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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 · 11 $\beta$ -HSD1: 11 $\beta$ -hydroxysteroid dehydrogenase 1 (encoded by the gene *HSD11B1*) · L-PK: liver pyruvate kinase · LXR: liver X receptor · PGC-1 $\alpha$ : PPAR $\gamma$  coactivator 1 $\alpha$  · 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

### 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.

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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 phosphatidylinositol-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.

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### 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 gluconeogenic 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-phospha-

tase (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 gluconeogenic 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.

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### 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  $\beta$ -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

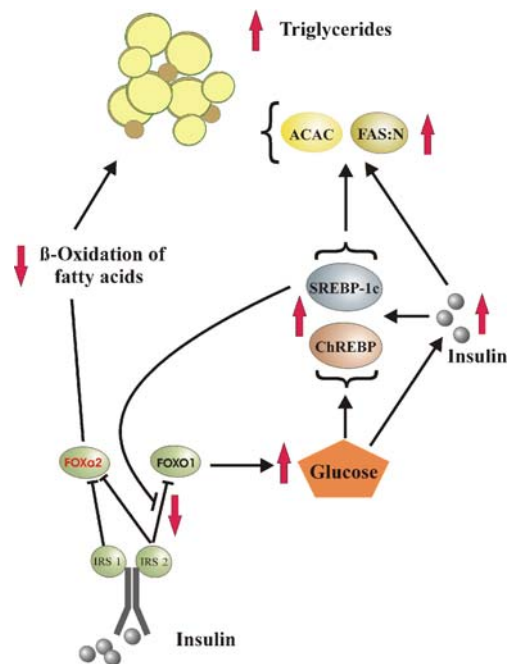
Insulin is commonly viewed as a positive regulator of fatty acid synthesis, as it promotes the expression of *FASN* and *ACAC*. However, when acutely elevated, insulin can reduce liver fat accumulation in normoinsulinaemic mice [29]. Following insulin-induced phosphorylation of the insulin receptor and 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



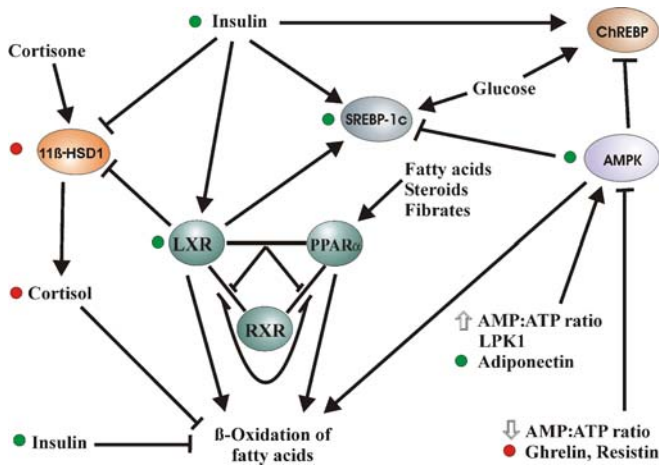
**Fig. 1** Model of signalling mechanisms resulting in hepatic triglyceride accumulation in insulin-resistant states. In sensitive states, receptor-bound insulin activates insulin receptor substrates IRS1 and IRS2, which, via PKB/Akt, block fatty acid oxidation (FOXO2) and gluconeogenesis (FOXO1). The 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

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).

### Liver X receptor $\alpha$

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, LXR $\alpha$  and LXR $\beta$ . The beta isoform is ubiquitously expressed and has recently been implicated in adipocyte growth, glucose homeostasis and beta cell function [32].

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



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

[34], resulting in increased levels of lipogenic enzymes and the suppression of key gluconeogenic enzymes, including PEPCK and G-6-Pase [35]. LXR $\alpha$  also plays an important role in the regulation of glucocorticoid action, through inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) [36, 37]. LXR $\alpha$  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]. LXR $\alpha$  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 PPAR $\alpha$  prevents the heterodimerisation of LXR $\alpha$  with RXR [40], and it follows that LXR $\alpha$  can antagonise the functions of PPAR $\alpha$  [41]. A direct interaction between LXR $\alpha$  and PPAR $\alpha$  has been proposed [42], which would be a logical way of preventing the simultaneous activation of the opposing pathways [43] (Fig. 2).

LXRs, PPAR $\alpha$  and RXR are likely to interact with each other to prevent the simultaneous activation of  $\beta$ -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 LXR $\alpha$  agonist induces peroxisomal  $\beta$ -oxidation in PPAR $\alpha$ -null mice, indicating an alternative PPAR $\alpha$ -independent pathway that might serve as a counter-regulatory mechanism against LXR agonist-induced liver steatosis [48]. However, compared with PPAR $\alpha$ -induced  $\beta$ -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 PPAR $\alpha$  agonist. The results showed that dietary fat or fatty acid pools newly synthesised by hepatic FASN (new fat) activated PPAR $\alpha$ , 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 $\alpha$

PPARs are ligand-activated transcription factors that play an important role in adipocyte differentiation and fatty acid catabolism. Three subtypes ( $\alpha$ ,  $\delta$  [also known as  $\beta$ ],  $\gamma$ ) have been identified and show tissue-specific expression [51]. PPAR $\gamma$  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. PPAR $\delta$  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].

PPAR $\alpha$ , 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, PPAR $\alpha$  stimulates hepatic fatty acid oxidation to supply substrates that can be metabolised by other tissues. Supporting evidence is provided by the finding that PPAR $\alpha$ -null mice exposed to prolonged fasting develop fatty liver and hypoglycaemia [59]. The hepatic expression of PPAR $\alpha$  is nutritionally regulated: fasting activates PPAR $\alpha$ , and fasted PPAR $\alpha$ -null mice develop hypoglycaemia, hypoketonaemia, hyperlipidaemia and hepatic steatosis [59]. As mentioned above, PPAR $\alpha$  forms heterodimers with RXR $\alpha$ , which enhances its binding to peroxisome proliferator response elements in target genes [41]. Thus, PPAR $\alpha$  activation can suppress the LXR $\alpha$ -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 PPAR $\alpha$  agonists, and decrease plasma triglycerides and increase HDL levels, presumably through induction of genes involved in fatty acid  $\beta$ -oxidation [60]. In addition, PPAR $\alpha$  agonists cause favourable changes in the particle size and subclass distribution of lipoproteins [61]. PPAR $\alpha$  agonists reduce *Hsd11b1* mRNA in the liver after chronic treatment, likely by an indirect mechanism, whereas PPAR $\gamma$  agonists do not (probably because of the very low expression of PPAR $\gamma$  in the liver) [62]. The existence of a negative feedback loop between PPAR $\alpha$  and the glucocorticoid receptor has been proposed. Furthermore, PPAR $\alpha$  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, PPAR $\alpha$  agonists have been shown to promote hepatocarcinogenesis [65]. However, PPAR $\alpha$  activation has not been found to have tumorigenic effects in human hepatocytes [66].

Activation of PPAR $\alpha$  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 LXR $\alpha$  [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 PPAR $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), a co-regulator that activates PEPCK promoter activity and gluconeogenesis [77]. This effect of SREBP-1c seems to work in concert with insulin to suppress PGC-1 $\alpha$  [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 LXR $\alpha$  [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 PPAR $\gamma$ , 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.

## 11 $\beta$ -Hydroxysteroid dehydrogenase 1

11 $\beta$ -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, 11 $\beta$ -HSD1 converts inactive cortisone to active cortisol in humans (or inactive 11-dehydrocorticosterone to active corticosterone in rodents) and 11 $\beta$ -HSD2 catalyses the reverse reaction. Glucocorticoids,

PPAR- $\gamma$  agonists and proinflammatory cytokines increase 11 $\beta$ -HSD1 activity. Insulin has been shown to suppress expression of the gene for 11 $\beta$ -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 11 $\beta$ -HSD1 activity has been suggested to explain the obvious phenotypic similarities with patients with glucocorticoid excess (Cushing's syndrome) [91]. In uncomplicated obesity, 11 $\beta$ -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  $\beta$ -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 11 $\beta$ -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 LXR $\alpha/\beta$ -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 11 $\beta$ -HSD1-null mice [98]. To circumvent these potential problems, highly selective inhibitors of 11 $\beta$ -HSD1 have recently been developed. Treatment of rodents with a non-steroidal selective inhibitor of 11 $\beta$ -HSD1 for 7 days significantly decreased both hepatic *G-6Pase* 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-1 $\alpha$ , 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  $\beta$ -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.

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## 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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## References

1. O'Brien RM, Streeper RS, Ayala JE, Stadelmaier BT, Hornbuckle LA (2001) Insulin-regulated gene expression. *Biochem Soc Trans* 29:552–558
2. Fougere F, Ferre P (2002) New perspectives in the regulation of hepatic glycolytic and lipogenic genes by insulin and glucose: a role for the transcription factor sterol regulatory element binding protein-1c. *Biochem J* 366:377–391
3. Dentin R, Girard J, Postic C (2005) Carbohydrate responsive element binding protein (ChREBP) and sterol regulatory element binding protein-1c (SREBP-1c): two key regulators of glucose metabolism and lipid synthesis in liver. *Biochimie* 87:81–86
4. Ishii S, Iizuka K, Miller BC, Uyeda K (2004) Carbohydrate response element binding protein directly promotes lipogenic enzyme gene transcription. *Proc Natl Acad Sci USA* 101:15597–15602
5. Steffensen KR, Gustafsson JA (2004) Putative metabolic effects of the liver X receptor (LXR). *Diabetes* 53(Suppl 1):S36–S42
6. Marchesini G, Brizi M, Bianchi G et al (2001) Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 50:1844–1850
7. Angulo P (2002) Nonalcoholic fatty liver disease. *N Engl J Med* 346:1221–1231
8. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM et al (2002) Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab* 87:3023–3028
9. Sutinen J, Hakkinen AM, Westerbacka J et al (2003) Rosiglitazone in the treatment of HAART-associated lipodystrophy—a randomized double-blind placebo-controlled study. *Antivir Ther* 8:199–207
10. Gavrilova O, Marcus-Samuels B, Graham D et al (2000) Surgical implantation of adipose tissue reverses diabetes in lipodystrophic mice. *J Clin Invest* 105:271–278
11. Kim JK, Gavrilova O, Chen Y, Reitman ML, Shulman GI (2000) Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. *J Biol Chem* 275:8456–8460
12. Samuel VT, Liu ZX, Qu X et al (2004) Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *J Biol Chem* 279:32345–32353
13. Petersen KF, Dufour S, Befroy D et al (2005) Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 54:603–608
14. Gastaldelli A, Toschi E, Pettiti M et al (2001) Effect of physiological hyperinsulinemia on gluconeogenesis in nondiabetic subjects and in type 2 diabetic patients. *Diabetes* 50:1807–1812
15. Boden G (2003) Effects of free fatty acids on gluconeogenesis and glycogenolysis. *Life Sci* 72:977–988
16. Roden M, Bernroider E (2003) Hepatic glucose metabolism in humans—its role in health and disease. *Best Pract Res Clin Endocrinol Metab* 17:365–383
17. Nordlie RC, Foster JD, Lange AJ (1999) Regulation of glucose production by the liver. *Annu Rev Nutr* 19:379–406
18. Pilkis SJ, Granner DK (1992) Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. *Annu Rev Physiol* 54:885–909
19. Shao J, Qiao L, Janssen RC, Pagliassotti M, Friedman JE (2005) Chronic hyperglycemia enhances PEPCK gene expression and hepatocellular glucose production via elevated liver activating protein/liver inhibitory protein ratio. *Diabetes* 54:976–984
20. Lam TK, Gutierrez-Juarez R, Poci A, Rossetti L (2005) Regulation of blood glucose by hypothalamic pyruvate metabolism. *Science* 309:943–947
21. Poci A, Obici S, Schwartz GJ, Rossetti L (2005) A brain–liver circuit regulates glucose homeostasis. *Cell Metab* 1:53–61
22. Horton JD, Shah NA, Warrington JA et al (2003) Combined analysis of oligonucleotide microarray data from transgenic and knockout mice identifies direct SREBP target genes. *Proc Natl Acad Sci USA* 100:12027–12032
23. Randle PJ (1998) Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metab Rev* 14:263–283
24. Ruderman NB, Saha AK, Vavvas D, Witters LA (1999) Malonyl-CoA, fuel sensing, and insulin resistance. *Am J Physiol* 276:E1–E18
25. McGarry JD (2002) Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* 51:7–18
26. Vaulont S, Vasseur-Cognet M, Kahn A (2000) Glucose regulation of gene transcription. *J Biol Chem* 275:31555–31558
27. Koo SH, Dutcher AK, Towle HC (2001) Glucose and insulin function through two distinct transcription factors to stimulate expression of lipogenic enzyme genes in liver. *J Biol Chem* 276:9437–9445
28. Shimomura I, Matsuda M, Hammer RE et al (2000) Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Mol Cell* 6:77–86
29. Najjar SM, Yang Y, Fernstrom MA et al (2005) Insulin acutely decreases hepatic fatty acid synthase activity. *Cell Metab* 2:43–53
30. Wolfrum C, Asilmaz E, Luca E, Friedman JM, Stoffel M (2004) Foxa2 regulates lipid metabolism and ketogenesis in the liver during fasting and in diabetes. *Nature* 432:1027–1032
31. Kalaany NY, Gauthier KC, Zavacki AM et al (2005) LXRs regulate the balance between fat storage and oxidation. *Cell Metab* 1:231–244
32. Gerin I, Dolinsky VW, Shackman JG et al (2005) LXRbeta is required for adipocyte growth, glucose homeostasis, and beta cell function. *J Biol Chem* 280:23024–23031
33. Repa JJ, Mangelsdorf DJ (2000) The role of orphan nuclear receptors in the regulation of cholesterol homeostasis. *Annu Rev Cell Dev Biol* 16:459–481
34. Tobin KA, Ulven SM, Schuster GU et al (2002) Liver X receptors as insulin-mediating factors in fatty acid and cholesterol biosynthesis. *J Biol Chem* 277:10691–10697
35. Cao G, Liang Y, Broderick CL et al (2003) Antidiabetic action of a liver x receptor agonist mediated by inhibition of hepatic gluconeogenesis. *J Biol Chem* 278:1131–1136
36. Stulnig TM, Oppermann U, Steffensen KR, Schuster GU, Gustafsson JA (2002) Liver X receptors downregulate 11beta-hydroxysteroid dehydrogenase type 1 expression and activity. *Diabetes* 51:2426–2433
37. Stulnig TM, Steffensen KR, Gao H et al (2002) Novel roles of liver X receptors exposed by gene expression profiling in liver and adipose tissue. *Mol Pharmacol* 62:1299–1305
38. Glass CK (1994) Differential recognition of target genes by nuclear receptor monomers, dimers, and heterodimers. *Endocr Rev* 15:391–407
39. Chen G, Liang G, Ou J, Goldstein JL, Brown MS (2004) Central role for liver X receptor in insulin-mediated activation of SREBP-1c transcription and stimulation of fatty acid synthesis in liver. *Proc Natl Acad Sci USA* 101:11245–11250
40. Yoshikawa T, Ide T, Shimano H et al (2003) Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. I. PPARs suppress sterol regulatory element binding protein-1c promoter through inhibition of LXR signaling. *Mol Endocrinol* 17:1240–1254
41. Ide T, Shimano H, Yoshikawa T et al (2003) Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. II. LXRs suppress lipid degradation gene promoters through inhibition of PPAR signaling. *Mol Endocrinol* 17:1255–1267



42. Miyata KS, McCaw SE, Patel HV, Rachubinski RA, Capone JP (1996) The orphan nuclear hormone receptor LXR alpha interacts with the peroxisome proliferator-activated receptor and inhibits peroxisome proliferator signaling. *J Biol Chem* 271:9189–9192
43. Anderson SP, Dunn C, Laughter A, et al (2004) Overlapping transcriptional programs regulated by the nuclear receptors peroxisome proliferator-activated receptor alpha, retinoid X receptor, and liver X receptor in mouse liver. *Mol Pharmacol* 66:1440–1452
44. Grefhorst A, Elzinga BM, Voshol PJ et al (2002) Stimulation of lipogenesis by pharmacological activation of the liver X receptor leads to production of large, triglyceride-rich very low density lipoprotein particles. *J Biol Chem* 277:34182–90
45. Grefhorst A, van Dijk TH, Hammer A et al (2005) Differential effects of pharmacological liver X receptor activation on hepatic and peripheral insulin sensitivity in lean and ob/ob mice. *Am J Physiol Endocrinol Metab* 289:E829–E838
46. Miyazaki M, Ntambi JM (2003) Role of stearoyl-coenzyme A desaturase in lipid metabolism. *Prostaglandins Leukot Essent Fatty Acids* 68:113–21.
47. Vessby B, Unsitupa M, Hermansen K et al (2001) Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. *Diabetologia* 44:312–319
48. Hu T, Foxworthy P, Siesky A et al (2005) Hepatic peroxisomal fatty acid beta oxidation is regulated by liver X receptor alpha. *Endocrinology* 146:5380–5387
49. Chakravarthy MV, Pan Z, Zhu Y et al (2005) 'New' hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. *Cell Metab* 1:309–322
50. Gibbons G (2005) Old fat, make way for new fat. *Nat Med* 11:722–723
51. Lemberger T, Braissant O, Juge-Aubry C et al (1996) PPAR tissue distribution and interactions with other hormone-signaling pathways. *Ann N Y Acad Sci* 804:231–251
52. Browning JD, Horton JD (2004) Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest* 114:147–152
53. Lee CH, Chawla A, Urbiztondo N et al (2003) Transcriptional repression of atherogenic inflammation: modulation by PPAR-delta. *Science* 302:453–457
54. Tanaka T, Yamamoto J, Iwasaki S et al (2003) Activation of peroxisome proliferator-activated receptor delta induces fatty acid beta-oxidation in skeletal muscle and attenuates metabolic syndrome. *Proc Natl Acad Sci USA* 100:15924–15929
55. Reddy JK, Hashimoto T (2001) Peroxisomal beta-oxidation and peroxisome proliferator-activated receptor alpha: an adaptive metabolic system. *Annu Rev Nutr* 21:193–230
56. Vidal-Puig AJ, Considine RV, Jimenez-Linan M et al (1997) Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids. *J Clin Invest* 99:2416–2422
57. Bernal-Mizrachi C, Weng S, Feng C et al (2003) Dexamethasone induction of hypertension and diabetes is PPAR-alpha dependent in LDL receptor-null mice. *Nat Med* 9:1069–1075
58. Koo SH, Satoh H, Herzig S et al (2004) PGC-1 promotes insulin resistance in liver through PPAR-alpha-dependent induction of TRB-3. *Nat Med* 10:530–534
59. Kersten S, Seydoux J, Peters JM, et al (1999) Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. *J Clin Invest* 103:1489–1498
60. Linton MF, Fazio S (2000) Re-emergence of fibrates in the management of dyslipidemia and cardiovascular risk. *Curr Atheroscler Rep* 2:29–35
61. Bays H, Stein EA (2003) Pharmacotherapy for dyslipidaemia—current therapies and future agents. *Expert Opin Pharmacother* 4:1901–1938
62. Hermanowski-Vosatka A, Gerhold D, Mundt SS et al (2000) PPARalpha agonists reduce 11beta-hydroxysteroid dehydrogenase type 1 in the liver. *Biochem Biophys Res Commun* 279:330–336
63. Guerre-Millo M, Gervois P, Raspe E et al (2000) Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. *J Biol Chem* 275:16638–16642
64. Staels B, Fruchart JC (2005) Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* 54:2460–2470
65. Rao MS, Reddy JK (1996) Hepatocarcinogenesis of peroxisome proliferators. *Ann N Y Acad Sci* 804:573–587
66. Knight B, Yeap BB, Yeoh GC, Olynyk JK (2005) Inhibition of adult liver progenitor (oval) cell growth and viability by an agonist of the peroxisome proliferator activated receptor (PPAR) family member gamma, but not alpha or delta. *Carcinogenesis* 26:1782–1792
67. Shimomura I, Shimano H, Horton JD, Goldstein JL, Brown MS (1997) Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells. *J Clin Invest* 99:838–845
68. Horton JD, Goldstein JL, Brown MS (2002) SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest* 109:1125–1131
69. Yamamoto T, Shimano H, Nakagawa Y et al (2004) SREBP-1 interacts with hepatocyte nuclear factor-4 alpha and interferes with PGC-1 recruitment to suppress hepatic gluconeogenic genes. *J Biol Chem* 279:12027–12035
70. Chakravarty K, Cassuto H, Reshef L, Hanson RW (2005) Factors that control the tissue-specific transcription of the gene for phosphoenolpyruvate carboxykinase-C. *Crit Rev Biochem Mol Biol* 40:129–154
71. Shimano H, Horton JD, Shimomura I et al (1997) Isoform 1c of sterol regulatory element binding protein is less active than isoform 1a in livers of transgenic mice and in cultured cells. *J Clin Invest* 99:846–854
72. Foretz M, Guichard C, Ferre P, Foufelle F (1999) Sterol regulatory element binding protein-1c is a major mediator of insulin action on the hepatic expression of glucokinase and lipogenesis-related genes. *Proc Natl Acad Sci USA* 96:12737–12742
73. Ribaux PG, Iyenedjian PB (2003) Analysis of the role of protein kinase B (cAKT) in insulin-dependent induction of glucokinase and sterol regulatory element-binding protein 1 (SREBP1) mRNAs in hepatocytes. *Biochem J* 376:697–705
74. Foretz M, Pacot C, Dugail I et al (1999) ADD1/SREBP-1c is required in the activation of hepatic lipogenic gene expression by glucose. *Mol Cell Biol* 19:3760–3768
75. Zhou G, Myers R, Li Y et al (2001) Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 108:1167–1174
76. Jump DB, Botolin D, Wang Y et al (2005) Fatty Acid regulation of hepatic gene transcription. *J Nutr* 135:2503–2506
77. Puigserver P, Rhee J, Donovan J et al (2003) Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1alpha interaction. *Nature* 423:550–555
78. Barthel A, Schmolle D (2003) Novel concepts in insulin regulation of hepatic gluconeogenesis. *Am J Physiol Endocrinol Metab* 285:E685–E692
79. Ide T, Shimano H, Yahagi N et al (2004) SREBPs suppress IRS-2-mediated insulin signalling in the liver. *Nat Cell Biol* 6:351–357
80. Hasty AH, Shimano H, Yahagi N et al (2000) Sterol regulatory element-binding protein-1 is regulated by glucose at the transcriptional level. *J Biol Chem* 275:31069–31077
81. Matsuzaka T, Shimano H, Yahagi N et al (2004) Insulin-independent induction of sterol regulatory element-binding protein-1c expression in the livers of streptozotocin-treated mice. *Diabetes* 53:560–569
82. Xu J, Cho H, O'Malley S, Park JH, Clarke SD (2002) Dietary polyunsaturated fats regulate rat liver sterol regulatory element binding proteins-1 and -2 in three distinct stages and by different mechanisms. *J Nutr* 132:3333–3339
83. Pawar A, Botolin D, Mangelsdorf DJ, Jump DB (2003) The role of liver X receptor-alpha in the fatty acid regulation of hepatic gene expression. *J Biol Chem* 278:40736–40743

84. Liang G, Yang J, Horton JD et al (2002) Diminished hepatic response to fasting/refeeding and liver X receptor agonists in mice with selective deficiency of sterol regulatory element-binding protein-1c. *J Biol Chem* 277:9520–9528
85. Stoekman AK, Ma L, Towle HC (2004) Mlx is the functional heteromeric partner of the carbohydrate response element-binding protein in glucose regulation of lipogenic enzyme genes. *J Biol Chem* 279:15662–15669
86. He Z, Jiang T, Wang Z, Levi M, Li J (2004) Modulation of carbohydrate response element-binding protein gene expression in 3T3-L1 adipocytes and rat adipose tissue. *Am J Physiol Endocrinol Metab* 287:E424–E430
87. Promrat K, Lutchman G, Uwaifo GI et al (2004) A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 39:188–196
88. Uyeda K, Yamashita H, Kawaguchi T (2002) Carbohydrate responsive element-binding protein (ChREBP): a key regulator of glucose metabolism and fat storage. *Biochem Pharmacol* 63:2075–2080
89. Dentin R, Benhamed F, Pegorier JP et al (2005) Polyunsaturated fatty acids suppress glycolytic and lipogenic genes through the inhibition of ChREBP nuclear protein translocation. *J Clin Invest* 115:2843–2854
90. Tomlinson JW, Walker EA, Bujalska IJ et al (2004) 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev* 25:831–866
91. Bujalska IJ, Kumar S, Stewart PM (1997) Does central obesity reflect ‘Cushing’s disease of the omentum’? *Lancet* 349:1210–1213
92. Tomlinson JW, Stewart MP (2005) Mechanisms of disease: selective inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 as a novel treatment for the metabolic syndrome. *Nat Clin Pract Endocrinology & Metabolism* 1:92–99
93. Friedman JE, Yun JS, Patel YM, McGrane MM, Hanson RW (1993) Glucocorticoids regulate the induction of phosphoenolpyruvate carboxykinase (GTP) gene transcription during diabetes. *J Biol Chem* 268:12952–12957
94. Letteron P, Brahimi-Bourouina N, Robin MA et al (1997) Glucocorticoids inhibit mitochondrial matrix acyl-CoA dehydrogenases and fatty acid beta-oxidation. *Am J Physiol* 272:G1141–G1150
95. Tomlinson JW, Draper N, Mackie J et al (2002) Absence of Cushingoid phenotype in a patient with Cushing’s disease due to defective cortisone to cortisol conversion. *J Clin Endocrinol Metab* 87:57–62
96. Gruol DJ, Altschmied J (1993) Synergistic induction of apoptosis with glucocorticoids and 3',5'-cyclic adenosine monophosphate reveals agonist activity by RU 486. *Mol Endocrinol* 7:104–113
97. Lamberts SW, Koper JW, de Jong FH (1991) The endocrine effects of long-term treatment with mifepristone (RU 486). *J Clin Endocrinol Metab* 73:187–191
98. Harris HJ, Kotelevtsev Y, Mullins JJ, Seckl JR, Holmes MC (2001) Intracellular regeneration of glucocorticoids by 11beta-hydroxysteroid dehydrogenase (11beta-HSD)-1 plays a key role in regulation of the hypothalamic–pituitary–adrenal axis: analysis of 11beta-HSD-1-deficient mice. *Endocrinology* 142:114–120
99. Alberts P, Engblom L, Edling N et al (2002) Selective inhibition of 11beta-hydroxysteroid dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice. *Diabetologia* 45:1528–1532
100. Kahn BB, Alquier T, Carling D, Hardie DG (2005) AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* 1:15–25
101. Shaw RJ, Lamia KA, Vasquez D et al (2005) The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 310:1642–1646
102. Hardie DG, Scott JW, Pan DA, Hudson ER (2003) Management of cellular energy by the AMP-activated protein kinase system. *FEBS Lett* 546:113–120
103. Kawaguchi T, Osatomi K, Yamashita H, Kabashima T, Uyeda K (2002) Mechanism for fatty acid ‘sparing’ effect on glucose-induced transcription: regulation of carbohydrate-responsive element-binding protein by AMP-activated protein kinase. *J Biol Chem* 277:3829–3835
104. Lochhead PA, Salt IP, Walker KS, Hardie DG, Sutherland C (2000) 5-aminoimidazole-4-carboxamide riboside mimics the effects of insulin on the expression of the 2 key gluconeogenic genes PEPCK and glucose-6-phosphatase. *Diabetes* 49:896–903
105. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L (2001) Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J Clin Invest* 108:1875–1881
106. Yamauchi T, Kamon J, Minokoshi Y et al (2002) Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 8:1288–1295
107. Spranger J, Kroke A, Mohlig M et al (2003) Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–228
108. Kola B, Hubina E, Tucci SA et al (2005) Cannabinoids and ghrelin have both central and peripheral metabolic and cardiac effects via AMP-activated protein kinase. *J Biol Chem* 280:25196–25201
109. Murata M, Okimura Y, Iida K et al (2002) Ghrelin modulates the downstream molecules of insulin signaling in hepatoma cells. *J Biol Chem* 277:5667–5674
110. Ruderman NB, Saha AK, Kraegen EW (2003) Minireview: malonyl CoA, AMP-activated protein kinase, and adiposity. *Endocrinology* 144:5166–5171
111. Saha AK, Avilucea PR, Ye JM et al (2004) Pioglitazone treatment activates AMP-activated protein kinase in rat liver and adipose tissue in vivo. *Biochem Biophys Res Commun* 314:580–585
112. Kersten S, Desvergne B, Wahli W (2000) Roles of PPARs in health and disease. *Nature* 405:421–424
113. Klein J, Westphal S, Kraus D et al (2004) Metformin inhibits leptin secretion via a mitogen-activated protein kinase signaling pathway in brown adipocytes. *J Endocrinol* 183:299–307
114. Musi N, Goodyear LJ (2002) Targeting the AMP-activated protein kinase for the treatment of type 2 diabetes. *Curr Drug Targets Immune Endocr Metabol Disord* 2:119–127
115. Minokoshi Y, Alquier T, Furukawa N et al (2004) AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* 428:569–574
116. Carling D (2005) AMP-activated protein kinase: balancing the scales. *Biochimie* 87:87–91
117. Lin MH, Lu SC, Huang PC, Liu YC, Liu SY (2005) A high-cholesterol, n-3 polyunsaturated fatty acid diet causes different responses in rats and hamsters. *Ann Nutr Metab* 49:386–391