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REVIEW

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Signalling mechanisms linking hepatic glucose and lipid metabolism

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Abstract Fatty liver and hepatic triglyceride accumulation are strongly associated with obesity, insulin resistance and type 2 diabetes, and are subject to nutritional influences. Hepatic regulation of glucose and lipid homeostasis is influenced by a complex system of hormones, hormonally regulated signalling pathways and transcription factors. Recently, considerable progress has been made in elucidating molecular pathways and potential factors that are affected in insulin-resistant states. In this review we discuss some of the key factors that are involved in both the regulation of glucose and lipid metabolism in the liver. Understanding the molecular network that links hepatic lipid accumulation and impaired glucose metabolism may provide targets for dietary or pharmacological interventions.

Keywords Fatty liver · Hepatic glucose and lipid homeostasis · Insulin resistance · Signalling · Transcription factors

Abbreviations ACAC: Acetyl-CoA carboxylase · AMPK: AMP-activated protein kinase · CPT-1: carnitine palmitoyl transferase-1 · ChREBP: carbohydrate response element-binding protein · FASN: fatty acid synthase · FOX: forkhead transcription factor · G-6-Pase: glucose-6-phosphatase · 11β-HSD1: 11β-hydroxysteroid dehydrogenase 1 (encoded by the gene *HSD11B1*) · L-PK: liver pyruvate kinase · LXR: liver X receptor · PGC-1α: PPARγ coactivator 1α · PI-3-K: phosphatidyl inositol-3-kinase · PKB: protein kinase B/Akt · PPAR: peroxisome proliferator-activated receptor · PUFAs: polyunsaturated fatty acids · RXR: retinoid X receptor · SREBP: sterol response element-binding protein

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Introduction

The exact mechanisms that link obesity, impaired glucose metabolism, hepatic lipid accumulation and insulin resistance are unknown, but our knowledge is rapidly increasing. The expression of over 150 mammalian genes is modulated by insulin, mainly at the level of transcription [1]. In the liver, insulin induces the transcription of most of the genes encoding metabolic enzymes involved in hepatic glucose production. Only a limited number of genes in the liver are inhibited by insulin [2]. A number of key co-activators, co-repressors and transcription factors previously reported to interfere with either insulin-regulated hepatic lipid metabolism or glucose homeostasis have recently been shown to play roles in both pathways [3–5]. In this review we focus on some of these factors, which may be of interest as potential targets for dietary or pharmacological interventions aimed at reducing liver insulin resistance, or serve as markers for assessing hepatic insulin resistance.

> Hepatic insulin resistance can be defined as the failure of insulin to adequately suppress hepatic glucose production. The lipogenic actions of insulin do not appear to be compromised in insulin-resistant states.

The liver plays a major role in the regulation of glucose, lipid and energy metabolism. Increased hepatic fat depots are a very common feature in obese, insulin-resistant patients [6, 7], and insulin resistance per se is associated with hepatic fat accumulation, independently of BMI or intra-abdominal obesity [8]. Interestingly, increased liver fat is linked to severe insulin resistance in lean patients with pharmacologically induced lipodystrophy of the subcutaneous fat, e.g. during the treatment of human immunodeficiency virus with highly

active antiretroviral therapy (HAART) [9]. Furthermore, transplantation of subcutaneous fat reduces hepatic steatosis and reverses insulin resistance in lipoatrophic mice. [10]. Although a correlation between fatty liver and insulin resistance is well established, direct evidence for a causal relationship between fatty liver and insulin resistance is lacking. In mice, accumulation of intracellular fatty acid metabolites such as long-chain fatty acyl-CoAs reduces the activity of insulin-induced phosphatidyl inositol-3-kinase (PI-3-K)—a key step in the insulin signalling cascade [11]—and may thus interfere with insulin signalling. Conversely, the prevention of hepatic fat accumulation in rats fed a high-fat diet ameliorates hepatic insulin resistance [12]. The potential influence of the intrahepatic lipid pool on hepatic insulin resistance in type 2 diabetic patients was emphasised by a recent study in which a moderate weight reduction significantly decreased intrahepatic, but not intramyocellular, lipid content [13]. The decrease was associated with normalised rates of glucose production, which could be entirely attributed to reduced gluconeogenesis, and unchanged peripheral insulin resistance.

Insulin resistance can promote fatty liver, and vice versa: excessive hepatic accumulation of fat may promote insulin resistance and therefore contribute to the pathogenesis of the metabolic syndrome.

Role of the liver in glucose metabolism

In the liver, insulin regulates fasting glucose concentrations by inhibiting hepatic glucose production and stimulating glycogen synthesis. Hepatic glucose production involves two different mechanisms: glycogenolysis and gluconeogenesis. Glycogenolysis produces glucose during a relatively short-term fast of up to several hours, and is suppressed by insulin within 1–2 h after food intake in healthy subjects [14]. During longer periods of fasting (>12–14 h), liver glycogen stores become depleted and there is an increase in the percentage contribution made by gluconeogenesis to the total glucose supply [15]. This involves the de novo synthesis of glucose from precursors such as pyruvate, lactate and glycerol and glucogenic amino acids. Increased gluconeogenesis also occurs in other states involving low insulin concentration (e.g. type 1 diabetes, secondary types of diabetes), and in states of relative insulin deficiency where the liver is insulin resistant (e.g. obesity, type 2 diabetes). Notably, in diabetic states, the absolute amount of hepatic glucose production is only moderately increased relative to that in healthy controls, but is inadequately suppressed relative to the raised concentrations of insulin and glucose [16].

On a molecular level, increased hepatic glucose production involves changes in the activity of key gluconeogenic enzymes. PEPCK catalyses the conversion of oxaloacetic acid to phosphoenolpyruvate, a rate-limiting reaction in gluconeogenesis. Dephosphorylation of glucose 6-phosphate to free glucose—the final step in both glycogenolysis and gluconeogenesis—is catalysed by glucose-6-phosphatase (G-6-Pase). The activity of PEPCK and G-6-Pase, and thereby gluconeogenesis, is suppressed by insulin, and this action is compromised in insulin-resistant states. In addition to insulin, other hormones, principally glucagon and glucocorticoids, interact with key glucogenic enzymes at the transcriptional level. Acute elevations of circulating glucose concentrations have also been reported to directly suppress expression of the gene for PEPCK and gluconeogenesis [17]. Uptake of glucose by hepatocytes is mediated through the glucose transporter GLUT2, which does not require insulin for activation [18]. The inhibitory effect of glucose on gluconeogenesis is affected during prolonged hyperglycaemia by mechanisms that have yet to be fully elucidated [19]. Recent research shows that the brain has a substantial impact on the regulation of hepatic glucose metabolism. Moderate increases in extracellular glucose concentrations within a specific region of the hypothalamus markedly lower blood glucose through inhibition of hepatic glucose production [20]. Moreover, central inhibition of fat oxidation selectively activates neurons within the solitary tract nucleus and the vagal dorsal motor nucleus, leading to decreased levels of gluconeogenic enzymes and hepatic glucose production [21]. These studies indicate that central glucose- and lipid-sensing mechanisms communicate with the liver via the vagal nerve.

Insulin, circulating glucose concentrations, glucagon, glucocorticoids and central mechanisms in the brain play key roles in the regulation of hepatic glucose metabolism.

Role of the liver in lipid metabolism

Consistent with its function as an anabolic hormone, insulin promotes the synthesis, and inhibits the degradation of lipids. Insulin-regulated lipid homeostasis is modulated by sterol response element-binding proteins (SREBPs) that activate the expression of over 30 genes involved in the synthesis and uptake of fatty acids, triglycerides, cholesterol and phospholipids [22]. High glucose and insulin have also been shown to inhibit fatty acid oxidation [23]. When delivered to the liver in large quantities, glucose is first converted to glycogen and stored. Once glycogen stores are replenished, glucose enters the glycolysis pathway and thereby provides carbons for de novo lipogenesis. Lipids are then stored as triglycerides or exported from the liver as VLDL.

Insulin and transcription factors such as SREBP-1c and carbohydrate response element-binding protein (ChREBP) (see below) stimulate key lipogenic genes, including those encoding acetyl-CoA carboxylase (ACAC) and fatty acid synthase (FASN). There are two isoforms of ACAC: ACAC-1 represents the cytosolic enzyme and ACAC-2 functions as the mitochondrial regulatory unit. ACAC converts acetyl-CoA to malonyl-CoA, which in turn inhibits carnitine palmitoyl transferase-1 (CPT-1)-induced transport of fatty acids into mitochondria, thereby reducing mitochondrial fatty acid β-oxidation [24]. FASN catalyses the conversion of malonyl-CoA into long-chain saturated

fatty acids. The sensitivity of CPT-1 to malonyl-CoA is regulated by hormonal and nutritional factors [25]. De novo synthesis of fatty acids in the liver is independently regulated by glucose as well as insulin [26–28].

Even in the presence of marked insulin resistance, hepatic transcription of the gene encoding SREBP-1c is stimulated by both insulin and glucose, resulting in undamped rates of de novo fatty acid synthesis.

Acute vs prolonged exposure to insulin

Insulin is commonly viewed as a positive regulator of fatty acid synthesis, as it promotes the expression of *FASN* and *ACAC*. However, when acutely elevated, insulin can reduce liver fat accumulation in normoinsulinaemic mice [29]. Following insulin-induced phosphorylation of the insulin receptor and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), the proteins are internalised and interact with FASN, reducing its catalytic activity. This is not observed in hyperinsulinaemic mice, indicating that the acute effects of insulin on FASN activity are dependent upon the prior insulinaemic state.

Alternatively, chronic hyperinsulinaemia may be linked to hepatic fat accumulation by forkhead transcription factors [30]. Insulin is known to activate insulin receptor substrates IRS1 and IRS2, via phosphorylation by Akt and consequent inhibition of forkhead transcription factors (FOXO1 and FOXA2). FOXO1 is regulated via the IRS2 pathway, shutting down hepatic gluconeogenesis. FOXA2, which inhibits hepatic fatty-acid-oxidation when phosphorylated, can be induced both over the IRS2 and the IRS1 pathways, which may result in increased insulin sensitivity of FOXA2 compared with FOXO1. Therefore, in states of reduced insulin sensitivity, insulin fails to inhibit glucose production, which in turn increases insulin secretion and enhances hyperinsulinaemia. On the other hand, because of the increased sensitivity of the pathway shutting down fatty acid oxidation, triglycerides may accumulate in the liver, leading to hepatic steatosis in the longer term.

Increased glucose and insulin concentrations have been shown to activate SREBP-1c and ChREBP, which are known to activate lipogenic enzymes in the liver. In this scenario, both reduced fatty acid oxidation and increased de novo synthesis of fatty acids contribute to accumulation of liver fat in hyperinsulinaemic states (Fig. 1).

Prolonged, but not acute, exposure to high levels of insulin may induce fatty liver. Thus, restoring or imitating the physiological shape of the curve for insulin secretion by pharmacological measures may be an important aspect to reduce both insulin resistance and accumulation of fatty acids in the liver.

A network of transcription factors, co-repressors and co-activators act as sensors of hormonal and nutritional status in order to co-ordinate enzyme activities and metabolic pathways in the liver. The factors discussed in the following section are directly or indirectly linked at the molecular level and have recently been shown to play key roles in both hepatic glucose and lipid metabolism (Fig. 2).

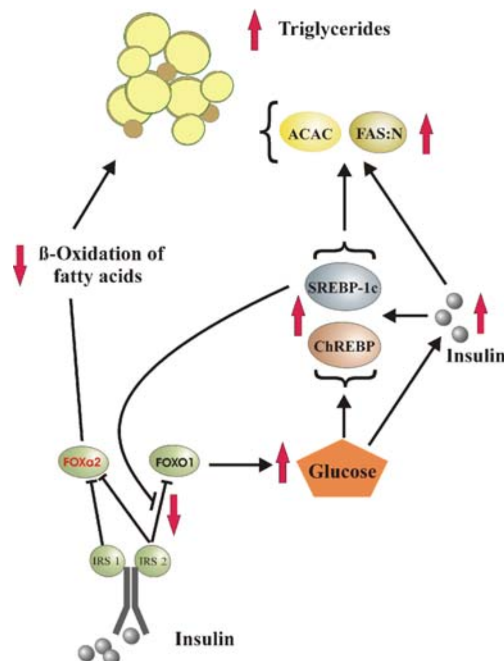

Fig. 1 Model of signalling mechanisms resulting in hepatic triglyceride accumulation in insulin-resistant states. In sensitive states, receptor-bound insulin activates insulin receptor substrates IRS1 and IRS2, which, via PKB/Akt, block fatty acid oxidation (FOXA2) and gluconeogenesis (FOXO1). The FOXA2 pathway is inhibited via IRS1 and IRS2, and may still react to insulin when inhibition of FOXO1 is already impaired [30]. This results in decreased fatty acid oxidation. Elevated glucose, in turn, activates ChREBP and SREBP-1c, and causes increased pancreatic insulin secretion. SREBP-1c blocks hepatic IRS2 signalling, further promoting hepatic glucose production, and probably counteracting the suppressive effect of SREBP-1c on gluconeogenic genes. Insulin, ChREBP and SREBP-1c induce FASN and ACAC, leading to increased production of fatty acids. Therefore hepatic triglycerides accumulate as a result of both increased fatty acid production and reduced fatty acid oxidation in insulin-resistant states. The *red arrows* indicate the direction of changes in insulin-resistant states

Liver X receptor α

Liver X receptors (LXRs) are members of the nuclear receptor family, and are now recognised as important regulators of cholesterol metabolism, lipid biosynthesis and glucose homeostasis [5]. LXRs are also involved in regulating the storage and oxidation of dietary fat [31]. Two isoforms have been described, LXRα and LXRβ. The beta isoform is ubiquitously expressed and has recently been implicated in adipocyte growth, glucose homeostasis and beta cell function [32].

LXRα is highly expressed in the liver, adipose tissue, macrophages and the small intestine [33]. In hepatocytes, LXRα expression is induced by oxysterols and insulin

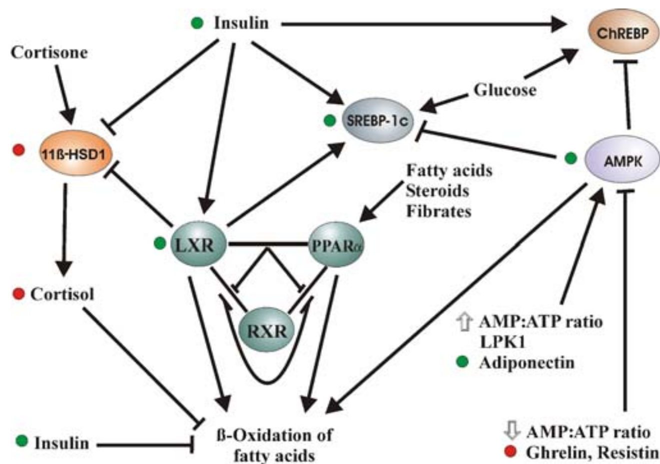

Fig. 2 Model of interactions between key factors involved in hepatic glucose and lipid metabolism. LXRα and PPARα interact or compete with each other by forming obligate heterodimers with RXRα, thereby reciprocally reducing other pairings [40, 41]. Activated LXRα induces SREBP-1c and blocks 11β-HSD1, thereby interfering with the inhibitory effect of cortisol on β-oxidation, and increasing synthesis of fatty acids via SREBP-1c. LXRα, PPARα, and AMPK activate β-oxidation of fatty acids. Cortisol and insulin inhibit fatty acid oxidation. Induction of hepatic glucose production is indicated by *red dots*, suppression of hepatic glucose production by *green dots*

[34], resulting in increased levels of lipogenic enzymes and the suppression of key gluconeogenic enzymes, including PEPCK and G-6-Pase [35]. LXRα also plays an important role in the regulation of glucocorticoid action, through inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β- HSD1) [36, 37]. LXRα forms obligate heterodimers with retinoid X receptors (RXRs), which bind to LXR response elements in promoter regions of genes, resulting in the modulation of transcriptional processes, through interactions with co-activator or co-repressor complexes [38]. LXRα has been shown to strongly induce transcription of the gene for SREBP-1c via this mechanism [39], leading to the activation of lipogenic genes. It is thought that the transcription factor PPARα prevents the heterodimerisation of LXRα with RXR [40], and it follows that LXRα can antagonise the functions of PPARα [41]. A direct interaction between LXRα and PPARα has been proposed [42], which would be a logical way of preventing the simultaneous activation of the opposing pathways [43] (Fig. 2).

> LXRs, PPARα and RXR are likely to interact with each other to prevent the simultaneous activation of β-oxidation of fatty acids and fatty acid synthesis.

LXR agonists have been proposed to act as glucose-lowering drugs. However, in mice, pharmacological LXR activation not only improves glucose metabolism, but also activates SREBP-1c and FASN, thereby causing severe hepatic steatosis [44], which, in turn, may have unfavourable effects on insulin sensitivity. Despite this, steatosis associated with LXR activation does not necessarily affect insulin-mediated suppression of hepatic glucose production. Indeed, glucose metabolism may even improve, as a result of increased peripheral glucose uptake and metabolism [45], maybe in response to potential counteracting glucose-lowering effects of LXR agonists or changes in hepatic fatty acid profile upon LXR activation. Changes in LXR-induced hepatic fatty acid profiles might be explained by enhanced transcription of the gene encoding stearoyl-CoA desaturase-1, which is involved in the conversion of saturated fatty acid into monounsaturated fatty acids [46]. Furthermore, an increased intake of dietary monounsaturated fatty acids improves insulin sensitivity in healthy humans [47]. Thus, hepatic accumulation of triglycerides, which are relatively rich in monounsaturated fatty acids, might be less deleterious than liver fat containing predominantly saturated fatty acids. Moreover, treatment with an LXRα agonist induces peroxisomal β-oxidation in PPARα-null mice, indicating an alternative PPARα-independent pathway that might serve as a counter-regulatory mechanism against LXR agonist-induced liver steatosis [48]. However, compared with PPARα-induced β-oxidation, this effect is modest.

> To date, the therapeutic use of synthetic LXR agonists is limited by LXR-induced activation of key lipogenic genes and hypertriglyceridaemia.

Further evidence that the source of fatty acids affect the maintenance of lipid, cholesterol and glucose metabolism has been provided by studies on genetically engineered '*Fasn* knockout in liver' (FASKOL) mice [49]. These mice are incapable of de novo fatty acid synthesis in the liver, leading to the development of hypoglycaemia and fatty liver in response to a zero-fat diet, which is reversed with dietary fat or treatment with a PPARα agonist. The results showed that dietary fat or fatty acid pools newly synthesised by hepatic FASN (new fat) activated PPARα, leading to increased fatty acid oxidation, whereas pre-existing stored fat released from adipose tissue into the circulation (old fat) did not. Based on these findings, compartmentalisation of fatty acid metabolism in hepatocytes has been suggested [50].

> Hepatic accumulation of previously stored body fat and saturated dietary fat may induce hepatic insulin resistance, whereas fat newly produced by the liver, and mono-and polyunsaturated dietary fat is likely to have less deleterious effects.

Peroxisome proliferator-activated receptor α

PPARs are ligand-activated transcription factors that play an important role in adipocyte differentiation and fatty acid catabolism. Three subtypes (α, δ [also known as β], γ) have been identified and show tissue-specific expression [51]. PPARγ is only expressed at very low levels in the

healthy liver, but levels are markedly increased in rodents with fatty liver and insulin resistance [52]. To date, it is unknown whether this phenomenon also exists in humans. PPARδ is ubiquitously expressed and is currently the least well understood of the PPAR subtypes. It has been shown to modulate the inflammatory status of foam cells in atherosclerotic lesions and to be involved in muscle lipid metabolism in mice [53, 54].

PPARα, the predominantly expressed form in the liver [55, 56], is involved in promoting gluconeogenesis [57, 58] and stimulates the transcription of genes that are critical for peroxisomal and mitochondrial oxidation of fatty acids [55]. By modulating gene expression, PPARα stimulates hepatic fatty acid oxidation to supply substrates that can be metabolised by other tissues. Supporting evidence is provided by the finding that PPARα-null mice exposed to prolonged fasting develop fatty liver and hypoglycaemia [59]. The hepatic expression of PPARα is nutritionally regulated: fasting activates PPARα, and fasted PPARα-null mice develop hypoglycaemia, hypoketonaemia, hyperlipidaemia and hepatic steatosis [59]. As mentioned above, PPARα forms heterodimers with RXRα, which enhances its binding to peroxisome proliferator response elements in target genes [41]. Thus, PPARα activation can suppress the LXRα-SREBP-1c pathway by interfering with the formation of SREBP-1c-activating LXR-RXR heterodimers [40] (Fig. 2).

The fibrate class of peroxisome proliferators act as PPARα agonists, and decrease plasma triglycerides and increase HDL levels, presumably through induction of genes involved in fatty acid β-oxidation [60]. In addition, PPARα agonists cause favourable changes in the particle size and subclass distribution of lipoproteins [61]. PPARα agonists reduce *Hsd11b1* mRNA in the liver after chronic treatment, likely by an indirect mechanism, whereas PPARγ agonists do not (probably because of the very low expression of PPARγ in the liver) [62]. The existence of a negative feedback loop between PPARα and the glucocorticoid receptor has been proposed. Furthermore, PPARα agonists have been shown to have an insulin-sensitising activity [63] and to offer protection from cardiovascular disease (reviewed in [64]). In the rodent liver, PPARα agonists have been shown to promote hepatocarcinogenesis [65]. However, PPARα activation has not been found to have tumorigenic effects in human hepatocytes [66].

> Activation of PPARα by fibrates has been shown to reduce major coronary events and to improve insulin sensitivity and blood lipids without significant toxicity.

Sterol regulatory element-binding protein 1c

SREBPs are membrane-bound transcription factors; they have been identified in three forms in humans and rodents. SREBP-1c and SREBP-2 are the predominant subtypes in the rodent and human liver [67]. The main role of SREBP-2 is cholesterol synthesis, whereas SREBP-1c activates a complete programme of hepatic fatty acid synthesis [68] and reciprocally inhibits the expression of the gene for PEPCK when carbohydrates are abundant [69, 70]. Overexpression of the gene for SREBP-1c leads to fatty liver in mice [71].

SREBP-1c gene transcription is activated by insulin [72], probably mediated via IRS1, PI-3-K and protein kinase B (PKB/Akt) [73]. The effect of insulin on expression of the SREBP-1c gene is opposed by glucagon [74]. Changes in the expression of integral membrane proteins have been shown to inhibit the proteolytic activation of SREBPs. SREBP-1c is inhibited by activation of AMP-activated protein kinase (AMPK), a major cellular regulator of lipid and glucose metabolism (see below) [75]. The promoter of the *SREBP-1c* gene contains a regulatory element for LXRα [76], which strongly induces its transcription [39]. In turn, activated SREBP-1c stimulates the transcription of genes involved in de novo lipogenesis, such as *ACAC* and *FASN*, and interacts with regulatory elements in the promoters of various insulin-regulated genes. This involves competitive inhibition of PPARγ coactivator 1α (PGC-1α), a co-regulator that activates PEPCK promotor activity and gluconeogenesis [77]. This effect of SREBP-1c seems to work in concert with insulin to suppress PGC-1α [78]. However, elevated levels of SREBP-1c have also been shown to induce insulin resistance by inhibiting hepatic IRS2 signalling. A reduction in *IRS2* expression restricts FOXO1 to the nucleus, leading to sustained gluconeogenesis [79]. This, in turn, may activate SREBP-1c, ChREBP and lipogenic enzymes, leading to triglyceride accumulation in the liver.

In addition to insulin, glucose has been shown to stimulate expression of the gene for SREBP-1c in a mouse hepatocyte cell line [80]. Exposure of insulin-depleted mice, generated by streptozotocin (STZ) administration, to fasting-refeeding protocols with glucose, fructose or sucrose showed markedly increased SREBP-1c on all carbohydrate diets. [81]. Thus, nutritional regulation of SREBP-1c and lipogenic genes might even be independent of insulin, provided sufficient carbohydrates are available. Nutrients other than dietary carbohydrates have been shown to influence SREBP-1c. Polyunsaturated fatty acids (PUFAs) suppress the proteolytic release of SREBP-1 [82], independently of LXRα [83]. SREBP-1c plays a major role in the long-term control of glucose and lipid metabolism [3]. However, selective knockout of the SREBP-1c gene in mice only reduces fatty acid synthesis by approximately 50%, and this reduction is more pronounced when all nuclear SREBP isoforms are absent. This indicates that other SREBP isoforms are able to partially compensate for the absence of SREBP-1c [84]. An alternative explanation may involve the transcription factor ChREBP, discussed in the next section, which has recently been shown to be regulated by factors similar to those involved in modulation of SREBP-1c (e.g. glucose, insulin, PUFA).

> SREBP-1c has both lipogenic and glucose-lowering moieties; thus, specific inhibition or activation of SREBP-1c may show unfavourable side effects.

Carbohydrate-response element-binding protein

The transcription factor ChREBP is translocated to the nucleus and activated in response to high glucose concentrations in the liver, independently of insulin. As the name suggests, it was first identified by its ability to bind the carbohydrate-response element of the gene encoding liver pyruvate kinase (L-PK). L-PK catalyses the conversion of phosphoenolpyruvate to pyruvate, which enters the Krebs cycle to generate citrate, the principal source of acetyl-CoA used for fatty acid synthesis [52]. Insulin indirectly regulates ChREBP through activation of glucokinase, which allows phosphorylated glucose to enter the pentose phosphate cycle, generating xylulose 5-phosphate and activating ChREBP via protein phosphatase 2A [3]. ChREBP has recently been shown to play a pivotal role in activating lipogenic genes [4]. ChREBP binds to its functional heterodimeric partner, Max-like protein X, and induces the transcription of lipogenic and glycolytic genes containing a carbohydrate response element, such as those encoding ACAC, FASN and L-PK [3, 85].

Current knowledge on the molecular actions of ChREBP is limited. In adipocytes, the thiazolidinedione (TZD) troglitazone has been shown to induce ChREBP gene expression in a dose-dependent manner [86], which may contribute to the glucose-lowering effects of TZDs. TZDs are thought to improve insulin sensitivity in adipose tissue mainly by acting on PPARγ, which is not known to have a relevant function in the human liver, and prolonged treatment with TZDs has been shown to reduce liver fat content and liver volume [87]. Moreover, it is unknown whether TZDs induce hepatic ChREBP gene expression in humans. Potential favourable effects of ChREBP activation on glucose metabolism may, however, have the disadvantage of increased hepatic fat accumulation. Polyunsaturated fatty acids (PUFAs) compromise the transcriptional activities of ChREBP by interfering with its translocation from the cytosol to the nucleus in response to glucose [88], independent of AMPK activation [89]. Thus, ChREBP is likely to be a major determinant of the inhibitory effect of PUFAs on both glycolytic and lipogenic genes [89].

> ChREBP acts in synergy with SREBP-1c to induce glycolytic and lipogenic gene expression. Pharmacological inhibitors of ChREBP have not been developed. However, PUFAs downregulate ChREBP gene expression.

11β-Hydroxysteroid dehydrogenase 1

11β-HSD1 is expressed in various—typically glucocorticoid-targeted—tissues. The highest levels of expression have been found in the liver, gonads, adipose tissue and the brain [90]. In vivo, 11β-HSD1 converts inactive cortisone to active cortisol in humans (or inactive 11-dehydrocorticosterone to active corticosterone in rodents) and 11β-HSD2 catalyses the reverse reaction. Glucocorticoids, PPAR-γ agonists and proinflammatory cytokines increase 11β-HSD1 activity. Insulin has been shown to suppress expression of the gene for 11β-HSD1 (*Hsd11b1*) in rat hepatocytes and hepatoma cells, while oestrogens, growth hormone and insulin reduce *Hsd11b1* expression in the rodent liver [90]. Although subjects with obesity and the metabolic syndrome have normal circulating levels of cortisol, tissue-specific cortisol excess due to increased 11β-HSD1 activity has been suggested to explain the obvious phenotypic similarities with patients with glucocorticoid excess (Cushing's syndrome) [91]. In uncomplicated obesity, 11β-HSD1 activity has been proposed to be downregulated, probably as a compensatory mechanism to prevent insulin resistance. This downregulation may be disturbed in type 2 diabetic patients, leading to insulin resistance and increased fat deposition in various organs, including the liver [92].

Glucocorticoids are essential factors involved in energy homeostasis, with cortisol being the principal active glucocorticoid in humans. Glucocorticoids stimulate the transcription of glucogenic genes (including those for PEPCK and G-6-Pase [70, 93]), inhibit mitochondrial matrix acyl-CoA dehydrogenases and fatty acid β-oxidation, and may produce fatty liver in humans [94]. In Cushing's syndrome, increased glucocorticoid production and activation of the glucocorticoid receptor leads to obesity and insulin resistance. Antagonism of the receptor prevents obesity in rodents. Furthermore, a defect in 11β-HSD1 activity prevented a classical cushingoid phenotype in a patient with confirmed Cushing's disease, despite the presence of systemic hypercortisolaemia [95].

Pharmacological treatment with LXR agonists has been demonstrated to downregulate gene expression and activity of *Hsd11b1* in liver and adipose tissue of wild-type mice, but not in LXRα/β-null mice. However, as already discussed, LXR agonists also activate SREBP-1c and thereby cause hepatic steatosis in mice, which may limit the therapeutic use of these agents. Another potential option to inhibit unfavourable glucocorticoid actions would be to block the glucocorticoid receptor [96]. However, long-term systemic therapy with glucocorticoid receptor antagonists may induce counter-regulatory mechanisms by activating the hypothalamic-pituitary-adrenal axis [97]. This phenomenon has also been suspected to appear in 11β-HSD1-null mice [98]. To circumvent these potential problems, highly selective inhibitors of 11β-HSD1 have recently been developed. Treatment of rodents with a non-steroidal selective inhibitor of 11β-HSD1 for 7 days significantly decreased both hepatic *G-6P-ase* and *PEPCK* mRNA as well as blood glucose and serum insulin concentrations [99].

> Selective inhibition of hepatic *HSD11B1* expression seems to be a promising target for lowering intracellular cortisol concentrations, and thereby enhancing insulin sensitivity and hepatic lipid metabolism in obesity and type 2 diabetes.

AMP-activated protein kinase

AMP-activated protein kinase (AMPK) belongs to a family of highly conserved serine-threonine kinases and is present in various organs, including the liver [100]. AMPK has a key role in the regulation of energy control as a metabolic sensor and regulator kinase. When activated, AMPK initiates a series of responses that are aimed at protecting the cell against ATP depletion, by stimulating fatty acid oxidation or glycolysis and inhibiting ATP-consuming anabolic pathways such as gluconeogenesis, protein and fatty acid synthesis [100]. AMPK is phosphorylated and thereby activated by the protein–threonine kinase LKB1, which seems to be the major upstream AMPK-activating factor [101]. Activation of AMPK results in inhibition of lipogenic factors such as SREBP-1c [75], FASN, ACAC [102] and ChREBP [103]. Induction of AMPK in hepatoma cells also decreases PEPCK and G-6-Pase transcription, likely in an insulin-independent manner [104]. AMPK is not known to be activated by insulin, raising the possibility that insulin and AMPK regulate PEPCK by different and, perhaps, converging pathways [70]. AMPK may prevent insulin resistance in part by inhibiting factors that antagonise insulin signalling [100]. Deletion of liver LKB1 in mice results in a near complete loss of AMPK activity, leading to lipogenic gene expression. Increased gluconeogenesis in these mice could be explained by the observed nuclear translocation of TORC2, which transcriptionally coactivates cAMP-response-element-binding protein (CREB), leading to increased expression of PGC-1α, thereby driving the expression of glucogenic genes [101].

A number of hormonal and nutritionally regulated factors have been proposed to be involved in the regulation of hepatic AMPK activity. The adipocyte-derived hormone adiponectin has been shown to activate AMPK (both in liver and skeletal muscle) and to reduce hepatic glucose production and the expression of hepatic gluconeogenic genes, while increasing β-oxidation of fatty acids in the liver [105, 106]. This may, at least in part, explain the positive associations between adiponectin and diabetes risk in epidemiological studies [107]. Conversely, the orexigenic hormone ghrelin inhibits AMPK in the rat liver and in adipose tissue, while stimulating AMPK activity in the heart and hypothalamus [108]. Ghrelin also decreases the effect of insulin on PEPCK in human hepatoma cells [109], and may therefore contribute to the development of hepatic insulin resistance and lipid accumulation. Other factors, such as adipocyte-secreted leptin or resistin (which is mainly expressed in monocytes and macrophages in humans) may be involved in the regulation of liver AMPK.

Hypoglycaemic agents such as metformin and rosiglitazone have been proposed to indirectly activate AMPK, probably by interference with the respiratory chain [100]. AMPK has been shown to be activated by metformin in skeletal muscle in vitro and in vivo (reviewed in [110]) and by pioglitazone in cultured cells and in rat liver and adipose tissue in vivo [111]. Interestingly, metformin action was turned off in the absence of LKB1, pointing to AMPK activation as an essential part of metformin action, at least in the mouse liver [101]. However, thiazolidinediones [112] and metformin [113] exert various other molecular actions, which are not well understood at present. Moreover, chronic pharmacological activation of AMPK may lead to inhibition of insulin release, and may have unfavourable effects on cell proliferation and glycogen storage in cardiomyocytes (reviewed in [114]). Fasting has been shown to increase hypothalamic AMPK activity, while refeeding inhibits it, with reduced hypothalamic AMPK activity exerting anorexigenic effects [115, 116]. Thus, non-selective AMPK activation may not be favourable in the context of body weight regulation.

An optimised pharmacological approach may include activation of liver (and skeletal muscle) AMPK, and inhibition of hypothalamic AMPK. However, information about selective pharmacological activation of AMPK in vivo is limited, and the safety of chronic AMPK activation needs to be established.

Concluding remarks

The studies discussed in this review indicate that hepatic fat accumulation, insulin resistance and disturbed glucose metabolism are inter-related at a molecular level. In insulin-resistant hyperglycaemic states the suppressive effects of insulin and glucose on hepatic glucose production is reduced, whereas undamped hepatic lipogenesis and non-insulin dependent glucose transport to the liver both contribute to hepatic lipid accumulation, which in turn may further deteriorate insulin signalling. Multiple organs, such as skeletal muscle, adipose tissue and the liver, are affected by insulin-resistant states and there has been considerable progress in identifying molecular pathways and potential factors involved. Skeletal muscle and fat tissue are relatively easily accessible for biopsy in humans. However, despite many similarities between molecular pathways in different tissues, there are also important differences. Thus, results obtained in other tissues cannot necessarily be transferred to the liver. Elucidating molecular pathways in human liver is more problematic due to the potential hazards involved in performing liver biopsies. It is therefore important to note that most studies that have investigated molecular pathways in the liver were performed in animal models or in vitro. Because molecular functions differ even between rodent species [117], it should be noted that, whilst results obtained in animal models provide valuable insights, they cannot necessarily be extrapolated to other species.

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