Insulin resistance is associated with numerous metabolic disorders, such as obesity and type II diabetes, that currently plague our society. Although insulin normally promotes anabolic metabolism in the liver by increasing glucose consumption and lipid synthesis, insulin-resistant individuals fail to inhibit hepatic glucose production and paradoxically have increased liver lipid synthesis, leading to hyperglycemia and hypertriglyceridemia. Here, we detail the intrahepatic and extrahepatic pathways mediating insulin's control of glucose and lipid metabolism. We propose that the interplay between both of these pathways controls insulin signaling and that mis-regulation between the 2 results in the paradoxical effects seen in the insulin-resistant liver instead of the commonly proposed deficiencies in particular branches of only the direct hepatic pathway. (Cell Mol Gastroenterol Hepatol 2019;7:447–456; https://doi.org/10.1016/j.jcmgh.2018.10.016)

Keywords: Insulin Signaling; Hepatic Insulin Resistance; PI3K/Akt Signaling Pathway; Hepatic Glucose Production; De Novo Lipogenesis; Metabolism.

Metabolic disorders such as obesity and type II diabetes mellitus (T2DM) have reached epidemic proportions and continue to be a leading cause of death worldwide.¹ The liver plays a central role in the systemic regulation of glucose and lipid metabolism and aberrant hepatic insulin action is thought to be a primary driver of insulin resistance, in which higher circulating insulin levels are necessary to adequately control blood glucose levels. During a normal physiologic fasting period, a high glucagon-to-insulin ratio decreases the rate of glucose consumption and shifts the liver to glucose production, first by consuming its stores of glycogen (glycogenolysis) and then from gluconeogenic precursors in a synthetic pathway (gluconeogenesis).² In the postprandial state, decreasing glucagon and increasing insulin levels signal the liver to increase glucose consumption, stop glucose production, and store excess nutrients in the form of glycogen and lipids.³ In pathologic states, such as obesity and T2DM, insulin fails to appropriately regulate hepatic metabolism, leading to excess production of glucose despite accelerated rates of lipid synthesis, a condition now commonly referred to as selective hepatic insulin resistance.⁴ As a consequence, insulin-resistant disorders such as obesity and T2DM are closely linked to nonalcoholic fatty liver disease (NAFLD), a disorder that can lead to liver dysfunction and progress to deadly nonalcoholic steatohepatitis.⁵

Increased rates of glucose production and lipogenesis are well documented in insulin-resistant human beings. Patients with NAFLD almost universally show hyperinsulinemia.⁶ In addition, both obese and diabetic human beings show a higher prevalence of NAFLD than lean ones.⁷ Isotope labeling experiments in subjects with NAFLD showed that subjects with increased hepatic steatosis had 2-fold higher rates of de novo lipogenesis and increased plasma levels of free fatty acids (FFAs) and insulin.⁸ In addition to increased lipid synthesis, insulin-resistant individuals have increased rates of hepatic glucose production (HGP).⁹ Indeed, there is a significant correlation between rates of gluconeogenesis and the extent of liver fat in NAFLD patients.¹⁰ Therefore, during the progression of insulin resistance, insulin fails to suppress HGP yet continues to drive excess lipid synthesis, leading to the sequela of NAFLD, hyperglycemia, and hypertriglyceridemia.

Experiments in both mice and human beings have shown the essential role for hepatic insulin action in the regulation of glucose production and lipogenesis. Liver insulin resistant knockout mice (LIRKO) mice fail to inhibit glucose production and cannot induce de novo lipogenesis.¹¹-¹⁴ In addition, LIRKO mice fail to accumulate lipids and do not develop fatty liver, even when fed a high-fat diet, despite increased blood glucose and insulin levels.¹² These
liver-specific knockout mouse models resemble human beings that lack a functioning insulin receptor and show extremely high blood glucose levels, however, hepatic steatosis fails to arise. The clinical findings corroborate the concept that the liver is the key driver of insulin’s whole-body action on glucose and lipid homeostasis. Further supporting this statement, fat-specific deletion of the insulin receptor results in lipodystrophy along with insulin resistance and hyperglycemia. However, these mice are not protected from NAFLD, and eventually develop nonalcoholic steatohepatitis, unlike the LIRKO mice and human beings with insulin-receptor mutations. Experiments using congenital mouse models can pose some issues because off-target effects of genetic manipulation can develop over time and obscure results. For example, LIRKO mice are typically smaller than wild-type mice, possibly because of defects in the insulin-like growth factor axis, and eventually the observed effects, such as hyperglycemia, disappear as a result of liver failure. In these instances, inducible genetic knockouts hold some benefit because one can observe the direct effects of the knockout before the off-target effects begin to manifest. In this case, inducible knockout of the insulin receptor reciprocates the glucose intolerance and hyperinsulinemia of the LIRKO mice without the off-target metabolic effects. These mice also fail to promote hepatic lipogenesis in response to a high carbohydrate meal. Resolving what specific factors mediate insulin action on the liver to generate these paradoxical effects has become a major focus in obesity and T2DM studies and has provided many insights into the molecular mechanisms of insulin action and hepatic metabolism. Here, we discuss these pathways in depth and suggest an integrated model to deconvolute the paradox of hepatic insulin action that integrates the direct effects of insulin action on the liver with many extrahepatic pathways from peripheral metabolic organs.

**Hepatic Insulin Signaling and Lipid Metabolism**

Strong evidence has indicated that the phosphoinositide-3-phosphate kinase (PI3K)/Akt pathway is the key signaling pathway that mediates the effects of insulin on anabolic metabolism in all organisms. When insulin binds to the insulin receptor (IR), it recruits and activates PI3K through insulin-receptor substrates (IRS), generating phosphatidylinositol (3,4,5)-trisphosphate (PIP3). IRS proteins link the insulin receptor (IR), it recruits and activates PI3K through phosphotyrosine residues on the insulin receptor. Knockout of multiple insulin-receptor substrates prevents activation of the pathway in response to insulin, leading to insulin resistance and hyperglycemia, but not hepatic steatosis. PIP3 initiates recruitment of Akt (named as such when it was discovered to be the oncogene responsible for thymoma in Ak mice, also called protein kinase B) and activates it through 3-phosphoinositide-dependent protein kinase 1 via phosphorylation of Thr308 on Akt (Figure 1). Hepatic PI3K deletion in mice prevents steatosis; however, the mice still show significant glucose intolerance, hyperinsulinemia, and impaired Akt activity. In addition, deficiency in 3-phosphoinositide-dependent protein kinase 1 in mouse liver causes glucose intolerance and results in liver failure. Opposing the action of PI3K, phosphatase and tensin homolog (PTEN) dephosphorylates PIP3, rendering it inactive (Figure 1). In vivo deletion of PTEN results in substantial lipid accumulation in the liver. Studies have shown that deletion of Akt2 is sufficient to prevent lipid accumulation in livers with PTEN also removed, suggesting that Akt serves as the essential downstream signaling kinase. Full activation of Akt also requires an additional phosphorylation by mechanistic target of rapamycin complex 2 (mTORC2) at Ser473 (Figure 1). Of the 3 isoforms of Akt, Akt2 (protein kinase Bβ) plays the most substantial role in metabolic regulation because mice with germline deletion of Akt2 show insulin resistance and a diabetes-like phenotype. Mice lacking hepatic Akt2, the most abundant hepatic isoform, have decreased lipid accumulation, and decreased de novo lipogenesis in the liver of ob/ob mice or mice subjected to a high-fat diet. However, despite its abundance, liver-specific deletion of Akt2 only results in mild insulin resistance owing to residual Akt1 activity. Knockout of both Akt1 and 2 is necessary to fully suppress Akt activity in the liver and leads to severe insulin resistance, glucose intolerance, and a reduction in hepatic lipid synthesis.

Because several studies support an obligate role of hepatic insulin action to regulate lipid metabolism, defining the mechanisms downstream of Akt are essential for understanding the pathogenesis of NAFLD during insulin resistance. One major downstream target of Akt is the mechanistic target of rapamycin complex 1 (mTORC1). Akt activates mTORC1 through inhibition of the tuberous sclerosis complex (TSC), a protein that inhibits mTORC1 localization to and activation at the lysosome through inhibition of Rheb (Figure 1). Activation of mTORC1 shifts the cell from a catabolic to an anabolic and proliferative state in which protein, lipid, and nucleic acid synthesis become greatly enhanced. Because one of the hallmarks of T2DM and insulin resistance is enhanced de novo lipogenesis, research has focused on determining the role of mTORC1 in de novo lipogenesis and hepatic lipid metabolism. Studies have shown that activation of mTORC1 is required for de novo lipogenesis, however, activation of mTORC1 alone is not sufficient to induce lipogenesis in the absence of hepatic insulin signaling. This is consistent with the phenotype of mice lacking Tsc specifically in hepatocytes because liver-specific TSC knockout fails to induce lipogenesis and lipogenic gene expression despite constitutive mTORC1 signaling, suggesting Akt regulates hepatic lipid metabolism via mTORC1-dependent and independent pathways.

Sterol regulatory element binding protein 1c (SREBP1c) is a member of the SREBP class of transcription factors that are key players in controlling cellular expression of genes required for lipid and cholesterol metabolism. Insulin regulates SREBP1c by both enhancing its gene expression and post-translational processing. Akt mediates these processes through multiple downstream pathways. mTORC1, in particular, is a key activator of SREBP1c because inhibiting
mTORC1 blocks insulin-dependent cleavage and activation of SREBP1c\textsuperscript{40,41} (Figure 1). For example, SREBP1c processing in transgenic rats requires S6K1, a target of mTORC1.\textsuperscript{41} Consistent with increased lipogenesis in insulin-resistant models, several models for diabetes in mice, such as \textit{ob/ob}, involve heightened levels of SREBP1c activity.\textsuperscript{42,43} SREBP cleavage-activating protein (SCAP) is a major regulator of SREBP activity because it chaperones SREBP proteins from the endoplasmic reticulum to the Golgi where it is cleaved, releasing the active part of SREBP to the nucleus where it regulates transcription.\textsuperscript{44} SCAP is required for activation of all isoforms of SREBP and its deletion significantly reduces cholesterol and fatty acid synthesis in the liver.\textsuperscript{45} In addition, eliminating SCAP specifically in hepatocytes reduces lipid accumulation in the liver and is sufficient to prevent hepatic steatosis in \textit{ob/ob} mice and sucrose-fed hamsters.\textsuperscript{43} Therefore, SREBP1c is a necessary factor in lipogenic gene expression and in the development of fatty liver.

In addition to SREBP1c, carbohydrate response element binding protein (ChREBP) is a well-studied, glucose-responsive transcription factor that may play a role in controlling hepatic lipid metabolism. Glucose-6-phosphate is the key activator of ChREBP, facilitating its migration to the nucleus.\textsuperscript{46} (Figure 1). Because insulin signaling enhances glucose uptake in the liver, ChREBP becomes activated. As a transcription factor, ChREBP activates similar lipogenic genes to SREBP1c, although its roles in insulin sensitivity remain controversial. Normal mice with ChREBP deleted globally show decreased lipogenesis as well as mild insulin resistance.

Figure 1. PI3K/Akt signaling in hepatocytes. Insulin binds to and activates the insulin receptor on the liver surface after a meal. After activation, the receptor recruits and activates IRS, which then activates PI3K. PI3K phosphorylates the signaling lipid molecule PIP\textsubscript{2} into PIP\textsubscript{3} in a process that is opposed by PTEN. PIP\textsubscript{3} activates 3-phosphoinositide-dependent protein kinase 1 (PDK1), which phosphorylates Akt at Thr308. To fully activate Akt, mTORC2 also must phosphorylate it at Ser473. From Akt, different pathways for controlling glucose and lipid homeostasis branch out. Glycogen synthesis is induced through Akt inhibition of GSK3. In addition, Akt can promote glycogen synthesis in a manner independent of GSK3, such as activation of GYS2 by glucose-6-phosphate (G6P). Akt inhibition of TSC activates mTORC1, which in turn activates the lipogenic gene program through activation of SREBP1c and Gck, which phosphorylates glucose to G6P, which feeds into glycolysis and glycogen synthesis. In addition, G6P activates ChREBP, which activates lipogenesis along with SREBP1c. Akt inhibits FoxO1, resulting in an inhibition of gluconeogenesis by suppressing expressing of the proteins glucose-6-phosphatase (G6pc) and Pck1. Externally, FFAs can promote gluconeogenesis and contribute to insulin resistance by being taken up by the liver and converted to Acetyl-CoA, which activates pyruvate carboxylase.
resistance. However, ChREBP deficiency in obese mice also results in decreased lipid accumulation and improved insulin sensitivity. Moreover, increased ChREBP is sufficient to increase fatty liver progression because over-expression of hepatic ChREBP in mice results in steatosis. Consistent with these mouse studies, obese human beings typically have higher ChREBP expression in the liver, which correlates with fatty liver. Recently, studies deleting ChREBP specifically in mouse hepatocytes showed mild insulin resistance and protection from hepatic steatosis when challenged with a high-carbohydrate diet, but had no effect on lipogenesis and lipogenic gene expression under normal chow. Hepatic deletion of ChREBP in mice following a high-carbohydrate diet caused a reduction in glycolytic and lipogenic gene expression, including a partial loss of SREBP1c expression. Restoration of nuclear SREBP1c signaling in liver-specific ChREBP knockout mice increased the expression of the lipogenic genes ACLY, ACC2, SCD1, and GPAT, but failed to restore them to control levels, suggesting that both SREBP1c and ChREBP are needed to fully regulate lipogenesis in the liver. In addition, SREBP1c overexpression had no effect on restoring glycolytic gene expression. Moreover, overexpressing ChREBP was not sufficient to regain any significant lipogenic gene induction in mice lacking SREBP after SCAP deletion, showing that SREBP is required for the induction of lipogenic expression. The interplay between ChREBP and SREBP1c in regulating lipogenic gene expression helps ensure that the liver does not initiate lipid synthesis unless both glucose and insulin are present, and future studies will continue to unravel their coordinated regulation of lipid synthesis.

Alongside de novo lipogenesis, insulin action also regulates lipid homeostasis by regulating triacylglycerol (TAG) secretion from the liver via very-low-density lipoprotein (VLDL)-TAG export. Enhanced secretion of VLDL-TAG is another hallmark of people with insulin-resistant conditions, such as obesity or NAFLD. In particular, a failure of insulin to facilitate degradation of apolipoprotein B, a major protein in VLDL synthesis, as well as increased levels of FFAs and increased lipogenesis in insulin-resistant disorders, are believed to stimulate VLDL secretion. The last point potentially carries the most weight because it may not be insulin resistance per se that stimulates VLDL secretion, but instead the hyperinsulinemia that results from it. Studies in rats have shown that hyperinsulinemia stimulates TAG turnover and VLDL secretion. In addition, disrupting insulin signaling in mouse livers by deleting Akt or the insulin receptor reduces VLDL secretion. Downstream of Akt, inhibiting or activating mTORC1 in the liver leads to decreased or increased VLDL secretion, respectively, through the regulation of phosphatidylinositol synthesis, a crucial part of VLDL synthesis and secretion. As such, insulin regulation of VLDL-TAG secretion is complex and the coordinated control of apolipoproteins, phospholipids, and TAG synthesis are essential for proper control of VLDL-TAG secretion.

In addition to mTORC1, strong evidence exists for FoxO1’s ability to regulate liver lipid synthesis downstream of hepatic Akt signaling. When activated by insulin, Akt phosphorylates FoxO1 and inactivates it via phosphorylation, leading to nuclear exclusion (Figure 1). Transgenic mice with livers expressing a constitutively active form of FoxO1 that cannot be phosphorylated by Akt due to its three active serine residues being mutated to alanines, FoxoAAA, fail to initiate transcription of lipogenic genes after feeding, leading to a reduction in lipogenesis and triglyceride secretion. Conversely, deletion of all FoxO isoforms from the liver activates lipogenic gene expression and induces de novo lipogenesis correlating with hepatic steatosis. Because FoxO1 is thought to be a transcriptional activator, the specific mechanisms governing its inhibition of lipogenesis is unclear. However, recent studies have argued that FoxO1 directly represses the transcription of SREBP1c. In addition, FoxO1 has been implicated in regulating the expression of glucokinase (Gck) through a repression mechanism mediated by Sin3a and Sin3b (Figure 1). Importantly, Gck expression depends on insulin signaling via Akt, and deletion of FoxO1 partially increases Gck expression. In addition to FoxO1, full activation of Gck also requires activation of mTORC1 (Figure 1). It is attractive to speculate that FoxO1 inhibition of Gck could affect expression of lipogenic factors such as ChREBP, which are dependent on intracellular glucose concentrations for activation. Mechanistically, both activation of mTORC1 and inhibition of FoxO1 are required and sufficient to regulate hepatic lipogenesis in the absence of insulin signaling in vivo. In summary, both human and mouse data support an obligate role for hepatic insulin signaling via Akt in the regulation of hepatic lipid synthesis and fatty liver. For the remainder of this review, we focus on the molecular mechanisms mediating insulin’s control of HGP.

**Direct Regulation of HGP by Insulin**

Together with enhanced lipogenesis, insulin-resistant livers fail to suppress glycogenolysis and gluconeogenesis despite hyperinsulinemia resulting in increased HGP. Activation of Akt by insulin inhibits both glycogenolysis and gluconeogenesis through multiple downstream pathways including glycogen synthase kinase 3 (GSK3) and FoxO1. The canonical model of insulin suppression of glycogen synthesis is Akt-mediated phosphorylation and inhibition of GSK3 (Figure 1). However, recent studies in mice with a mutant form of GSK3 that cannot be phosphorylated and inhibited by Akt, still induce glycogen synthesis in response to insulin, indicating that Akt can suppress glycogenolysis through pathways separate from Akt-dependent GSK3 phosphorylation. One such independent pathway involves direct activation of glycogen synthase (GYS2). GYS2 is considered a downstream target of GSK3, however, studies have indicated that glucose-6-phosphate also directly can activate GYS2 (Figure 1). Because insulin signaling increases Gck expression and glucose uptake and restoration of Gck expression in the absence of Akt is sufficient to restore glycogen content, insulin signaling via Akt to Gck may represent a GSK3 phosphorylation-independent mechanism for glycogen synthesis.

Classic studies in vivo and in the perfused liver have shown that insulin’s direct action on glucose regulation
suppresses HGP in a fashion dependent on Akt. Along with its roles in inhibiting lipogenesis, FoxO1 also regulates HGP downstream of Akt. FoxO1 promotes gluconeogenesis by regulating expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (Figure 1), and its inhibition improves glycemia in insulin-resistant and diabetic mice. Hepatic deletion of FoxO1 in mice results in significant decreases in glycogenolysis and gluconeogenesis. Surprisingly, deletion of FoxO1 in IR, IRS, and Akt knockout mice is sufficient to restore insulin’s suppressive effects on HGP in vivo despite a lack of autonomous insulin action. These data provide genetic evidence that supports classic physiological studies by Cherrington and Bergman that extrahepatic mechanisms contribute to the regulation of HGP in vivo. Together with the obligate role of hepatic insulin action for lipid metabolism, these data challenge the classic model of selective insulin resistance in the liver and instead implicate the role of extrahepatic mechanisms in the control of HGP by insulin.

**Insulin’s Indirect Regulation of HGP**

The central nervous system plays an integral role in glucose and lipid homeostasis. Nutrients, metabolites, and hormones signal in various regions of the hypothalamus to control metabolism. Insulin can act on neurons in the hypothalamus, particularly agouti-related peptide– and proopiomelanocortin-expressing neurons. Knockout of the insulin receptor in agouti-related peptide–expressing neurons results in a failure of insulin to inhibit HGP but had no impact on insulin’s effects on body weight. In response to insulin, activation of potassium adenosine triphosphate channels in the hypothalamus signals through the vagus nerve to the liver, which inhibit hepatic gluconeogenesis. Studies from several labs, including the Rosetti Lab, have identified a brain–liver axis involving signal transducer and activator of transcription 3 signaling in hepatocytes (Figure 2). However, denervation of the hepatic branch of the vagus nerve fails to prevent insulin’s ability to suppress HGP in mice during a peripheral infusion of insulin under euglycemic clamp conditions. In addition, mice lacking hepatic Akt and FoxO1 suppress glucose production during hyperinsulinemic–euglycemic clamp conditions after a hepatic vagotomy, questioning the role of the brain–liver axis in the regulation of HGP. Moreover, recent studies in dogs have shown that blocking brain insulin signaling does not have any effect on insulin’s inhibition of HGP during clamp conditions. Glucagon is the principal counter-regulatory hormone that stimulates glycogenolysis and gluconeogenesis during fasting and opposes the hepatic actions of insulin. Glucagon increases HGP by acutely stimulating gluconeogenesis and chronically promoting gluconeogenesis (Figure 2). Under euglycemic clamp conditions, increased insulin concentrations led to a reduction in glucagon secretion. Moreover, human studies have indicated a close correlation of insulin action and decreased glucagon concentrations, implying some effect of insulin on glucagon secretion. Genetic evidence also supports this correlation, indicating that deletion of the insulin receptor from α cells in mouse pancreas leads to enhanced glucagon secretion, leading to mild glucose intolerance, hyperglycemia, and hyperglucagonemia. Because of hyperglucagonemia’s long association with diabetes, many commercial antidiabetic drugs target some part of the glucagon signaling mechanism with some success. Despite this well-established effect on glycemia, increasing glucagon levels acutely or blocking hepatic glucagon action fails to negate insulin’s ability to suppress glucose production, indicating that insulin’s actions on suppressing glucagon are not required to acutely inhibit HGP.

Insulin acts on adipose tissue to increase glucose uptake, suppress lipolysis, and drive lipid synthesis. As a result,
insulin suppresses circulating levels of FFAs and glycerol, which correlates with changes in HGP. Work in the canine model has shown that insulin inhibition of lipolysis contributes to the acute inhibition of hepatic glucose production. Increased gluconeogenic flux largely contributes to this effect on HGP. Recent genetic studies from several groups have supported these classic physiology studies and assert that FFA action on the liver drives HGP in insulin-resistant livers or livers completely devoid of hepatic insulin signaling. proposed that insulin’s indirect action on the liver negates the requirement for direct hepatic insulin signaling in the control of HGP. However, other work has shown that insulin’s direct action on the liver dominates.

Differences in experimental clamp conditions could underlie these contrasting results on the role of FFAs in the control of HGP. The experiments of Perry et al. involved overnight fasting mice, which left their glycogen stores depleted and made them dependent on gluconeogenesis, skewing the impact of insulin’s direct action on glycogenolysis. In addition, Perry et al. used acetate to mimic the effects of FFAs on HGP, which blocked insulin’s ability to suppress HGP. Other groups, including the Shulman laboratory, have used the physiological substrate FFAs to directly test the contribution of adipocyte lipolysis to HGP and found insulin can suppress HGP despite increased FFAs, confirming a dominant role for hepatic insulin action in the control of HGP. Moreover, studies comparing the effects of peripheral vs portal insulin infusion show significant differences in hepatic insulin levels. Peripheral insulin infusion is commonly performed during hyperinsulinemic–euglycemic clamp conditions in mice, but fails to recapitulate the proper portal insulin concentrations and may lead to an underinsulized liver, minimizing the direct effect of insulin on HGP. At the same time, increased insulin levels at the periphery exaggerates insulin’s indirect effects. Accounting for these factors in the clamp conditions shows that the direct effects of insulin on the liver prevail. Despite these experimental differences, an agreement has emerged that FFAs from the adipose tissue play essential roles in modulating HGP during the progression of insulin resistance and metabolic disease.

Extensive studies have outlined the major processes of direct insulin action on the liver via the PI3K/Akt pathway and its various methods of regulating glucose and lipid homeostasis. With this knowledge, investigators have put forth a massive effort to elucidate the mechanism of hepatic insulin resistance associated with conditions such as obesity and T2DM. An attractive hypothesis in the field suggests that hepatic insulin action is selective, suggesting a bifurcation occurs distal to Akt to control lipogenesis and HGP via distinct and independent pathways. However, directly testing this model using mouse models fails to explain the pathophysiology of the insulin-resistant liver. It is becoming increasingly clear that insulin’s direct action on the liver is the driving force of hepatic de novo lipogenesis and that both direct and indirect mechanisms exist to control insulin’s regulation of hepatic glucose production. Going forward, unraveling the mechanisms of how these extrahepatic factors communicate to and regulate the liver and its ability to promote HGP in the face of increased hyperinsulinemia and subsequent lipogenesis will be paramount to fully disentangling the paradox of hepatic insulin resistance during metabolic disease.

References

1. Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414:782–787.
2. Ramnanan CJ, Edgerton DS, Kraft G, Cherrington AD. Physiologic action of glucagon on liver glucose metabolism. Diabetes Obes Metab 2011;13(Suppl 1):118–125.
3. Lin HV, Accili D. Hormonal regulation of hepatic glucose production in health and disease. Cell Metab 2011; 14:9–19.
4. Brown MS, Goldstein JL. Selective versus total insulin resistance: a pathogenic paradox. Cell Metab 2008; 7:95–96.
5. James OFW, Day CP. Non-alcoholic steatohepatitis (NASH): a disease of emerging identity and importance. J Hepatol 1998;29:495–501.
6. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shifman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001;120:1183–1192.
7. Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y, Berria R, Buzzigoli E, Sironi AM, Cersosimo E, Ferrannini E, DeFronzo RA. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology 2007;133:496–506.
8. Lambert JE, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. Gastroenterology 2014;146:726–735.
9. Roden M, Stingl H, Chandramouli V, Schumann WC, Hofer A, Landau BR, Nowotny P, Waldhäusl W, Shulman GI. Effects of free fatty acid elevation on and gluconeogenesis in humans. Endocrinol Metab 2000; 49:701–707.
10. Sunny NE, Parks EJ, Browning JD, Burgess SC. Excessive hepatic mitochondrial TCA cycle and gluconeogenesis in humans with nonalcoholic fatty liver disease. Cell Metab 2011;14:804–810.
11. Biddinger SB, Hernandez-Ono A, Rask-Madsen C, Haas JT, Alemán JO, Suzuki R, Scapa EF, Agarwal C, Carey MC, Stephanopoulos G, Cohen DE, King GL, Ginsberg HNN, Kahn CR. Hepatic insulin resistance is sufficient to produce dyslipidemia and susceptibility to atherosclerosis. Cell Metab 2008;7:125–134.
12. Haas JT, Miao J, Chanda D, Wang Y, Zhao E, Haas ME, Hirschy M, Vaiitheswaran B, Farese RV Jr, Kurland LJ, Graham M, Crooke R, Foufelle F, Biddinger SB. Hepatic insulin signaling is required for obesity-dependent expression of SREBP-1c mRNA but not for feeding-dependent expression. Cell Metab 2012;15:873–884.
13. Semple RK, Sleigh A, Murgatroyd PR, Adams CA, Bluck L, Jackson S, Vottero A, Kanabar D, Charlton-Menys V, Durrington P, Soos MA, Carpenter TA, Lomas DJ, Cochran EK, Gorden P, O’Rahilly S, Savage DB. Postreceptor insulin resistance contributes to human dyslipidemia and hepatic steatosis. J Clin Invest 2009;119:315–322.

14. Michael MD, Kulkarni RN, Postic C, Previs SF, Shulman GI, Magnunson MA, Kahn CR. Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. Mol Cell 2000;6:87–97.

15. Softic S, Boucher J, Solheim MH, Fujisaka S, Haering MF, Homan EP, Winnay J, Perez-Atayde AR, Kahn CR. Lipodystrophy due to adipose tissue-specific insulin receptor knockout results in progressive NAFLD. Diabetes 2016;65:2187–2200.

16. Titchenell PM, Chu Q, Monks BR, Birnbaum MJ. Hepatic insulin signaling is dispensable for suppression of glucose output by insulin in vivo. Nat Commun 2015;6:7078.

17. Taniguchi CM, Emanuelli B, Solheim MH, Fujisaka S, Semple RK, Sleigh A, Murgatroyd PR, Adams CA. Paradox of Hepatic Insulin Resistance 453

18. Softic S, Boucher J, Solheim MH, Fujisaka S, Haering MF, Homan EP, Winnay J, Perez-Atayde AR, Kahn CR. Lipodystrophy due to adipose tissue-specific insulin receptor knockout results in progressive NAFLD. Diabetes 2016;65:2187–2200.

19. Dong XC, Copps KD, Guo S, Li Y, Kolippara R, DePinho RA, White MF. Inactivation of hepatic Foxo1 by insulin signaling is required for adaptive nutrient homeostasis and endocrine growth regulation. Cell Metab 2008;8:65–76.

20. Kubota N, Kubota T, Kajiwara E, Iwamura T, Kumagai H, Watanabe T, Inoue M, Takamoto I, Sasako T, Kumagai K, Kohjima M, Nakamura M, Moroi M, Sugi K, Noda T, Terauchi Y, Ueki K, Kadowaki T. Differential hepatic distribution of insulin receptor substrate causes selective insulin resistance in diabetes and obesity. Nat Commun 2016;7:12977.

21. Miyake K, Ogawa W, Matsumoto M, Nakamura T, Sakaue H, Kasuga M. Hyperinsulinemia, glucose intolerance, and dyslipidemia induced by acute inhibition of phosphoinositide 3-kinase via Akt and PKC. Diabetes 2011;60:1483–1491.

22. Titchenell PM, Quinn WJ, Lu M, Chu Q, Monks BR, Ahima RS, Ueki K, Kahn CR, Birnbaum MJ. Insulin regulates liver metabolism in vivo in the absence of hepatic Akt and Foxo1. Nat Med 2012;18:388–395.

23. Menon S, Dibble CC, Talbott G, Hoxhaj G, Valvezan AJ, Takahashi H, Cantley LC, Manning BD. Spatial control of the TSC complex integrates insulin and nutrient regulation of mtorc1 at the lysosome. Cell 2014;156:1771–1785.

24. Schwarz JM, Linfoot P, Dare D, Aghajanian K. Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets. Am J Clin Nutr 2003;77:43–50.

25. Sekiguchi CM, Emanuelli B, Solheim MH, Fujisaka S, Semple RK, Sleigh A, Murgatroyd PR, Adams CA. Paradox of Hepatic Insulin Resistance 453

26. He L, Hou X, Kanel G, Zeng N, Galicia V, Wang Y, Yang J, Wu H, Birnbaum MJ, Stiles BL. The critical role of Akt2 in hepatic steatosis induced by PTEN loss. Am J Pathol 2010;176:2302–2308.

27. Sarbassov DD, Guertin DA, Ali SM. Phosphorylation and Regulation of Akt/PKB by the rictor-mTOR complex. Science 2005;307:1098–1102.

28. Garofalo RS, Orena SJ, Rafidi K, Torchia AJ, Stock JL, Hildebrandt AL, Coskran T, Black SC, Brees DJ, Wicks JR, McNeish JD, Coleman KG. Severe diabetes, age-dependent loss of adipose tissue, and mild growth deficiency in mice lacking Akt2/PKBβ. J Clin Invest 2003;112:197–208.

29. Cho H, Mu J, Kim JK, Thorvaldsen JL, Chu Q, Crenshaw EB III, Kaestner KH, Bartolomei MS, Shulman GI, Birnbaum MJ. Insulin resistance and diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKBβa). Science 2001;292:1728–1731.

30. Leavens KF, Easton RM, Shulman GI, Previs SF, Birnbaum MJ. Akt2 is required for hepatic lipid accumulation in models of insulin resistance. Cell Metab 2009;10:405–418.

31. Lu M, Wan M, Leavens KF, Chu Q, Monks BR, Ahima RS, Ueki K, Kahn CR, Birnbaum MJ. Insulin regulates liver metabolism in vivo in the absence of hepatic Akt and Foxo1. Nat Med 2012;18:388–395.

32. Chattopadhyay M, Selinger ES, Ballou LM, Lin RZ. Abolition of P13K p110α prevents high-fat diet-induced liver steatosis. Diabetes 2011;60:1483–1492.

33. Mora A, Lipina C, Tronche F, Sutherland C, Alessi DR. Deficiency of PDK1 in liver results in glucose intolerance, impairment of insulin-regulated gene expression and liver failure. Biochem J 2005;385:639–648.

34. Horie Y, Suzuki A, Kataoka E, Sasaki T, Hamada K, Sasaki J, Mizuno K, Hasegawa G, Kishimoto H, Iizuka M, Naito M, Enomoto K, Watanabe S, Mak TW, Nakano T. Hepatocyte-specific Pten deficiency results in steatohepatitis and hepatocellular carcinomas. J Clin Invest 2004;113:1774–1783.

35. He L, Hou X, Kanel G, Zeng N, Galicia V, Wang Y, Yang J, Wu H, Birnbaum MJ, Stiles BL. The critical role of Akt2 in hepatic steatosis induced by PTEN loss. Am J Pathol 2010;176:2302–2308.
and lipogenesis through parallel mTORC1-dependent and independent pathways. Cell Metab 2011;14:21–32.

39. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 2002; 109:1125–1131.

40. Düvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, Triantafellow E, Ma Q, Gorski R, Cleaver S, Vander Heiden MG, MacKeigan JP, Finan PM, Clish CB, Murphy LO, Manning BD. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. Mol Cell 2010;39:171–183.

41. Owen JL, Zhang Y, Bae S-H, Farooqi MS, Liang G, Hammer RE, Goldstein JL, Brown MS. Insulin stimulation of SREBP-1c processing in transgenic rat hepatocytes requires p70 S6-kinase. Proc Natl Acad Sci U S A 2012; 109:16184–16189.

42. Shimomura I, Bashmakov Y, Horton JD. Increased levels of nuclear SREBP-1c associated with fatty livers in two mouse models of diabetes mellitus increased levels of nuclear SREBP-1c associated with fatty livers in two mouse models of diabetes mellitus. J Biol Chem 1999; 274:30028–30032.

43. Moon YA, Liang G, Xie X, Frank-Kamenetsky M, Fitzgerald K, Kotelański V, Brown MS, Goldstein JL, Horton JD. The Scap/SREBP pathway is essential for developing diabetic fatty liver and carbohydrate-induced hypertriglyceridemia in animals. Cell Metab 2012; 15:240–246.

44. Brown MS, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell 1997; 89:331–340.

45. Matsuda M, Korn BS, Hammer RE, Moon YA, Komuro R, Horton JD, Goldstein JL, Brown MS, Shimomura I. SREBP cleavage-activating protein (SCAP) is required for increased lipid synthesis in liver induced by cholesterol deprivation and insulin elevation. Genes Dev 2001; 15:1206–1216.

46. Dentin R, Tomas-Cobos L, Foufelle F, Leopold J, Girard J, Postic C, Férre P. Glucose 6-phosphate, rather than xylulose 5-phosphate, is required for the activation of ChREBP in response to glucose in the liver. J Hepatol 2012;56:199–209.

47. Iizuka K, Brück RK, Liang G, Horton JD, Uyeda K. Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. Proc Natl Acad Sci U S A 2004; 101:7281–7286.

48. Iizuka K, Miller B, Uyeda K. Deficiency of carbohydrate-activated transcription factor ChREBP prevents obesity and improves plasma glucose control in leptin-deficient (ob/ob) mice. Am J Physiol Endocrinol Metab 2006; 291:E358–E364.

49. Benhamed F, Denechaud PD, Lemoine M, Robichon C, Moldes M, Bertrand-Michel J, Ratziu V, Serfaty L, Houssset C, Capeau J, Girard J, Guillou H, Postic C. The lipogenic transcription factor ChREBP dissociates hepatic steatosis from insulin resistance in mice and humans. J Clin Invest 2012;122:2176–2194.

50. Hurtado Del Pozo C, Vesperinas-Garcia G, Rubio MA, Corripio-Sánchez R, Torres-Garcia AJ, Obregon MJ, Calvo RM. ChREBP expression in the liver, adipose tissue and differentiated preadipocytes in human obesity. Biochim Biophys Acta 2011;1811:1194–1200.

51. Jois T, Chen W, Howard V, Harvey R, Youngs K, Thalmann C, Saha P, Chan L, Cowley MA, Sleeman MW. Deletion of hepatic carbohydrate response element binding protein (ChREBP) impairs glucose homeostasis and hepatic insulin sensitivity in mice. Mol Metab 2017; 6:1381–1394.

52. Linden AG, Li S, Choi HY, Fang F, Fukasawa M, Uyeda K, Hammer RE, Horton JD, Engelking LJ, Liang G. Interplay between ChREBP and SREBP-1c coordinates postprandial glycolysis and lipogenesis in livers of mice. J Lipid Res 2018;59:475–487.

53. Poulsen MK, Nellemann B, Stedkilde-Jørgensen H, Pedersen SB, Gronbæk H, Nielsen S. Impaired insulin suppression of VLDL-triglyceride kinetics in nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2016; 101:1637–1646.

54. Lewis GF, Uffelman KD, Szeto LW, Steiner G. Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL ApoB production in normal weight and obese individuals. Diabetes 1993;42:833–842.

55. Ginsberg HN, Zhang Y-L, Hernandez-ono A. Metabolic syndrome: focus on dyslipidemia. Obesity 2006; 14:41–49.

56. Steiner G, Haynes FJ, Yoshino G, Vranic M. Hyperinsulinemia and in vivo very-low-density lipoprotein-triglyceride kinetics. Am J Physiol Endocrinol Metab 1984; 246:187–192.

57. Han S, Liang CP, Westerterp M, Senokuchi T, Welch CL, Wang O, Matsumoto M, Accili D, Tall AR. Hepatic insulin signaling regulates VLDL secretion and atherogenesis in mice. J Clin Invest 2009;119:1029–1041.

58. Quinn WJ, Wan M, Shewale SV, Gelfer R, Rader DJ, Birnbaum MJ, Titchenell PM. MTORC1 stimulates phosphatidylcholine synthesis to promote triglyceride secretion. J Clin Invest 2017;127:4207–4215.

59. Gross DN, Wan M, Birnbaum MJ. The role of FOXO in the regulation of metabolism. Curr Diab Rep 2008; 9:208–214.

60. Zhang W, Patil S, Chauhan B, Guo C, Powell DR, Le J, Klotzas A, Matika R, Xiao X, Franks R, Heidenreich KA, Sajan MP, Farese RV, Stolz DB, Tso P, Koo SH, Montminy M, Unterman TG. FoxO1 regulates multiple metabolic pathways in the liver effects on gluconeogenic, glycolytic, and lipogenic gene expression. J Biol Chem 2006;281:10105–10117.

61. Zhang W, Bu SY, Mashek MT, O-Sullivan I, Sibai Z, Khan SA, Ikayeva O, Newgard CB, Mashek DG, Unterman TG. Integrated regulation of hepatic lipid and glucose metabolism by ATGL and FoxO proteins. Cell Rep 2016;15:349–359.

62. Haeusler RA, Hartil K, Vaitheesvaran B, Arrieta-Cruz I, Knight CM, Cook JR, Kammoun HL, Febbraio MA, Gutierrez-Juarez R, Kurland IJ, Accili D. Integrated control of hepatic lipogenesis versus glucose production requires FoxO transcription factors. Nat Commun 2014;5:5190.
63. Deng X, Zhang W, O-Sullivan IS, Williams JB, Dong Q, Park EA, Raghow R, Unterman TG, Elam MB. FoxO1 inhibits sterol regulatory element-binding protein-1c (SREBP-1c) gene expression via transcription factors Sp1 and SREBP-1c. J Biol Chem 2012; 287:20132–20143.

64. Hirota K, Sakamaki JI, Ishida J, Shimamoto Y, Nishihara S, Kodama N, Ohta K, Yamamoto M, Tanimoto K, Fukamizu A. A combination of HNF-4 and Foxo1 is required for reciprocal transcriptional regulation of glucokinase and glucose-6-phosphatase genes in response to fasting and feeding. J Biol Chem 2008; 283:32432–32441.

65. Langlet F, Haeusler RA, Lindén D, Ericson E, Norris T, Rizza RA. Pathogenesis of fasting and postprandial hyperglycemia in type 2 diabetes: implications for therapy. Diabetes 2010;59:2697–2707.

66. Moore MC, Coate KC, Winnick JJ, An Z, Cherrington AD. The direct and indirect effects of insulin on hepatic glucose production in vivo. Diabetologia 1998;41:987–996.

67. Edgerton DS, Kraft G, Smith M, Farmer B, Williams PE, Coate KC, Printz RL, O'Brien RM, Cherrington AD. Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. JCI Insight 2017;2:e91863.

68. Cherrington AD, Moore MC, Sindelar DK, Edgerton DS. Insulin action on the liver in vivo. Biochem Soc Trans 2007;35:1171–1174.

69. Altomont J, Richter A, Harbaran S, Suriawinata J, Nakae J, Thung SN, Mesec M, Accili D, Dong H. Inhibition of Foxo1 function is associated with improved fasting glycemia in diabetic mice. Am J Physiol Endocrinol Metab 2003;285:E718–E728.

70. Matsumoto M, Pocai A, Rossetti L, DePinho RA, Accili D. Impaired regulation of hepatic glucose production in mice lacking the forkhead transcription factor Foxo1 in liver. Cell Metab 2007;6:208–216.

71. Titchenell PM, Lazar MA, Birnbaum MJ. Unraveling the regulation of hepatic metabolism by insulin. Trends Endocrinol Metab 2017;28:497–505.

72. Myers MG, Olson DP. Central nervous system control of metabolism. Nature 2012;491:357–363.

73. Belgardt BF, Okamura T, Brüning JC. Hormone and glucose signalling in POMC and AgRP neurons. J Physiol 2009;587:5305–5314.

74. Könner AC, Janoschek R, Plum L, Jordan SD, Rother E, Ma X, Xu C, Enriori P, Hampel B, Barsh GS, Kahn CR, Cowley MA, Ashcroft FM, Brüning JC. Insulin action in AgRP-expressing neurons is required for suppression of hepatic glucose production. Cell Metab 2007; 5:438–449.

75. Pocai A, Lam TKT, Gutierrez-Juarez R, Obici S, Schwartz GJ, Bryan J, Aguilar-Bryan L, Rossetti L. Hypothalamic KATP channels control hepatic glucose production. Nature 2005;434:1026–1031.

76. Inoue H, Ogawa W, Asakawa A, Okamoto Y, Nishizawa A, Matsumoto M, Teshigawara K, Matsuji 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 2006; 3:267–275.
glucose production is dominant, even with hyper-glucoagonemia. J Clin Invest 1997;100:3121–3130.

92. 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 1995;44:1038–1045.

93. 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 1997;46:187–196.

94. Chu CA, Sherck SM, Igawa K, Sindelar DK, Neal DW, Emshwiller M, Cherrington AD. Effects of free fatty acids on hepatic glycogenolysis and gluconeogenesis in conscious dogs. Am J Physiol Endocrinol Metab 2002;282:E402–E411.

95. Perry RJ, Camporez JG, Kursawe R, Titchenell PM, Zhang D, Perry CJ, Jurczak MJ, Abudukadier A, Han S, Zhang XM, Ruan HB, Yang X, Caprio S, Susan M, Sul HS, Birbaum MJ, Davis RJ, Cline GW, Falk K, Shulman GI. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes 2015;160:745–758.

96. Chen C, Williams PF, Cooney GJ, Caterson ID, Turtle JR. The effects of fasting and refeeding on liver glycogen synthase and phosphorylase in obese and lean mice. Horm Metab Res 1992;24:161–166.

97. Kim JK, Kim YJ, Fillmore JJ, Chen Y, Moore I, Lee J, Yuan M, Li ZW, Karin M, Perret P, Shoelson SE, Shulman GI. Prevention of fat-induced insulin resistance by salicylate. J Clin Invest 2001;108:437–446.

98. 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 2006;116:521–527.