct effects on the liver dominate the control of hepatic glucose production. *J Clin Invest* 116:521–527, 2006
 45. Komjati M, Bratusch-Marrain P, Waldhausl W: Superior efficacy of pulsatile versus continuous hormone exposure on hepatic glucose production in vitro. *Endocrinology* 118:312–319, 1986
 46. Maheux P, Chen Y, Polonsky K, Reaven G: Evidence that insulin can directly inhibit hepatic glucose production. *Diabetologia* 40:1300–1306, 1997
 47. Cherrington A, Sindelar D, Edgerton D, Steiner K, McGuinness O: Physiological consequences of phasic insulin release in the normal animal. *Diabetes* 51 (Suppl. 1):S103–S108, 2002
 48. Okamoto H, Obici S, Accili D, Rossetti L: Restoration of liver insulin signaling in Insr knockout mice fails to normalize hepatic insulin action. *J Clin Invest* 115:1314–1322, 2005
 49. Girard J: Insulin's effect on the liver: "Direct or indirect?" continues to be the question. *J Clin Invest* 116:302–304, 2006
 50. Burgess SC, Jeffrey FMH, Storey C, Milde A, Hausler N, Merritt ME, Mulder H, Holm C, Sherry AD, Malloy CR: Effect of murine strain on metabolic pathways of glucose production after brief or prolonged fasting. *Am J Physiol* 289:E53–E61, 2005
 51. Chiasson JL, Liljenquist JE, Finger FE, Lacy WW: Differential sensitivity of glycogenolysis and gluconeogenesis to insulin infusion in dogs. *Diabetes* 25:283–291, 1976
 52. Chiasson JL, Atkinson RL, Cherrington AL, Sinclair-Smith BC, Lacy WW, Liljenquist JE: Effects of insulin at two dose levels on gluconeogenesis from alanine in fasting man. *Metabolism* 29:810–818, 1980
 53. Shimazu T: Neuronal regulation of hepatic glucose metabolism in mammals. *Diabetes Metab Rev* 3:185–206, 1987
 54. Jungermann K, Gardemann A, Beuers SU, Balle C, Sannemann J, Beckh K, Hartmann H: Regulation of liver metabolism by hepatic nerves. *Adv Enzyme Regul* 26:63–88, 1987
 55. Magnusson I, Rothman D, Katz L, Shulman R, Shulman G: Increased rate of gluconeogenesis in type II diabetes mellitus: a ¹³C nuclear magnetic resonance study. *J Clin Invest* 90:1323–1327, 1992
 56. Reaven GM, Chen YDI, Golay A, Swislocki ALM, Jaspan JB: Documentation of hyperglucagonemia throughout the day in nonobese and obese patients with non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 64:106–110, 1987
 57. Granner DK, Pilkis SJ: The genes of hepatic glucose metabolism. *J Biol Chem* 265:10173–10176, 1990
 58. Drucker DJ: Biologic actions and therapeutic potential of the proglucagon-derived peptides. *Nature Clin Pract Endocrinol Metab* 1:22–31, 2005