Hepatic lipid accumulation: cause and consequence of dysregulated glucoregulatory hormones

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Abstract

Fatty liver can be diet, endocrine, drug, virus or genetically induced. Independent of cause, hepatic lipid accumulation promotes systemic metabolic dysfunction. By acting as peroxisome proliferator-activated receptor (PPAR) ligands, hepatic non-esterified fatty acids upregulate expression of gluconeogenic, beta-oxidative, lipogenic and ketogenic genes, promoting hyperglycemia, hyperlipidemia and ketosis. The typical hormonal environment in fatty liver disease consists of hyperinsulinemia, hyperglucagonemia, hypercortisolemia, growth hormone deficiency and elevated sympathetic tone. These endocrine and metabolic changes further encourage hepatic steatosis by regulating adipose tissue lipolysis, liver lipid uptake, *de novo* lipogenesis (DNL), beta-oxidation, ketogenesis and lipid export. Hepatic lipid accumulation may be induced by 4 separate mechanisms: (1) increased hepatic uptake of circulating fatty acids, (2) increased hepatic *de novo* fatty acid synthesis, (3) decreased hepatic beta-oxidation and (4) decreased hepatic lipid export. This review will discuss the hormonal regulation of each mechanism comparing multiple physiological models of hepatic lipid accumulation. Nonalcoholic fatty liver disease (NAFLD) is typified by increased hepatic lipid uptake, synthesis, oxidation and export. Chronic hepatic lipid signaling through PPARgamma results in gene expression changes that allow concurrent activity of DNL and beta-oxidation. The importance of hepatic steatosis in driving systemic metabolic dysfunction is highlighted by the common endocrine and metabolic disturbances across many conditions that result in fatty liver. Understanding the mechanisms underlying the metabolic dysfunction that develops as a consequence of hepatic lipid accumulation is critical to identifying points of intervention in this increasingly prevalent disease state.

Key Words

- insulin resistance
- obesity
- nonalcoholic fatty liver disease
- peroxisome proliferator-activated receptor

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Introduction

Fatty liver is common to a wide range of human conditions. Nonalcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease in developed countries and its increased prevalence parallels the rise in obesity, type 2 diabetes and metabolic syndrome in recent decades (Tuyama & Chang 2012, Yki-Jarvinen 2016). NAFLD encompasses hepatic steatosis driven by factors other than excessive alcohol consumption and is estimated to affect 25% of the global population (Zhu et al. 2015). While NAFLD most commonly refers to

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fatty liver resulting from overnutrition and consumption of a western diet, NAFLD may also be induced by endocrine disorders, viral infections or side effects of pharmacological therapies.

The prevalence of alcoholic fatty liver disease (AFLD) in the general population is approximately 8% (Kotronen *et al.* 2010, Kim *et al.* 2014*b*). Like NAFLD, the prevalence of AFLD is expected to rise (Toshikuni *et al.* 2014). While both AFLD and NAFLD have similar histology and disease progression, AFLD also induces molecular and clinical changes that are attributed to high alcohol consumption, and not as a result of hepatic lipid accumulation (Toshikuni *et al.* 2014, Rasineni *et al.* 2016). Interestingly, both AFLD and NAFLD are strongly associated with metabolic syndrome and type 2 diabetes (Kotronen *et al.* 2010), suggesting that fatty liver, independent of origin, promotes systemic metabolic dysfunction.

The severity of fatty liver disease is directly related to classic components of the metabolic syndrome including central obesity, insulin resistance, hyperinsulinemia, hypertriglyceridemia and hyperglycemia (Bedogni *et al.* 2005, Wainwright & Byrne 2016). In fact, 60–70% of type 2 diabetics and 65–85% of obese patients (BMI ≥ 30) are comorbid with NAFLD (Schindhelm *et al.* 2007, Fabbrini *et al.* 2010, Chon *et al.* 2016). Postprandial hyperinsulinemia is present in 100% of NAFLD cases independent of diabetes status (Manchanayake *et al.* 2011). Furthermore, sympathetic nervous system activity and circulating norepinephrine concentrations are commonly elevated in obesity and fatty liver disease (Pratley *et al.* 1995, Thorp & Schlaich 2015). Nearly all nonalcoholic steatohepatitis (NASH) patients display insulin resistance independent of body weight (Chitturi *et al.* 2002). In fact, peripheral insulin resistance is now considered a better predictor of hepatic injury in NAFLD than visceral adiposity or the commonly used fibrosis scoring system (Ercin *et al.* 2015, Rosso *et al.* 2016).

Dysregulated glucagon secretion and signaling is also associated with fatty liver disease. NAFLD patients both with and without type 2 diabetes display fasting hyperglucagonemia (Bernsmeier *et al.* 2014, Junker *et al.* 2016). In fact, the suppression of plasma glucagon in response to a meal or hyperglycemia is impaired or eliminated in prediabetic and diabetic individuals (Muller *et al.* 1970, Unger *et al.* 1972, Rohrer *et al.* 2012, Foghsgaard *et al.* 2016). Glucose-mediated inhibition of glucagon secretion from pancreatic alpha cells occurs indirectly and relies on paracrine signaling from insulin secreting beta cells (Le Marchand & Piston 2010). Loss of this paracrine inhibition in diabetes promotes hypersecretion of glucagon, and the hyperglycemia and hyperketonemia of diabetes classically thought to be a consequence of blunted insulin signaling are mediated, in part, by excess glucagon (Brand *et al.* 1996, Lee *et al.* 2011, Unger & Cherrington 2012). Therefore, abnormal alpha-cell function and an increased glucagon:insulin ratio are central to the pathology of fatty liver disease.

Hepatic lipid accumulation occurs transiently as a metabolic adaptation to fasting. In this review, fasting is defined by an increase in circulating ketone bodies and hepatic glucose output attributed to continuous food deprivation. In mice, this occurs between 4 and 8 h of food deprivation, while in humans, this corresponds to 12–24 h without food intake (Katz & Tayek 1998, Browning *et al.* 2012, Geisler *et al.* 2016). Early in a fast, hepatic glucose output is derived both from gluconeogenesis and glycogenolysis. In conjunction with a robust reduction of hepatic glycogen stores, which occurs by 12 and 40 h of fasting in mice and humans, respectively (Rothman *et al.* 1991, Geisler *et al.* 2016), total hepatic glucose output declines as gluconeogenic flux remains constant (Katz & Tayek 1998). In order to meet the systemic energy demands during a fast, hormonal signals stimulate adipose tissue to release non-esterified fatty acids (NEFA) into circulation at a rate which exceeds clearance by non-hepatic tissues (Patel *et al.* 2002, Djurhuus *et al.* 2004). Additionally, depression of hepatic glycogen stores during fasting further stimulates adipose tissue lipolysis, indicating that in addition to external hormonal signals, internal liver-derived signals regulate systemic energy metabolism and promote lipid mobilization (Izumida *et al.* 2013). To better clear circulating fatty acids, the liver upregulates expression of the hepatic fatty acid transporter Cd36 (Xu *et al.* 2013). In the mouse, significant accumulation of hepatic NEFAs and triglycerides occurs within 4 and 12 h fasting, respectively (Geisler *et al.* 2016). These hepatic lipids spare the oxidation of gluconeogenic amino acids and serve as substrates to generate ketones. Prolonged (>50 h) fasting in humans also results in insulin resistance, which develops after the accumulation of hepatic lipids and prevents glucose clearance by non-glucose obligate tissues (Hoeks *et al.* 2010, Browning *et al.* 2012, Hanssen *et al.* 2015). Thus, fasting shares a metabolic profile common to hepatic lipid accumulation including systemic insulin resistance and activation of hepatic gluconeogenesis and ketogenesis.

Given that hormonal signals are integral to hepatic lipid accumulation during fasting, it may be expected that endocrine disorders commonly result in

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NAFLD. Hypogonadism, polycystic ovarian syndrome, hypothyroidism, growth hormone deficiency, hypercortisolemia, hyperaldosteronism and hyperpro-lactemia all are associated with a higher prevalence of NAFLD and insulin resistance (Hazlehurst & Tomlinson 2013, Marino & Jornayvaz 2015). In one cohort of growth hormone-deficient patients, 77% presented with NAFLD (Nishizawa *et al.* 2012). Conversely, individuals with NAFLD were found to have significantly lower growth hormone levels than controls (Xu *et al.* 2012). Cushing's syndrome is present in 0.00025% of the general population, yet exists in 1.4% of type 2 diabetics with 3.4% displaying hypercortisolemia (Steffensen *et al.* 2016). Daily hydrocortisone dose is positively associated with hepatic lipid accumulation in humans, and exogenous corticosterone treatment in rats induces hepatic steatosis (D'Souza A *et al.* 2012, Auer *et al.* 2016). Furthermore, NAFLD patients have chronic hypothalamic–pituitary–adrenal (HPA) axis hyperactivity and subclinical hypercortisolemia (Targher *et al.* 2006). Dysfunction of a number of hormonal systems can contribute to NAFLD pathogenesis, as correction of underlying endocrine disorders alleviates hepatic steatosis (Marino & Jornayvaz 2015).

Hepatic steatosis in humans can also be virus or drug induced. Hepatitis B, C and HIV infection are all mechanistically linked to hepatic lipid accumulation, and hepatic steatosis occurs in 40–50% of HIV-infected patients (Lemoine *et al.* 2006, Macias *et al.* 2014, Matthews *et al.* 2015, Wu *et al.* 2016). The common HIV therapeutic, highly active antiretroviral therapy (HAART), encourages lipodystrophy and can itself induce hepatic steatosis (Vallet-Pichard *et al.* 2012). Cancer therapeutics including tamoxifen, irinotecan and cisplatin are additionally known to promote fatty liver (Satapathy *et al.* 2015, Pan *et al.* 2016).

In this review, we aim to compare multiple models of hepatic lipid accumulation (diet, drug, genetic and hormone induced) to better isolate the specific phenotypes that accompany hepatic steatosis. Accordingly, we will discuss how hepatic lipids function as signaling molecules and regulators of hepatic metabolic activity to potentiate systemic metabolic dysfunction. Finally, we will compare the metabolic adaptation in models with hepatic lipid accumulation resulting from (1) increased mobilization of adipose tissue lipid stores and accumulation in the liver, (2) increased hepatic *de novo* lipogenesis (DNL), (3) decreased hepatic beta-oxidation and ketogenesis, or (4) decreased export of lipids from the liver in very low density lipoproteins (VLDL).

Hepatic lipids as signaling molecules

Hepatic fatty acids act as endogenous ligands that activate peroxisome proliferator receptor alpha (PPARa) regulated pathways to produce metabolic products required to meet whole body nutritional demands while fasting (Kersten *et al.* 1999). Fatty acid binding to nuclear PPARa allows for PPARa activation and binding to the PPAR response element (PPRE) in the promoter of many genes (Ellinghaus *et al.* 1999, Elholm *et al.* 2001). During a fast, PPARa expression is increased in response to glucagon signaling and by fatty-acid-induced PPARa-mediated self-upregulation (Pineda Torra *et al.* 2002, Berglund *et al.* 2010). This increased expression ensures that PPARa availability is not limiting to the signal generated by hepatic lipid accumulation.

PPARa signaling increases transcription of target genes in gluconeogenesis (phosphoenolpyruvate carboxykinase; PEPCK, glucose 6-phosphatase; G6Pase), beta-oxidation (carnitine palmitoyltransferase 1; CPT1) and ketogenesis (hydroxy-3-methyl glutaryl CoA synthase 2; HMGCS2) (Rodriguez *et al.* 1994, Pineda Torra *et al.* 2002, Napal *et al.* 2005, Tachibana *et al.* 2005, Im *et al.* 2011). PPARa transcriptional activity is further enhanced by the coactivator peroxisome proliferator-activated receptor gamma coactivator 1alpha (PGC-1a) (Vega *et al.* 2000, Song *et al.* 2010). As evidence for the central role of PPARa in coordinating the hepatic adaptation to fasting, fasted PPARa null mice are hypoglycemic and fail to become ketotic (Kersten *et al.* 1999, Leone *et al.* 1999). Additionally, PPARa null mice exhibit impaired gluconeogenesis from lactate, pyruvate and glycerol (Le May *et al.* 2000, Xu *et al.* 2002, Patsouris *et al.* 2004). Furthermore, blunted G6Pase upregulation in fasted PPARa null mice directs glucose 6-phosphate toward glycogen synthesis rather than hepatic export (Bandsma *et al.* 2004). PPARa-mediated upregulation of lipid oxidative genes also encourages maximal hepatic glucose output during fasting, since acetyl-CoA serves as an ample source of carbons for oxidation in the TCA cycle, which allows for flux of gluconeogenic substrates toward gluconeogenesis and away from TCA cycle oxidation (Pettit *et al.* 1975, Tutwiler & Dellevigne 1979, Chow *et al.* 1990, Gonzalez-Manchon *et al.* 1992). In response to a fast, PPARa null mice also develop more severe hepatic steatosis than controls. By encouraging flux through beta-oxidation and ketogenesis, PPARa signaling limits the hepatic accumulation of lipids (Aoyama *et al.* 1998, Hashimoto *et al.* 2000). This prevents hepatic oxidative stress that results from the generation of reactive oxygen

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species and lipid peroxidation products in response to excess hepatic lipid accumulation (Pawlak *et al.* 2015). Thus, under periods of food deprivation, PPARa promotes hepatic glucose and ketone production and prevents lipotoxicity.

Gluconeogenic gene expression is upregulated in response to elevated circulating NEFA (Massillon *et al.* 1997). Like in fasting, the elevation of gluconeogenic enzyme expression in NAFLD is dependent upon PPARa (Im *et al.* 2011). Hepatic PPARa expression and transcriptional activity are induced by high-fat diet feeding (Kim *et al.* 2004, Patsouris *et al.* 2006), and elevated hepatic glucose output in diabetes is a dominant factor underlying abnormal glucose homeostasis (Consoli 1992). However, diet-induced obesity does not increase hepatic glucose production or result in hyperglycemia in mice that lack PPARa (Guerre-Millo *et al.* 2001, Cha *et al.* 2007). Interestingly, the PPARa agonist-mediated increase in G6Pase and PEPCK mRNA expression is exacerbated by dexamethasone (Lemberger *et al.* 1996, Bernal-Mizrachi *et al.* 2007), suggesting that the hypercortisolemia observed in both obesity and fasting is important in enhancing the response to PPARa signaling generated from hepatic lipid accumulation. Glucagon and glucocorticoids upregulate the expression of PGC-1a, the PPARa coactivator, and glucocorticoid-induced gluconeogenesis is dependent upon PPARa signaling (Yoon *et al.* 2001, Bernal-Mizrachi *et al.* 2007). In fact, decreased local glucocorticoid production impairs the hepatic induction of PEPCK and G6Pase during fasting and prevents diet-induced hyperglycemia (Kotelevtsev *et al.* 1997). Because of reduced hepatic glucose production, mice that lack PPARa maintain glucose tolerance and insulin sensitivity when challenged with high-fat diet (Guerre-Millo *et al.* 2001, Cha *et al.* 2007).

PPARa is also essential for the upregulation in flux through beta-oxidation and ketogenesis in response to diet-induced hepatic lipid accumulation. PPARa knockout reduces fasting-stimulated hepatic beta-oxidation and HMGCS2 upregulation (Le May *et al.* 2000). Glucagon and glucocorticoids induce HMGCS2 expression (Hegardt 1999), possibly depending upon PPARa signaling. The PPARa target and major stimulator of ketone production in mice, fibroblast growth factor 21 (FGF21), is required for the increase in beta-oxidation and ketone synthesis common to fatty liver disease (Badman *et al.* 2007, Xu *et al.* 2009*b*, Fisher *et al.* 2014). However, despite a similar obesity-induced rise in FGF21 in mice and humans, FGF21, which rises only in response to an extended 7-day fast, does not appear to drive ketogenesis in the human (Dushay *et al.* 2010, Fisher *et al.* 2010, Fazeli *et al.* 2015).

PPARa signaling in fatty liver disease promotes lipid catabolism and ketone production. Interestingly, PPARa signaling also upregulates expression of UCP2 (Kelly *et al.* 1998). UCP2 separates electron transport chain activity from ATP synthesis, leading to the decline in hepatic ATP in fatty livers. Under conditions of abundant substrate availability (e.g., hepatic lipid accumulation), this uncoupling allows for continued oxidation of fatty acids beyond that required to meet cellular energy requirements (Chavin *et al.* 1999). In fact, despite increased TCA cycle activity, hepatic ATP depletion is a consistent finding in hepatic steatosis (Chavin *et al.* 1999, Koliaki & Roden 2013, Patterson *et al.* 2016). In fatty liver disease, hepatic lipid accumulation, hyperglucagonemia and hypercortisolemia synergistically increase PPARa activity and upregulate gluconeogenic, beta-oxidative and ketogenic gene expression. By increasing the potential for hepatic glucose output, lipid catabolism and ketone production, PPARa-induced changes in gene expression limit the lipotoxicity of hepatic lipid accumulation. In both alcohol- and methionine-choline-deficient models of hepatic lipid accumulation, elimination of PPARa signaling increases the resulting hepatic lipid accumulation (Ip *et al.* 2003, Li *et al.* 2014). Accordingly, PPARa agonist treatment in fatty liver models consistently decreases hepatic steatosis (Ide *et al.* 2004, Larter *et al.* 2012, Barbosa-da-Silva *et al.* 2015, Souza-Mello 2015).

Several models of fatty liver disease have reported increased expression of both PPARa and peroxisome proliferator-activated receptor gamma (PPARg) (Memon *et al.* 2000, Lopez-Soldado *et al.* 2015). PPARg expression is mainly limited to the adipocyte, but under conditions of chronic hepatic lipid accumulation, the liver expresses considerable amounts of PPARg (Vidal-Puig *et al.* 1996, Pettinelli & Videla 2011, Schultz *et al.* 2013, Barbosa-da-Silva *et al.* 2015). Both PPARa and PPARg recognize the same fatty acids and eicosanoids ligands (Xu *et al.* 1999). In fact, liver fatty acid-binding protein (L-FABP), which is upregulated in diabetes and obesity, transports fatty acids into the nucleus for both PPARa and PPARy activation (Wolfrum *et al.* 2001, Atshaves *et al.* 2010). However, the metabolic influences of each differ dramatically. PPARa is integral to limiting hepatic lipid accumulation by upregulating pathways that allow for fatty acid oxidation, ketogenesis and fatty acid export (Rakhshandehroo *et al.* 2007), while PPARg encourages fatty acid storage by upregulating lipogenic genes including fatty acid transporters and enzymes in fatty

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acid and triglyceride synthesis (Schadinger *et al.* 2005). However, in fatty liver disease, PPARg can also upregulate traditionally PPARa target genes (Patsouris *et al.* 2006, Moran-Salvador *et al.* 2011). Hepatic-specific PPARg knockout protects high-fat diet-fed mice from hepatic lipid accumulation, improves glucose tolerance and prevents upregulation of lipogenic, beta-oxidative and gluconeogenic genes (Moran-Salvador *et al.* 2011). Thus, induction of both PPARg and PPARa by hepatic lipid accumulation directs hepatic metabolic flux toward hepatic glucose and ketone production.

PPARg is a master transcriptional regulator of adipogenesis and is required for adipocyte differentiation (Takahashi *et al.* 2008, Hamza *et al.* 2009). High-fat diet feeding elevates hepatic expression of many classically adipocyte-specific genes, making fatty livers more functionally and histologically similar to adipose tissue (Pan *et al.* 2015). Therefore, upregulated PPARg signaling in hepatic steatosis may promote expression of an adipogenic gene profile. This suggests that while hepatocytes adapt to chronic lipid accumulation by increasing lipid oxidation and ketogenesis, hepatocytes additionally adapt by promoting long-term storage of lipids in a manner similar to adipocytes.

Mechanisms of hepatic steatosis—influence of glucoregulatory hormones

An increase in hepatic lipid content can be generated through *de novo* fatty acid synthesis or influx of diet or adipose-tissue-derived fatty acids, while beta-oxidation and lipoprotein secretion decrease hepatic lipid content. The typical hormonal environment in fatty liver disease is characterized by hyperinsulinemia, hyperglucagonemia, elevated sympathetic tone, hypercortisolemia and growth hormone deficiency. This hormonal milieu alters whole body lipid metabolism and can promote the progression of more severe hepatic steatosis.

Adipose tissue lipolysis and hepatic lipid uptake

When energy demand exceeds metabolic energy from the diet, NEFAs are mobilized from white adipose tissue (WAT). Insulin and catecholamines are the dominant inhibitory and stimulatory regulators, respectively, of adipose lipolysis (Fig. 1). During fasting and exercise, insulin levels are low, allowing norepinephrine, cortisol and growth hormone to synergistically stimulate lipolysis and increase systemic fatty acid availability (Marcus *et al.* 1994, Djurhuus *et al.* 2004). Similarly, hepatic lipid accumulation induces endocrine changes that dysregulate adipose tissue lipolysis, including insulin resistance, increased sympathetic tone and HPA axis activity (Pratley *et al.* 1995, Ward *et al.* 1996, Targher *et al.* 2006, Armstrong *et al.* 2014, Thorp & Schlaich 2015). The lipolytic hormone profile along with increased adipose tissue mass results in more adipose-tissue-derived fatty acids entering circulation in obese than in normal-weight individuals (Mittendorfer *et al.* 2009, Howe *et al.* 2011).

Hormonally regulated lipolysis depends on the activity of the lipolytic enzyme, hormone-sensitive lipase (HSL)

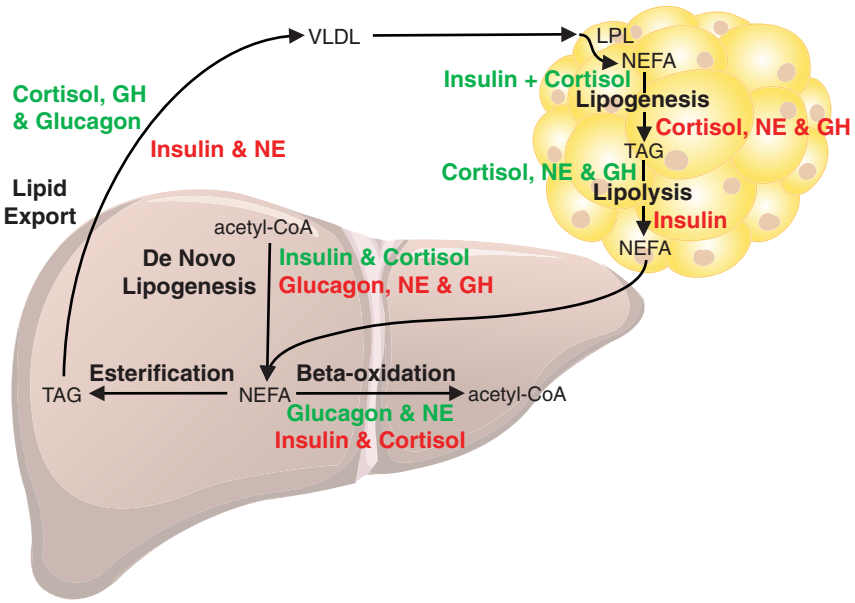

Figure 1
Effect of glucoregulatory hormones on hepatic lipid metabolism. Glucagon, cortisol, growth hormone (GH) and norepinephrine (NE) all act counter-regulatory to insulin to affect glucose homeostasis, yet have divergent effects on lipid homeostasis. Hormone signaling can induce an increase in hepatic lipid accumulation through increased adipose tissue lipolysis and hepatic lipid clearance, increased *de novo* lipogenesis, decreased beta-oxidation or decreased lipid export as VLDL particles. Hormones written in green text activate the indicated pathway, while hormones in red text inhibit the pathway. NEFA–Non-esterified fatty acid, TAG–Triglycerol, LPL–lipoprotein lipase.

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(Large *et al.* 1998). Insulin and catecholamines modulate HSL activity by decreasing and increasing adipocyte cAMP concentrations, respectively (Meijssen *et al.* 2001, Watt *et al.* 2006, Nishino *et al.* 2007). Sympathetic nervous system activity also stimulates cortisol release (Pacak *et al.* 1995), and may underlie the hypercortisolemia common in NAFLD. Cortisol differentially regulates adipose tissue metabolism depending on insulin signaling. When insulin is low, as would occur during a fast, cortisol stimulates lipolysis and inhibits lipogenesis in WAT (Djurhuus *et al.* 2004, Gathercole *et al.* 2011). Yet, in the presence of elevated insulin, cortisol synergistically stimulates lipogenesis (Fig. 1) (Ottosson *et al.* 1994, Wang *et al.* 2004). The metabolic response of adipose tissue to glucocorticoids also depends on the duration of exposure. There is not an acute lipolytic response to glucocorticoids, yet, chronically elevated glucocorticoids stimulate lipolysis in adipocytes (Xu *et al.* 2009*a*). This chronic induction of lipolysis is transcriptionally regulated, as glucocorticoids upregulate HSL expression and downregulate phosphodiesterase 3B expression, which increases HSL activity by limiting cAMP degradation (Xu *et al.* 2009*a*). Glucocorticoids also increase catecholamine-induced cAMP signaling by enhancing beta-adrenergic receptor expression, resulting in a more robust elevation in adenylyl cyclase and PKA activity (Lamberts *et al.* 1975, Lacasa *et al.* 1988). In line with the catabolic response to glucocorticoid exposure, hypercortisolemia decreases insulin-induced adipose tissue glucose clearance (Hasni Ebou *et al.* 2016). Moreover, chronic hypercortisolemia, obesity and NAFLD increase adipose tissue expression of 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1), an enzyme that catalyzes the production of cortisol from cortisone (Candia *et al.* 2012, Wang *et al.* 2015). In fact, transgenic overexpression of adipose specific 11beta-HSD1 in lean mice results in visceral obesity and insulin-resistant diabetes (Masuzaki *et al.* 2001). Thereby, enhanced local cortisol synthesis at adipose tissue in obesity promotes adipose tissue insulin resistance.

Excessive lipolysis and adipose tissue fatty acid release into circulation results in ectopic accumulation of lipids. Hepatic lipid accumulation is limited in mice that lack HSL and thus have muted adipose tissue lipolytic capacity. These HSL null mice have improved insulin sensitivity and systemic glucose clearance (Girousse *et al.* 2013, Wang *et al.* 2016*b*). Fasting and NAFLD are characterized by a rise in sympathetic activity and adipose tissue lipolysis (Migliorini *et al.* 1997, Grassi *et al.* 2005, Thorp & Schlaich 2015). The lipolytic response to obesity depends on the adipose tissue depot, with decreased lipolytic capacity in subcutaneous adipose tissue and increased lipolysis from visceral adipose tissue (Jensen *et al.* 1989, Busetto *et al.* 1993). Adipose triglyceride lipase primarily mediates basal lipolysis, while HSL mediates catecholamine-stimulated lipolysis, and the lipolytic capacity of subcutaneous adipose tissue is largely determined by HSL expression (Large *et al.* 1998, Langin *et al.* 2005). In subcutaneous adipose tissue, obesity decreases HSL expression, limiting sensitivity to adrenergic stimulation (Langin *et al.* 2005, Jocken *et al.* 2007). Yet, in the more metabolically active visceral adipose tissue depots, sensitivity to beta3-adrenoceptor-induced lipolysis is increased in obesity (Hoffstedt *et al.* 1996). Thus, catecholamine-stimulated lipolysis depends on the regional adipose tissue depot.

Despite increased adipose tissue lipolysis, skeletal muscle lipid clearance is decreased in obese, type 2 diabetics (Kelley & Simoneau 1994, Turpeinen *et al.* 1999, Blaak *et al.* 2000, Blaak 2003, Goossens *et al.* 2016). The combination of increased fatty acid release from adipose tissue and decreased clearance by skeletal muscle results in hyperlipidemia and increased reliance on the liver to clear fatty acids (Lewis *et al.* 2002, Jonkers *et al.* 2013, Janssens *et al.* 2015). Hepatic expression of Cd36, a fatty acid transporter, is increased with alcohol or high-fat feeding in mice and in NAFLD (Miquilena-Colina *et al.* 2011, Clugston *et al.* 2014). Hyperinsulinemia alone can stimulate hepatic Cd36 expression, and is suggested as a primary mechanism driving hepatic lipid accumulation (Steneberg *et al.* 2015). Hepatic-specific knockout of Cd36 protects mice from high-fat diet-induced fatty liver and insulin resistance, supporting the hypothesis that increased hepatic lipid uptake is critical for the development of hepatic triglyceride accumulation (Wilson *et al.* 2016). Hepatic lipoprotein lipase (LPL) expression and activity are also increased in high-fat diet-fed mice and obese individuals, offering another mechanism for increased hepatic lipid uptake in fatty liver disease (Pardina *et al.* 2009, Ahn *et al.* 2011). These data support that dysregulated adipose tissue lipolysis and hepatic clearance are integral for the development of fatty liver in obesity.

Lipodystrophy disorders, characterized by impaired adipocyte triglyceride storage, also result in hepatic steatosis and insulin resistance (Rochford 2014). Genetic mouse models of lipodystrophy develop markedly depleted adipose stores, severe fatty liver disease and systemic insulin resistance (Saha *et al.* 2004, Softic *et al.* 2016). Due to limited adipose tissue lipid storage, patients with lipodystrophy frequently develop NAFLD and are at an increased risk for developing hypertriglyceridemia

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and diabetes (Safar Zadeh *et al.* 2013, Akinci *et al.* 2015). Antiretroviral therapy (HAART) for HIV infection commonly results in lipodystrophy. This is a consequence of adipocyte apoptosis, impaired adipogenesis and increased lipolysis, leading to hepatic lipid accumulation and insulin resistance (Nerurkar *et al.* 2001, Giralt *et al.* 2010, Goulbourne & Vaux 2010, Kumar *et al.* 2015, Mandal *et al.* 2016). Common phenotypes between NAFLD, fasting and alcohol-induced fatty liver, and lipodystrophy patients point to the importance of hepatic lipid accumulation in driving metabolic dysregulation.

Through the multiple models of increased adipose tissue lipolysis that result in hepatic lipid accumulation (i.e. fasting, diet-induced obesity, chronic alcohol consumption and lipodystrophies), it is evident that increased fatty acid availability can drive hepatic lipid accumulation, insulin resistance and impaired glucose clearance. Moreover, hepatic lipid accumulation appears to feed forward to further increase adipose tissue lipolysis by limiting insulin sensitivity, increasing HPA axis activity and increasing catecholaminergic tone.

De novo lipogenesis

Although an influx of fatty acids from adipose tissue robustly and quickly increases hepatic lipid content, hepatic steatosis may also occur as a result of increased *de novo* fatty acid synthesis. Under normal physiological conditions, an elevation in circulating glucose upregulates lipogenic enzyme expression to encourage hepatic glucose clearance and storage of the carbons as fatty acids and triglycerides. Blood glucose enhances DNL through two signaling pathways. First, by increasing circulating insulin, glucose stimulates sterol response element-binding protein 1c (SREBP1c) signaling. Second, glucose can directly activate the carbohydrate response element-binding protein (ChREBP) (Iizuka *et al.* 2004). Both SREBP1c and ChREBP upregulate lipogenic enzymes such as acetyl-CoA carboxylase 1 (ACC1) and fatty acid synthase (FAS). Hyperinsulinemia increases SREBP1c and ChREBP expression and further promotes hepatic DNL by inhibiting FoxO1, which normally downregulates SREBP1c expression and promotes ChREBP degradation (Deng *et al.* 2012, Ido-Kitamura *et al.* 2012, Zhang *et al.* 2006). This coordinated response stimulates storage of excess dietary energy as triglycerides for future oxidation under energy-deplete conditions. However, chronic overconsumption of carbohydrates, a diet high in fructose, hepatic PPARg signaling, alcohol and hypercortisolemia all activate the lipogenic pathways resulting in hepatic lipid accumulation.

While a single exposure to fructose has minimal effects of hepatic lipid metabolism, a diet rich in fructose can increase flux through DNL by increasing lipogenic substrate and by promoting lipogenic gene expression. The importance of fructose as a lipogenic substrate results from the outsized role of the liver in fructose clearance. In the first pass through the liver sequesters 71% of dietary fructose, while only clearing 13% of dietary glucose (Muratoglu *et al.* 1986). In addition to providing the carbons necessary for fatty acid synthesis, fructose also induces signaling pathways that encourage lipogenesis. Fructose potentiates glucose-stimulated insulin secretion (Kyriazis *et al.* 2012), increasing insulin-mediated SREBP1c signaling in the hepatocyte. Fructose also increases SREBP1c expression and activity independent of insulin. In liver-specific insulin receptor null mice, fructose stimulates SREBP1c expression, nuclear localization and the expression of target lipogenic enzymes (Haas *et al.* 2012). Without altering ChREBP nuclear localization, a diet rich in fructose increases ChREBP binding to DNA nearly 4 fold (Koo *et al.* 2009). Interestingly, dietary fructose more robustly induces DNL in patients with fatty liver disease (Lambert *et al.* 2014). Thus, dietary fructose contributes to the development of NAFLD through increased DNL and NAFLD feeds forward to increase DNL from fructose.

Increased DNL is also a key factor in alcohol-induced fatty liver. Acute ethanol consumption only modestly stimulates DNL with 5% of consumed alcohol entering lipogenesis (Siler *et al.* 1999). However, ethanol induces transcriptional changes that encourage DNL. Ethanol inhibits hepatic 5′ adenosine monophosphate-activated protein kinase (AMPK), simultaneously inhibiting beta-oxidation and activating fatty acid synthesis. This decrease in AMPK is integral to the increased SREBP1c and ACC activity induced by ethanol (You *et al.* 2004). The SREBP1c-induced increase in ACC activity directly increases fatty acid synthesis, while suppressing fatty acid oxidation. SREBP1c also upregulates lipin-1 expression and localization to the cytosol (Hu *et al.* 2012). Within the cytosol, lipin-1 acts as a phosphatidate phosphatase, enzymatically converting phosphatidate to diacylglycerol and promoting triglyceride synthesis. In the nucleus, lipin-1 acts as a PPARa coactivator and facilitates the upregulation of beta-oxidative genes while suppressing lipogenic gene expression (Finck *et al.* 2006). By increasing lipin-1 expression and cytosolic localization, while reducing nuclear lipin-1 localization, ethanol

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simultaneously enhances triglyceride synthesis while limiting the nuclear action of lipin-1 to stimulate beta-oxidation (Bi *et al.* 2015). Chronic alcohol consumption induces hepatic steatosis and robustly elevates expression of PPARg, inducing the adipocyte-like gene expression profile commonly observed in NAFLD (Zhang *et al.* 2016).

Abnormal glucocorticoid signaling is implicated in the pathology of numerous metabolic disorders, and hepatic glucocorticoid signaling stimulates hepatic lipogenesis (Krausz *et al.* 1981). Glucocorticoids directly upregulate lipin-1 expression (Manmontri *et al.* 2008), representing an intriguing mechanism driving hepatic steatosis by simultaneously decreasing lipid oxidation and increasing DNL and triglyceride esterification. By removing hairy enhancer of split 1 (Hes1), a negative regulator of PPARg expression, hepatic glucocorticoid signaling enhances PPARg expression (Revollo *et al.* 2013, Wu *et al.* 2015). In obese db/db mice, transgenic overexpression of Hes1 prevents PPARg upregulation and corrects fatty liver (Lemke *et al.* 2008). Although systemic glucocorticoid concentrations are often normal in NAFLD patients, elevated adipocyte expression of 11beta-HSD1 and cortisol production induced either by obesity or genetic overexpression result in hypercortisolemia in the hepatic portal circulation, exposing the liver to excess glucocorticoids (Masuzaki *et al.* 2001, Candia *et al.* 2012). Similar to adipose tissue, hepatic expression of 11beta-HSD1 and local cortisol synthesis may be more metabolically relevant than circulating cortisol levels. Interestingly, obesity is initially characterized by a decrease in hepatic 11beta-HSD1 expression in mice and humans (Ahmed *et al.* 2012, Candia *et al.* 2012). This may serve as a protective mechanism to limit local glucocorticoid production in the face of increased hepatic glucocorticoid delivery. However, progression of hepatic steatosis to NASH is accompanied by increased hepatic 11beta-HSD1 mRNA expression and activity (Ahmed *et al.* 2012). Hepatic 11beta-HSD1 expression has clear systemic metabolic consequences as mice that overexpress 11beta-HSD1 have excess local hepatic glucocorticoid production, increased hepatic triglyceride accumulation and overexpress FAS (Paterson *et al.* 2004). Despite no change in body weight or adipose tissue mass, these mice are hyperinsulinemic and insulin resistant. Conversely, hepatic-specific knockdown of 11beta-HSD1 in mice protects against western-type diet-induced hepatic steatosis by reducing hepatic lipogenesis and increasing fatty acid oxidation (Li *et al.* 2011). Similarly, pharmacological 11beta-HSD1 inhibition in NAFLD patients decreases hepatic lipid accumulation (Stefan *et al.* 2014). Thus, the elevated glucocorticoid signaling, common in fatty liver, encourages hepatic DNL.

Unlike cortisol and insulin, glucagon, norepinephrine and growth hormone inhibit hepatic DNL (Fig. 1) (Stark and Keller 1987, Cordoba-Chacon *et al.* 2015, Wang *et al.* 2016*a*). Growth hormone deficiency in NAFLD may contribute to hepatic steatosis by removing GH-mediated suppression of DNL. In liver-specific growth hormone knockout mice, increased hepatic DNL is driven by enhanced glycolytic flux, supplying more substrate to enter the lipogenic pathway (Cordoba-Chacon *et al.* 2015). Although liver PPARg is upregulated in this model, PPARg is a consequence, not a cause, of steatosis, as knockout of hepatic PPARg does not prevent development of hepatic steatosis in the absence of growth hormone signaling (Kineman *et al.* 2016).

Insulin-resistant NAFLD patients have markedly upregulated hepatic lipogenic gene expression and DNL flux (Schwarz *et al.* 2003, Eissing *et al.* 2013). In fact, hyperinsulinemic obese subjects have higher rates of hepatic DNL following a high-fat meal than normoinsulinemic obese or lean subjects (Schwarz *et al.* 2003). Increased DNL represents an important mechanism driving hepatic triglyceride accumulation in fatty liver disease.

Beta-oxidation and ketogenesis

In fatty liver disease, hepatic beta-oxidation and ketogenesis are upregulated (Sunny *et al.* 2010, Mannisto *et al.* 2015). Hepatic beta-oxidation in response to lipid accumulation prevents lipotoxicity and supports gluconeogenesis and ketogenesis. Mice that are unable to normally upregulate lipid oxidative genes during fasting have severe hepatic steatosis, do not display ketosis and are hypoglycemic (Kersten *et al.* 1999, Leone *et al.* 1999). Similarly, individuals with mitochondrial fatty acid oxidation disorders (MFAOD), conditions that affect ~1 in 10,000 people, are sensitive to fasting and high-fat diets and present with hypoketotic hypoglycemic episodes (Pollitt 1995, Rector *et al.* 2008).

Hepatitis C infection impairs hepatic lipid oxidation by decreasing expression of the mitochondrial trifunctional protein (MTP), an enzyme that catalyzes the last 3 steps in mitochondrial beta-oxidation (Amako *et al.* 2015). Mouse models with genetically or pharmacologically induced deficits in beta-oxidation develop fatty liver disease. Mice heterozygous for MTP (MTP+/–) have a 50% reduction in hepatic

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beta-oxidation, hepatic steatosis and systemic insulin resistance (Ibdah *et al.* 2005, Rector *et al.* 2013). Hepatic microRNA-107, upregulated in metabolic syndrome, inhibits the expression of the MTP alpha subunit. Exogenous miR-107 induces hepatic lipid accumulation, hyperglycemia and decreases glucose tolerance (Bhatia *et al.* 2016). Further, hepatic carnitine deficiency limits entry of fatty acids into the mitochondria, impairing beta-oxidative flux and inducing a more robust hepatic triglyceride accumulation as a result of high-fat diet (Du *et al.* 2013). Together, these models establish that limiting beta-oxidation severely exacerbates hepatic lipid accumulation. Moreover, they propose that the PPARα-mediated increase in beta-oxidative gene expression is key to muting hepatic lipid accumulation during a fast.

Interestingly, the hepatic lipid accumulation resulting from dietary fructose also involves PPARa signaling. Chronic (>2 weeks) fructose feeding downregulates hepatic PPARa expression and activity, reducing the expression of PPARa-targeted beta-oxidative enzymes. Of note, PPARa agonists limit hepatic steatosis and improve systemic insulin sensitivity by stimulating beta-oxidation in this fructose consumption model (Nagai *et al.* 2002, Roglans *et al.* 2007). Although enhanced DNL is commonly blamed for the steatosis resulting from dietary fructose, the inhibition of beta-oxidation may be equally important. Fructose acutely inhibits CPT1 activity and beta-oxidation through a resulting increase in malonyl-CoA synthesis and chronically downregulates the expression of beta-oxidative genes.

Increased hepatic uptake of either diet or adipose-derived fatty acids stimulates hepatic beta-oxidation (Reed *et al.* 1991). Like fasting-induced hepatic lipid accumulation, high-fat diet feeding elevates hepatic CPT1 activity and beta-oxidative capacity (Stefanovic-Racic *et al.* 2008, Sunny *et al.* 2010, Zhang *et al.* 2014, Geisler *et al.* 2016). The acetyl-CoA derived through beta-oxidation can either be oxidized through the TCA cycle or enter ketogenesis. Accordingly, diet-induced obesity increases HMGCS2 mRNA expression, increasing flux through ketogenesis (Guo *et al.* 2013, Darkhal *et al.* 2015). Finally, to regenerate NAD+ and maintain maximal beta-oxidation, obesity increases expression of UCP2 (Chavin *et al.* 1999). Rodents with hepatic steatosis from diets rich in fructose or sucrose also aberrantly overexpress hepatic UCP2 mRNA (Ruiz-Ramirez *et al.* 2011, Schultz *et al.* 2015). These data recommend that transcriptional changes are central to the upregulation of beta-oxidation and ketogenesis in the adaptation to hepatic lipid accumulation.

The increased ketogenesis in obesity depends on increased flux through beta-oxidation which results in increased substrate (acetyl-CoA) availability. Activity of HMGCS2, the enzyme-regulating flux through ketogenesis, is decreased by acetylation and succinylation, and increased by phosphorylation (Quant *et al.* 1990, Shimazu *et al.* 2010, Grimsrud *et al.* 2012). HMGCS2 is phosphorylated by PKA, a downstream glucagon signaling molecule, and hyperphosphorylation of HMGCS2 occurs in obese rodents (Grimsrud *et al.* 2012). Therefore, hyperglucagonemia in fatty liver increases HMGCS2 activity and ketone production. Although increased hepatic ketone synthesis is integral to the development of ketosis in obesity, insulin resistance also decreases clearance of beta-OH butyrate (Nosadini *et al.* 1985). In turn, beta-OH butyrate has been shown to decrease peripheral insulin-stimulated glucose uptake, and may contribute to the development of insulin resistance in fatty liver disease (Tardif *et al.* 2001, Yamada *et al.* 2010). As evidenced, the individual metabolic and hormonal perturbations common to hepatic lipid accumulation are intertwined, making it difficult to isolate the response to changes in a single pathway.

The interplay of DNL and beta-oxidation

Diminished beta-oxidative capacity resulting from genetic disorders or viral infections establishes the central role of beta-oxidative flux in limiting steatosis. Accordingly, fasting and hypercaloric diets that increase hepatic lipid accumulation induce changes in gene expression that encourage fatty acid oxidation and ketone production. However, despite enhanced lipid catabolism and ketogenic capacity resulting from increased enzyme expression and hormonal changes that promote increased enzyme activity, each of these models still develop hepatic steatosis and insulin resistance. Hepatic DNL contributes directly to the development of steatosis in NAFLD. However, the inhibition of beta-oxidative flux, an indirect response to elevated DNL may more robustly encourage steatosis.

Fatty acid flux through beta-oxidation is inhibited by hepatic DNL. The production of malonyl-CoA inhibits activity of CPT1, limiting the mitochondrial entry of fatty acids for oxidation (Morillas *et al.* 2002). This interaction prevents newly synthesized fatty acids from undergoing oxidation and avoids futile nutrient cycling. Malonyl-CoA production is regulated by ACC1 and ACC2, while degradation is dependent upon the activity of malonyl-CoA decarboxylase (MCD). ACC1

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expression and activity increases in fatty liver disease, while ACC2 expression is independent of hepatic lipid accumulation (Yahagi *et al.* 2005, Kennedy *et al.* 2007, Kohjima *et al.* 2007). This increase in total ACC activity increases malonyl-CoA synthesis, hepatic malonyl-CoA concentration and flux through fatty acid synthesis (Zhao *et al.* 2009). The increase in hepatic malonyl-CoA would be expected to inhibit CPT1 and beta-oxidative flux. However, in fatty liver, both fatty acid synthesis and beta-oxidation can be simultaneously increased as a result of the subcellular distribution of ACC activity. ACC1 is located in the cytosol, while ACC2 is tethered to the outer mitochondrial membrane (Abu-Elheiga *et al.* 2000). Accordingly, ACC2 produces malonyl-CoA in close proximity to CPT1 and is therefore the enzyme more responsible for the inhibition of beta-oxidation. In fact, ACC2 deletion prevents hepatic lipid accumulation and increases fatty acid oxidation, while simultaneously preventing the diet-induced insulin resistance and glucose intolerance (Abu-Elheiga *et al.* 2003). The activity of ACC2 is inhibited by AMPK, a cellular energy sensor regulated by AMP, glucagon and insulin (Jeon *et al.* 2012). AMPK activity increases with a decrease in cellular energy. Accordingly, insulin inhibits AMPK to increase ACC2 activity and malonyl-CoA production (Witters *et al.* 1988, Shaw 2013, Valentine *et al.* 2014). This increase in malonyl-CoA production limits fatty acid oxidation. In contrast, glucagon increases AMPK activity to depress ACC2 activity and malonyl-CoA production, which encourages fatty acid oxidation (Geelen *et al.* 1978, Berglund *et al.* 2009, Cyphert *et al.* 2014).

In addition to altering the enzymes involved in malonyl-CoA synthesis, AMPK simultaneously alters malonyl-CoA breakdown. MCD catalyzes the conversion of malonyl-CoA to acetyl-CoA, relieving CPT1 inhibition (Dyck *et al.* 2000). A genetic model of hepatic MCD overexpression establishes that decreasing hepatic malonyl-CoA concentrations increases beta-oxidative flux, improves whole body insulin sensitivity and prevents hyperinsulinemia on a high-fat diet (An *et al.* 2004). Hepatic MCD expression is increased by PPARa agonism, representing another mechanism by which hepatic lipid-induced PPARa signaling accelerates fatty acid oxidation. (Lee *et al.* 2004). AMPK activates MCD (Sambandam *et al.* 2004). Through modulating AMPK signaling, glucagon increases MCD activity, promoting conversion of malonyl-CoA to acetyl-CoA and relieving CPT1 inhibition, while insulin inhibits MCD activity and reduces CPT1 activity (Dyck *et al.* 2000). Thus, as evidenced by the ACC2 knockout and MCD overexpression models, malonyl-CoA-mediated inhibition of CPT1 depresses maximal beta-oxidative capacity in fatty liver disease. However, given the subcellular distribution and divergent regulation of hepatic lipid accumulation on ACC expression, simultaneous stimulation of lipogenic and beta-oxidative flux can occur.

This concurrent flux through fatty acid synthesis and oxidation occurs normally in non-hepatic tissue as an adaptive mechanism to promote substrate utilization and increase cellular metabolic rate (Solinas *et al.* 2004, Mottillo *et al.* 2014, O'Sullivan *et al.* 2014). Like in fatty liver, this simultaneous induction of lipogenesis and oxidation is proposed to be dependent upon diminished ACC2-generated malonyl-CoA and submaximal CPT1 inhibition (Yu *et al.* 2002). In adipose tissue, PPARg-dependent DNL upregulation enhances glucose clearance and utilization, allowing adipocytes to act as a glucose sink to maintain euglycemia (Marcelino *et al.* 2013). Increased hepatic DNL in fatty liver disease may similarly serve as a mechanism to minimize hyperglycemia, while increased beta-oxidation allows energy dissipation and protects against lipotoxicity. The upregulation of PPARg and lipogenic gene expression in response to chronic hepatic lipid accumulation drives the increase in DNL in fatty liver disease (Matsusue *et al.* 2003), and supports the simultaneous induction of lipogenesis and beta-oxidation. The onset of this nutrient cycling represents another mechanism by which hepatocytes adopt metabolic characteristics of adipocytes to accommodate long-term lipid accumulation.

Hepatic lipid export and extrahepatic lipid clearance

Hepatocytes distribute lipids to peripheral tissues by exporting VLDL. Impaired VLDL export limits hepatic disposal of triglycerides and induces hepatic steatosis. Chronic ethanol consumption decreases VLDL synthesis and secretion, enhancing the development of fatty liver (Simpson *et al.* 1990, Kharbanda *et al.* 2009). However, since ethanol consumption increases DNL, inhibits hepatic beta-oxidation and increases adipose tissue lipolysis, the isolated response to inhibiting VLDL secretion can be better understood in genetic models with inhibited lipoprotein synthesis and release. Inhibited lipoprotein transfer increases steatosis without decreasing insulin sensitivity. Knockout of hepatic

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microsomal triglyceride transfer protein (MTTP) in mice prevents VLDL release and induces hepatic triglyceride accumulation, but does not affect systemic or hepatic insulin sensitivity (Minehira *et al.* 2008). Similarly in familial hypobetalipoproteinemia (FHBL), an autosomal codominant disorder, heterozygous individuals have a 60–75% reduction in VLDL production that commonly results in fatty liver (Elias *et al.* 1999, Lonardo *et al.* 2006). Again, in FHBL individuals, there is a dissociation between hepatic steatosis and insulin resistance (Della Corte *et al.* 2013). In BMI-matched controls, FHBL patients had the same degree of hepatic lipid accumulation as NAFLD patients (~20%) but retained similar hepatic insulin sensitivity as subjects with low hepatic triglyceride content (~3%) (Amaro *et al.* 2010). These genetic examples propose that hepatic steatosis resulting from depressed hepatic lipid export mechanistically differs from steatosis resulting from decreased beta-oxidation, increased DNL or increased circulating lipid clearance.

Interestingly, VLDL production and release are typically amplified in patients with NAFLD and the metabolic syndrome, contributing to hypertriglyceridemia and extrahepatic lipid uptake (Shojaee-Moradie *et al.* 2013). Glucagon, cortisol and growth hormone stimulate hepatic VLDL secretion, while norepinephrine inhibits secretion (Fig. 1) (Elam *et al.* 1992, Bjornsson *et al.* 1994, Yamauchi *et al.* 1998, de Guia *et al.* 2015). The high circulating glucagon and cortisol concentrations in fatty liver disease may contribute to hypercholesterolemia by enhancing VLDL export. Insulin signaling inhibits hepatic VLDL release (Chirieac *et al.* 2002). The hepatic transcription factor forkhead box protein O6 (FoxO6) upregulates MTTP, which catalyzes the rate limiting step in VLDL–triglyceride assembly. Insulin signaling inactivates FoxO6, reducing MTTP activity and VLDL production. Hepatic insulin resistance therefore prevents FoxO6 inactivation and promotes overactive assembly of VLDL particles, while FoxO6 knockdown in obese db/db mice ameliorates VLDL overproduction and hypertriglyceridemia (Kim *et al.* 2014*a*). Together, hyperglucagonemia, hypercortisolemia and insulin resistance encourage VLDL hypersecretion in fatty liver disease. Accordingly, while impaired hepatic VLDL release can cause hepatic steatosis, fatty liver disease is more commonly associated with enhanced VLDL secretion (Fujita *et al.* 2009). The hormonal environment of insulin resistance, hyperglucagonemia and hypercortisolemia in NAFLD encourages hepatic VLDL production and release and contributes to the hyperlipidemia of obesity. Thus, although VLDL release from hepatocytes decreases steatosis, the consequent hyperlipidemia appears to exacerbate metabolic dysfunction.

Conclusion

Hepatic lipid accumulation can result from excessive lipid influx or impaired lipid efflux. In response to elevated hepatic lipid uptake, as occurs in response to fasting, high-fat diet feeding or lipodystrophies, hepatocytes activate metabolic pathways (beta-oxidation, ketogenesis and VLDL export) to minimize lipotoxicity. Still, hepatic steatosis develops when lipid influx overwhelms these protective mechanisms. In numerous models of hepatic steatosis, including overconsumption of fat, fructose or ethanol, and genetic lipodystrophy and MFAOD conditions, fatty liver is accompanied by systemic insulin resistance. Thus, independent of origin, hepatic lipid accumulation is associated with peripheral metabolic dysfunction.

Altered hepatic metabolite flux as a consequence of hepatic lipid accumulation can affect systemic insulin signaling. Elevated circulating beta-OH butyrate concentrations, a result of upregulated ketogenesis, interfere with insulin-stimulated skeletal muscle glucose uptake, while increased hepatic glucose output exacerbates hyperglycemia and further promotes hyperinsulinemia. Enhanced VLDL secretion contributes to hypertriglyceridemia and encourages extrahepatic lipid uptake, which further impairs insulin-stimulated skeletal muscle glucose uptake. Thus, metabolic activity induced by hepatic lipid accumulation contributes to the dysregulated glucose homeostasis, which occurs in fatty liver disease.

NAFLD and insulin resistance are highly linked comorbidities. Although fatty liver develops in response to a wide diversity of physiological perturbations, these perturbations result in a similar metabolic phenotype that includes insulin resistance, hyperglucagonemia, hypertriglyceridemia, hyperglycemia and hyperketonemia. Of note, mouse models that lack hepatic lipid accumulation retain insulin sensitivity during obesity (Chen *et al.* 2002, Franckhauser *et al.* 2002, Haemmerle *et al.* 2006, Montgomery *et al.* 2013). Similarly, metabolically healthy obese humans are insulin sensitive with significantly less liver fat accumulation than obese, insulin resistance individuals (Stefan *et al.* 2008,

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Samocha-Bonet *et al.* 2012). Thus, understanding the mechanisms that result in hepatic lipid accumulation and underlie the metabolic dysfunction resulting from fatty liver is critical to identifying points of intervention to treat this increasingly prevalent disease state.

Declaration of Interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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C G and B R wrote and edited this review.

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