Published in final edited form as:

J Hepatol. 2019 February ; 70(2): 237–248. doi:10.1016/j.jhep.2018.10.037.

Effect of ethanol on lipid metabolism

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Summary

Hepatic lipid metabolism is a series of complex processes that control influx and efflux of not only hepatic lipid pools, but also organismal pools. Lipid homeostasis is usually tightly controlled by expression, substrate supply, oxidation and secretion that keep hepatic lipid pools relatively constant. However, perturbations of any of these processes can lead to lipid accumulation in the liver. Although it is thought that these responses are hepatic arms of the 'thrifty genome', they are maladaptive in the context of chronic fatty liver diseases. Ethanol is likely unique among toxins, in that it perturbs almost all aspects of hepatic lipid metabolism. This complex response is due in part to the large metabolic demand placed on the organ by alcohol metabolism, but also appears to involve more nuanced changes in expression and substrate supply. The net effect is that steatosis is a rapid response to alcohol abuse. Although transient steatosis is largely an inert pathology, the chronicity of alcohol-related liver disease seems to require steatosis. Better and more specific understanding of the mechanisms by which alcohol causes steatosis may therefore translate into targeted therapies to treat alcohol-related liver disease and/or prevent its progression.

Keywords

Alcohol-related liver disease; Steatosis; Lipid homeostasis; Metabolism

Introduction

Alcohol is highly prevalent in most societies and more than 50% of Americans consume alcohol at least once a month.[1] Heavy alcohol consumption associated with alcohol dependence and/or abuse (*i.e.*, binge drinking) is well known to damage the liver. Alcohol-

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Conflict of interest

Dr Arteel and Dr You report grants from National Institutes of Health, during the conduct of the study.
Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.037.

related liver disease (ALD) affects more than 10 million Americans each year, while treating the medical consequences of the disease costs more than $166 billion annually.[2] Furthermore, alcohol consumption can enhance damage to the liver caused by other diseases (*e.g.*, hepatitis virus infection) and drugs (*e.g.*, acetaminophen).[3,4] Although the progression of alcohol-induced liver injury is well characterised, there is no universally accepted therapy available to halt or reverse this process in humans. Therefore, there is an increasing focus on understanding the biochemical changes responsible for the development and progression of ALD. With better understanding of the mechanism(s) and risk factors that mediate the initiation and progression of this disease, rational targeted therapy can be developed to treat or prevent it in clinical practice.

The first and most common hepatic change caused by alcohol consumption is steatosis, or fatty liver (Fig. 1). The prevalence of steatosis is essentially 100% in those who consume alcohol at levels that increase their risk of liver disease.[5] Fat accumulation can be both macrovesicular (having one large fat droplet per hepatocyte and lateral displacement of the nucleus) or microvesicular (many small fat droplets per hepatocyte) (Fig. 1).[5] Alcohol-induced steatosis is rapidly and readily reversible upon cessation of alcohol consumption. Steatosis can also be clinically ‘silent,’ and can exist in the absence of increases in any other index of liver damage, such as plasma aminotransferases, for example. For these reasons, steatosis was originally viewed as an inert pathology in ALD (and in other fatty liver diseases). However, more recent studies have suggested that blunting or preventing steatosis could help attenuate the progression of ALD; in fact, the degree of steatosis is an early predictor of overall disease severity.[6] These facts challenge the assumption that steatosis is an inert pathology. Hepatic fat accumulation can invoke metabolic changes that sensitise the liver to further injury (see below). Therefore, a full understanding of how alcohol induces steatosis could be key in preventing progression to later stages of ALD.

The liver plays a central role in lipid metabolism for the entire organism. Hepatic free fatty acids (FAs) are not only directly synthesised from glycolytic end products and hepatic catabolism (*e.g.*, autophagy), but are also actively taken up by the liver from dietary, and extrahepatic (*e.g.*, adipose tissue lipolysis) sources. This pool of FAs can either be used for energy via β-oxidation, membrane synthesis or esterification into triglycerides by hepatocytes. Triglycerides are subsequently packaged as very low-density lipoproteins (VLDLs) that can be secreted into the bloodstream or serve as precursors for primary bile acids, which facilitate the emulsification of dietary lipids for delivery to the liver and extra-hepatic sites. There is intricate cross-talk between these systems. Hepatic lipid metabolism is controlled by a complex interplay of hormones, nuclear receptors, intracellular signalling pathways and transcription factors. Under homeostatic conditions, hepatic lipid flux maintains relatively low concentrations of hepatic lipid pools. However, dysregulation of this flux can cause lipids to accumulate in hepatocytes, leading to steatosis (Fig. 2).

Alcohol directly and indirectly impacts numerous aspects of hepatic lipid flux that ultimately lead to lipid accumulation. The simplest example is that alcohol metabolism itself directly causes steatosis. Concentrations of alcohol can easily reach the mM range in the portal/hepatic circulation during alcohol consumption. In the process of metabolising ethanol to acetate, 2 equivalents of reduced NADH are generated per equivalent of ethanol

oxidised. This metabolism robustly increases the ratio of NADH:NAD^+ within the cell, which then favours inhibition of FA β-oxidation in the liver. Furthermore, ethanol metabolism also increases the rate of esterification of Fas.[7] The net effect is to favour triglyceride accumulation in the hepatocytes. However, the impact of alcohol exposure on lipid metabolism is far more complex than simple redox inhibition of β-oxidation. The purpose of this review is to summarise the known impacts of ethanol on this process.

Effects of ethanol on fatty acid transporters

Circulating FAs are directly taken up by the liver, with a relatively high first pass extraction,[8,9] and are the largest source of lipid for triglyceride synthesis.[10] The liver also clears chylomicron-remnant triglyceride, which also contributes to the hepatic FA pool.[8] FA transporters, including CD36/FA translocase (FAT) and FA transport protein (FATP encoded by *SLC27A1*) and FA binding proteins, play important roles in FA uptake.[11,12] Although the liver is not the main site of CD36/FAT expression, stimulation of CD36/FAT promotes hepatic free FA uptake, which can lead to hepatic lipid accumulation and liver injury in rodents and humans.[11–13] Ethanol exposure increases hepatic uptake of exogenous FAs and subsequent incorporation of FAs (*e.g.* palmitate) into triglycerides or total lipid in the liver.[14–16] Ethanol-mediated upregulation of hepatic FA transporters, in particular, CD36/FAT, FATP1 and FATP5 promotes FA uptake, excessive fat accumulation, and development of steatosis in mice and rats.[17–21] Co-administration of recombinant adiponectin to ethanol-fed mice markedly suppresses hepatic CD36/FAT expression and alleviates steatosis.[22] Genetic ablation of mitoNEET (*CISD1*), a potential inducer of CD36/FAT, ameliorates experimental alcoholic steatohepatitis in mice, partially by downregulating CD36/FAT.[23] These studies suggest the involvement of FA transporters, particularly CD36/FAT, in the pathogenesis of alcoholic fatty liver disease (AFLD).

Effects of ethanol on FA and triglyceride synthesis: potential key players

As mentioned, the liver can generate FAs from non-lipid precursors via *de novo* lipogenesis. This process is predominantly regulated by insulin and glucose flux in the liver and serves to provide a storage source of energy during times of fasting. Pyruvate from glycolysis enters the citric acid cycle and is converted to citrate, which is subsequently converted to acetyl- and malonyl-CoA and used to synthesise FAs. Rate-limiting enzymes in this process include acetyl-CoA carboxylases 1 and 2 (ACC-1 and −2 which convert acetyl-CoA to malonyl-CoA), FA synthase (FASN which synthesise saturated FAs from malonyl-CoA), and steryl-CoA-desaturase-1 (SCD-1 which converts saturated FAs to monounsaturated FAs). The synthesis of glycerolipid (*i.e.*, triglycerides) from FAs is mediated by key acetyltransferases (*e.g.*, GPAT, AGPAT and DGAT) and phosphatidate phosphatases (*e.g.*, lipin-1).

SREBP-1c and ChREBP and transcriptional control of lipogenesis

Although they are controlled at several levels, the dominant regulation of the lipogenic genes described above is transcriptional (Fig. 1). The most potent inducers of these genes are the transcription factors SREBP-1c and ChREBP. The canonical activator of SREBP-1c is insulin and its inhibitor is glucagon. In contrast, substrate supply (glucose and citrate) regulates the expression of ChREBP. Under normal conditions, lipogenesis is thus

maximally induced after the intake of nutrients and is downregulated during fasting. Previous studies have indicated that both SREBP-1c and ChREBP are activated by alcohol exposure,[24–27] which clearly explains the induction of lipogenic genes by alcohol. However, alcohol and/or its metabolites blunt glucose-induced insulin release from the pancreas and activate glucagon release.[28] Furthermore, alcohol causes insulin resistance and inhibits gluconeogenesis, which should decrease intrahepatic glucose concentrations. These net effects should in principle disfavour activation of these transcription factors, suggesting that alternate activation pathways are in play, as discussed later.

Lipin-1

Lipin-1 protein plays a pivotal role in lipid synthesis as a mammalian Mg^{2+}-dependent phosphatidic acid phosphohydrolase (PAP), which catalyses the penultimate step in triglyceride synthesis.[29–34] In addition to PAP activity, lipin-1 contains a putative nuclear localisation signal, and acts as a transcriptional co-regulator of the expression of genes involved in lipid metabolism in the nucleus.[29–34]

Lipin-1 pre-mRNA alternative splicing generates 3 lipin-1 protein isoforms, lipin-1α, lipin-1β, and lipin-1γ.[29,30,34] Lipin-1α and lipin-1β are expressed in various organs, such as the liver and adipose, while lipin-1γ is predominately expressed in the brain.[29,30,34] The variant splicing of lipin-1α and lipin-1β is partially regulated by a splicing factor, arginine/serine-rich 10 (SFRS10 or TRA2B).[35]The consequent protein products exert different functions. Lipin-1β serves as a PAP enzyme, which catalyses phosphatidate to diacylglycerol, facilitating the synthesis of triglycerides and phospholipids at the endoplasmic reticulum.[29,30,32] In contrast, lipin-1α is predominately localised to the nucleus, where it acts as a transcriptional co-regulator, activating PGC-1α, PPARα and inhibiting SREBP-1c.[31–33] The overall effects of lipin-1α are to increase β-oxidation of free FAs and reduce lipid synthesis.

Aberrant lipin-1 contributes to the abnormalities in lipid metabolism associated with AFLD in rodents and in humans.[29,33,36–45] Owing to its inhibition of AMPK activity and activation of SREBP-1c, ethanol upregulates lipin-1, induces accumulation of cytosolic lipin-1 protein, enhances PAP activity, and promotes triglyceride synthesis in the livers of rodents and human alcoholics.[33,39–46] Ethanol also blocks lipin-1 nuclear entry, inhibits nuclear lipin-1-mediated FA oxidation and perturbs VLDL secretion in mouse liver.[42] Furthermore, ethanol suppresses lipin-1 alternative pre-mRNA splicing and subsequently increases the ratio of lipin-1β/α by disrupting the SIRT1-SFRS10 axis.[41,43] Abnormalities in lipin-1 are also involved in the ethanol-induced production of a panel of pro-inflammatory cytokines.[45] These ethanol-mediated alterations in lipin-1 promote steatosis, exacerbate inflammation and cause liver injury.

ER stress and the UPR

The endoplasmic reticulum (ER) is critically involved in the proper folding and assembly of secreted and membrane proteins. Homeostasis between the protein load and the capacity of the ER to process this load must be maintained to ensure proper protein folding. Physiological and pathological stimuli can disrupt this homeostasis causing misfolded or

unfolded proteins to accumulate, leading to ER stress. In attempts to reestablish homeostasis, the ER activates a signalling network known as the unfolded protein response (UPR). One downstream effect of activation of the UPR by ER stress is the insulin-independent proteolytic activation of SREBP-1c. This effect of the UPR makes teleological sense, in that increasing lipogenesis would increase lipid substrate supply to the ER for protein processing.[47] It has been shown that alcohol induces ER stress in the liver, at least in part by causing hyperhomocysteinaemia.[24,48]

TNFα

It is well known that both the basal and lipopolysaccharide-stimulated production of TNFα (or TNF) are increased in humans consuming alcohol and in experimental ALD.[49,50] The role of TNFα and other pro-inflammatory cytokines in hepatic inflammation is well known. However, studies in experimental ALD indicate that they may also contribute to lipogenesis. Specifically, genetic or pharmacologic inhibition of TNFα signalling blunted steatosis caused by alcohol.[51–53] This effect of TNFα may be mediated at several levels of lipid metabolism. For example, TNFα increases free FA release from adipocytes in the periphery, [54] increases lipogenesis in hepatocytes,[55] and inhibits β-oxidation of Fas.[56] Moreover, prooxidant production stimulated by TNFα in hepatocytes could impair mitochondrial electron flow and cause lipid peroxidation, processes that could also slow the metabolism of fat by mitochondria. Other studies demonstrated transcription and activation of SREBP-1c is enhanced by TNFα in hepatocytes,[57,58] which yields another mechanistic link between TNFα and lipogenesis. Other cytokines induced by alcohol (*e.g.*, IL-1 and IL-6) may also impair transport and secretion of triglycerides.[59]

PPARγ

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear hormone receptor that is known to impact on lipid metabolism and glucose homeostasis. The *PPARG* gene encodes 2 splice isoforms of the protein product, PPARγ1 and PPARγ2; the former is constitutively expressed at low levels in most tissues, whereas the latter is expressed predominantly in adipose tissue under basal conditions.[60] Although the liver normally expresses low levels of PPARγ2, expression is elevated in steatotic livers, both alcoholic and non-alcoholic.[60–62] The activation of PPARγ may be pleiotropic in fatty liver disease. Specifically, PPARγ agonists exert beneficial effects in both diet-induced and alcohol-induced fatty liver injury;[63–65] these protective effects are largely attributed to increasing adiponectin production in adipocytes (66; see later). In contrast, studies in hepatocyte-specific knockout mice indicate that PPARγ2 activation is detrimental to the liver in experimental alcoholic and non-alcoholic liver disease.[15] This hepatic effect of PPARγ appears to be mediated via induction of SREBP-1c and other genes key to lipogenesis.

AMPK and SIRT1

The protein kinase complex, AMPK, provides another level of control over lipid metabolism. AMPK acts as a “sensor” of cellular energy status and helps to maintain homeostasis.[67] In general, the downstream effects of AMPK activation are considered catabolic and favour ATP generation during energy depletion. For example, glycolysis is enhanced by AMPK. Signalling downstream of AMPK also inhibits ATP-consuming

processes, such as *de novo* lipogenesis.[68] More specifically, AMPK phosphorylates a number of serine residues on both isoforms of ACC (ACC-1 and ACC-2), which inhibits their activity, even in the presence of citrate.[69] In addition to blocking the activity of key lipogenic enzymes, AMPK indirectly decreases lipogenesis by phosphorylating ChREBP, thereby hindering its nuclear translocation and transcriptional activity.[70] Likewise, AMPK directly phosphorylates SREBP-1c, which also causes an inhibition of this factor's transcriptional activity.[71] Ethanol has been demonstrated to inhibit AMPK phosphorylation, thereby inhibiting ACC, SREBP-1c and ChREBP.[33,72,73,27] The mechanisms appear to involve activation of the dephosphorylase PP2A via aSMase-mediated ceramide signalling[74,75] and and/or via inhibition of upstream activation pathways (*e.g.*, LKB1[76]).

SIRT-1 is an NAD^+-dependent protein deactylase. Targets of its deactylase activity include several key players in SREBP-1 and ChREBP-1 signalling.[77–80] SIRT-1 also deacetylates histones, namely H3 and H4, which could epigenetically increase expression of lipogenic genes (*e.g., SREBF1*[78]). Ethanol exposure downregulates expression of SIRT-1,[78,81] likely at multiple levels of control.[78] Additionally, the deactylase activity of SIRT-1 is sensitive to the NADH redox state of the cell.[82] Thus, the increased ratio of NADH: NAD^+ in the more reduced state caused by ethanol metabolism may not only blunt FA oxidation, but also directly contribute to increased *de novo* lipogenesis by blunting SIRT-1 activity. AMPK and SIRT-1 share many overlapping targets of regulation, the former via phosphorylation and the latter via deacetylation. Indeed, it is thought that these overlapping functions are at least permissive to each other and that maximal inhibition of lipogenesis is only affected when both AMPK and SIRT-1 are activated.[83] Thus, the fact that both are inhibited by ethanol implies that lipogenesis will be effectively disinhibited.

Molecular chaperones

Stress induced heat shock proteins (Hsps) such as Hsp90, Hsp70, and Hsp72 are ubiquitous and highly conserved, and can be induced by a wide variety of physiological and environmental insults.[84] Heat shock factors (HSFs) upregulate a family of Hsp genes by binding to the heat shock-binding element (HSE).[85–87] Hsps serve as chaperones that maintain the function of signalling molecules in lipid metabolism. For instance, Hsp90 alters lipid homeostasis by regulating SREBP-1.[86]

Hsps play pivotal pathophysiological roles in AFLD.[87] Like other stress signals, ethanol consumption results in accumulation of stress proteins such as hepatic Hsp70, Hsp72, Hsp90 and HSF-1 in human and experimental murine AFLD.[87–97] For example, ethanol exposure induces hepatic Hsp90 in mice and contributes to the development of steatosis and liver injury via dysregulation of molecules important in lipid metabolism, including SREBP-1, SCD-1, FASN and ACC-1.[97] Pharmacologic inhibition of Hsp90 ameliorates fatty liver injury during chronic or acute ethanol exposure in rodents. These studies have demonstrated the clear and direct regulation of hepatic lipid metabolism by Hsps in rodents in response to ethanol challenge. In addition to Hsps, sestrins are a family of stress-sensitive genes regulating lipid metabolism.[97] The inhibitory effect of ethanol on sestrin 3 contributes to the development of steatosis by disrupting AMPK signalling, which leads to alterations in the genes involved in FA synthesis and oxidation.[98] Future studies are needed to delineate the

precise role of Hsps and sestrins in lipid metabolism and its contribution to alcoholic steatosis.

Adiponectin and FGF-15 axis

Adiponectin is an adipose-derived hormone that circulates in the plasma as low, middle, and high molecular weight multimers.[99,100] Adiponectin is a pivotal player in the regulation of lipid metabolism (Fig. 1). After reaching the liver, adiponectin transduces signals via 2 major adiponectin receptors AdipoR1 and AdipoR2. Adiponectin inhibits lipid synthesis and stimulates FA oxidation, in part by activating SIRT1, AMPK, PGC-1α and PPARα, and suppressing SREBP-1.[99,100] Fibroblast growth factor (FGF) 15 (human homolog FGF19), is a terminal small intestine (ileum)-derived hormone.[101] Circulating FGF15/19 signalling regulates bile acid and lipid metabolism in the liver through activation of a receptor complex comprised of fibroblast growth factor receptor 4 (FGFR4)/β-Klotho.[101]

Ethanol impairs adiponectin synthesis and production in adipocytes and downregulates hepatic adiponectin receptors.[39,44,97,100,102–106] Adiponectin elicits profound lipid lowing effects in rodents administered ethanol and in patients with AFLD.[39,44,97,100,102–106] Aberrant hepatic adiponectin signalling is associated with lower activities of AMPK and SIRT1 and elevated levels of downstream molecules such as SREBP-1, ACC and lipin-1β in the livers of ethanol-fed rodents and patients with AFLD.[39,44,97,100,102–106] These findings all point to a critical link between altered hepatic adiponectin signalling and AFLD.

Adipose-derived adiponectin and gut-derived FGF15/19 associate with each other, with the endocrine adiponectin-FGF15/19 axis a pivotal regulator of lipid metabolism.[107,108] Chronic or chronic-binge ethanol feeding concomitantly reduces adiponectin and FGF15/19 levels in mice.[23,109,110] Remarkably, the concurrent elevation of adiponectin and FGF15 is associated with inhibition of the genes involved in lipid uptake (*e.g.* CD36/FAT) and activation of the genes (*e.g.* PPARα and medium chain acyl-CoA dehydrogenase) implicated in lipid oxidation and the presence of ethanol-induced steatohepatitis in *Cisd1* knockout mice.[23] These findings suggest that endocrine adiponectin-FGF15/19 signalling protects against AFLD, at least in part by ameliorating the ethanol-induced abnormality in lipid metabolism.

Overall effect of ethanol exposure on lipogenesis

In summary, the net effect of ethanol is to activate (*e.g.*, via ER stress, TNFα and/or hepatic PPARγ) *de novo* lipogenesis, while concomitantly inhibiting processes that block this response (*e.g.*, AMPK and SIRT1). Although some of this net effect results from the direct action of ethanol on lipogenic enzymes (*e.g.*, disinhibition of ACC by AMPK inhibition), it is primarily the result of ethanol activating the transcriptional activity of SREBP-1c and ChREBP. This explains why these transcription factors are activated even when ethanol decreases the canonical inducers of these pathways (see earlier). In NAFLD, a similar loss of negative regulation of SREBP-1c and ChREBP is hypothesised to contribute to *de novo* lipogenesis, even in the fasting state.[111] Although the effect of ethanol on fasting *de novo* lipogenesis is less clear, a similar mechanism which contributes to the loss of diurnal regulation of lipid metabolism could be in play (see later).

Effects of ethanol on mitochondrial β-oxidation: potential key players

Mitochondrial β-oxidation shortens FAs into acetyl-CoA subunits, which can either enter the citric acid cycle, or be used to synthesise ketone bodies.[112] Although short-chain FAs can readily cross the outer and inner mitochondrial membranes, medium- and long-chain FAs are actively transported into the inner mitochondrial space via the carnitine shuttle. The rate-limiting enzyme in this process is carnitine palmytoyl transferase I (CPTI), which is regulated both transcriptionally and post-transcriptionally. Ethanol causes several changes that can directly or indirectly impair β-oxidation.

Transcriptional inhibition of mitochondrial β-oxidation by ethanol

Despite a net increase in the supply of FAs for β-oxidation, there is no apparent induction of β-oxidation genes during alcohol exposure. The major mechanism of action underlying this effect is hypothesised to be the inhibition of peroxisome proliferator-activated receptor alpha (PPARα) signalling.[113] PPARα is a nuclear hormone receptor that regulates expression of numerous genes involved in mitochondrial β-oxidation.[114,115] Ethanol exposure decreases PPARα DNA binding activity, without decreasing PPARα expression;[116] this effect is potentially mediated via decreasing protein levels of the retinoid X receptor (RXR), which heterodimerises with PPARα to bind to target DNA.[116]

Nutritional deficiencies

Alcoholics replace in excess of 50% of their total daily calories with ethanol.[117] Furthermore, alcohol consumption often causes malabsorption,[118] which may further exacerbate nutrient deficiencies. As the name implies, the carnitine shuttle requires carnitine as a cofactor. Roughly 25% of carnitine is synthesised endogenously from lysine and methionine, with the remainder derived from dietary sources.[119] Several experimental lines of evidence support the hypothesis that nutritional deficiencies may lead to functional carnitine deficiency, via restricting precursor supply and/or carnitine proper.[120,121] In contrast, the impact of alcohol on circulating levels of carnitine metabolites is equivocal at this time.[122–124] Nevertheless, alcohol consumption may cause nutritional deficiencies that potentially impair mitochondrial β-oxidation.

Inhibition of β-oxidation activity

As mentioned, the increase in the NADH:NAD^+-ratio caused by alcohol metabolism directly inhibits mitochondrial β-oxidation. This effect is thought to be predominantly mediated by the NAD+ reducing enzyme, 3-hydroxy-CoA dehydrogenase, the final step in generating acetyl-CoA during β-oxidation.[125] Furthermore, the disinhibition of ACC caused by impairing AMPK activity (see earlier) increases the carboxylation of acetyl-CoA to malonyl-CoA, which inhibits CPTI activity.[73,126] Coupled to the activity of CPTI, voltage-dependent anion channels (VDACs) are required to transport acyl-CoA esters through the outer membrane to the intermembrane space. Ethanol and acetaldehyde cause VDACs on hepatocyte mitochondria to close, which also impairs mitochondrial β-oxidation.[127,128] Lastly, ethanol exposure damages the mitochondria and leads to mitochondria dysfunction;[129] this impact on mitochondrial function can indirectly impair the ability of the organelles

to oxidise free FAs. This latter point is likely exacerbated by the impaired autophagy of damaged mitochondria that is associated with alcohol exposure.[130]

Effect of ethanol exposure on mitochondrial β-oxidation

In summary, the net effect of ethanol is to inhibit mitochondrial β-oxidation by blunting the induction of β-oxidation genes, even in the context of increased FA supply (*e.g.*, via inhibition of PPARα signalling), through potential functional deficiencies in critical cofactors for β-oxidation (*e.g.*, carnitine), directly (*e.g.*, increased NADH malonyl-CoA), and indirectly (via VDAC closure and mitochondrial dysfunction). Ethanol's myriad of inhibitory effects on mitochondrial β-oxidation likely explain the continued inhibition of this process during chronic ethanol consumption, even after the ratio of NADH:NAD+ appears to normalise.[131]

Effects of ethanol on cholesterol synthesis and secretion

Another mechanism by which lipids can accumulate in the liver is via alterations in the packaging of triglycerides into lipoproteins to form cholesterol. Some studies have indicated that chronic experimental ethanol impairs hepatic cholesterol synthesis,[20,132] whereas others have shown no effect.[133,134] However, few studies suggest that hepatic cholesterol synthesis is increased by alcohol. In this context, the lack of response of this system to the increase in lipid flux through the hepatocyte may contribute indirectly to the steatosis caused by ethanol consumption. The rate of cholesterol synthesis and release is controlled predominantly by the supply of apoliprotein B and the activity of microsomal triglyceride transfer protein (MTTP). A key regulator of both processes is hepatocyte growth factor (HGF) signalling via its receptor c-Met.[135] The activation of hepatic nuclear receptor 4α (HNF-4α) is also hypothesised to play a key role in this process.[136,137]

Activation of c-Met by HGF stimulates VLDL synthesis in hepatocytes through upregulation of apoliprotein B synthesis.[138] HGF administration has also been shown to enhance the rate of recovery from experimental alcohol-induced fatty liver and is associated with increased synthesis and secretion of apolipoprotein B and subsequent formation of VLDL.[139,140] The protective effect of medium chain triglycerides[20] and the PPARγ agonist pioglitazone[132] are hypothesised to be mediated, at least in part, by enhancing the capacity of hepatocytes to synthesise cholesterol. Enhancing the post-translational formation of HGF has also been shown to be protective against ethanol-induced steatosis. For example, although the canonical role of plasminogen activator inhibitor-1 (PAI-1) is to inhibit fibrinolysis by plasminogen activators, such as urokinase plasminogen activator (uPA),[141] uPA also activates pro-HGF to mature HGF.[142,143] Indeed, genetic or pharmacologic inhibition of PAI-1 prevents ethanol-induced steatosis, in part, by enhancing HGF-mediated VLDL synthesis.[133]

It is highly likely that other processes impacted by alcohol exposure (*e.g.*, ER stress[48]) contribute to altered/impaired VLDL synthesis during ALD. This area of research has been somewhat underappreciated partly because of the difficultly in studying cholesterol metabolism in intact organisms. The advent of more advanced stable isotope labelling approaches and lipidomic analyses may now make this possible.[144]

Other mechanisms by which ethanol impacts lipid metabolism

Lipocalin-2

Lipocalin-2 is an important innate immune protein belonging to the lipocalin family.[145] Emerging evidences demonstrate a pivotal and multifunctional role of lipocalin-2 in the early stages of ALD and in alcoholic steatosis.[23,42–44,109,146,147] Ethanol administration in mice or rats markedly increases liver and adipose lipocalin-2 expression and elevates circulating lipocalin-2 levels.[23,42–44,109,146,147] In a cellular model of alcoholic steatosis, recombinant lipocalin-2 or over-expression of lipocalin-2 exacerbates the ethanol-induced fat accumulation, whereas knocking down lipocalin-2 prevents steatosis in hepatocytes exposed to ethanol.[147] Consistently, global ablation of lipocalin-2 partially but significantly prevents experimental alcoholic fatty liver injury in mice.[147] Lipocalin-2 also promotes liver inflammation after alcohol intake by mediating neutrophil infiltration into liver and prolonging neutrophil lifespan in rodents and humans.[148] Mechanistically, abnormally elevated lipocalin-2 plays a causative role in the experimental cellular and animal models of alcoholic steatosis by disrupting signalling cascades involved in lipid metabolism, including the phosphoribosyltransferase-SIRT1 axis, chaperone-mediated autophagy, FA oxidation and endocrine metabolic regulatory hepatic FGF15/19 signalling.[147]

Autophagy

Macroautophagy (herein, referred to as autophagy) is a genetically programmed and highly conserved intracellular lysosomal degradation mechanism.[149,150] Autophagy maintains normal cellular functions and regulates lipid homeostasis, including lipid droplet turnover and formation. Aberrant autophagic machinery is associated with the development and progression of AFLD.[147,149–161] However, because of the complexity of autophagic machinery and differences in animal AFLD models, experimental findings are controversial. The induction of autophagy by acute ethanol treatment eliminates hepatic intracellular lipid droplets and reduces lipid accumulation in rodents.[151–153] However, chronic ethanol administration at higher dosages inhibits autophagy, coupled with accumulation of hepatic triglycerides in mice.[147,154,155]

In summary, regardless of acute or chronic ethanol exposure in animals, autophagy serves as a cellular adaptive mechanism and protects against ethanol-induced detrimental effects on lipid metabolism by removing lipid droplets and/or damaged mitochondria.[147,151–161] Although the mechanisms by which ethanol regulates autophagic machinery are not fully understood, ethanol metabolism-induced oxidative stress is likely to participate in the activation of autophagy.[149,150,158] In addition, regulation of autophagy by acute *vs.* chronic ethanol exposure may be determined by a gene transcription programme in liver.[156,157]

Circadian clock

The circadian clock regulates circadian rhythms and is maintained by a complex circuitry of transcriptional/translational regulatory loops at molecular levels.[162,163] The circadian clock plays an essential role in orchestrating many physiological processes, including lipid metabolism. Derangements in the finely tuned circadian clock can contribute to dyslipidaemia and liver diseases.[162,163]

Circadian clock disruption is an important contributor to aberrant lipid metabolism and ethanol-induced steatosis.[164] Chronic ethanol exposure results in the disturbance of the hepatic circadian clock and time-of-day specific regulation of lipid homeostasis in rodents.[165–169] Large time-of day-dependent increases in triglyceride and cholesterol levels have been demonstrated in the livers of mice receiving chronic ethanol-administration.[165–169] Changes in the diurnal oscillations of core clock genes (*Arntl*, *Clock*, *Cry1*, *Cry2*, *Per1*, *Per2*) and clock-controlled genes (*e.g. Dbp*, *Hlf*, *Noct*, *Npas2*, *Nr1d1*, *Tef*) were observed in the steatotic livers of ethanol-fed rodents.[165] *Per1* knockout mice have lower levels of triglyceride synthesis genes following acute alcohol administration.[166] Chronic ethanol administration to mice disrupts diurnal rhythms in hepatic lipid metabolism at gene and protein levels.[167,168,170] Ethanol-mediated alterations in the hepatic NAD^+/NADH ratio are also under clock control.[167]

The exact underlying mechanisms through which ethanol negatively impacts circadian clock-mediated lipid metabolism and contributes to steatosis, remain to be elucidated. Ethanol-mediated alterations in 2 key energy sensing metabolites, NAD + and ATP, may disturb the liver circadian clock by disrupting post-transcriptional modification events (*e.g.* acetylation, and ADP-ribosylation, and phosphorylation) mediated by the molecules involved in lipid metabolism (*e.g.* SIRT1, AMPK and poly ADP-ribose polymerase 1).[164,165,167] Further, deciphering the mechanisms that link ethanol, lipid metabolism and circadian responses will provide valuable insights for the development of innovative therapeutic strategies.

Emerging areas

There are several new areas, including long non-coding RNAs, pre-mRNA splicing, and gut micro-biota that deserve further investigation in the context of alcohol and steatosis.

Alternate mRNA processing

A regulatory role for microRNAs in AFLD has been suggested.[171] For example, microRNA-217 promotes ethanol-induced fat accumulation in hepatocytes by disrupting the SIRT1-lipin-1 axis.[40] Whether and how ethanol-mediated alterations in specific microRNA expression are linked to dysregulated lipid metabolism in alcoholic steatosis will need further investigation. Long noncoding RNAs (lncRNAs) influence lipid homeostasis by controlling the lipid metabolism-related gene expression, either by base-pairing with RNA and DNA or by binding to proteins.[172,173] Alterations in lncRNA expression have been linked to a number of liver diseases including ALD.[173,174] It is worthwhile exploring whether, and how, ethanol disrupts hepatic IncRNAs and subsequently causes fatty liver injury. Alternative splicing of precursor messenger RNA (pre-mRNA) is a pivotal step in gene expression, eliminating the introns and ligating the exons to form mature mRNAs that can be translated into proteins.[175,176] Defects in the pre-mRNA splicing machinery can impact on lipid homeostasis and contribute to steatosis.[176–178] Ethanol exposure causes changes in pre-mRNA splicing.[179] However, alternative pre-mRNA splicing is an underappreciated mechanism in the pathogenesis of AFLD.[180] It will be of importance to

investigate whether aberrant splicing machinery contributes to ethanol-mediated dysregulation of lipid metabolism and alcoholic steatosis.

Microbiome

Growing evidence demonstrates the involvement of gut microbiota in the development and progression of ALD.[180] The influences of gut microbiota on ethanol-mediated dysregulation of lipid metabolism and the relationship between gut microbiota and AFLD warrant future investigation. Undoubtedly, illuminating the mechanistic connections between these newly understood machineries and ethanol will provide a more cohesive picture of how ethanol deranges hepatic lipid metabolism and results in steatosis and liver injury.

Concluding remarks

Hepatic lipid metabolism is a series of complex processes that control influx and efflux of not only hepatic lipid pools, but also organismal pools. As mentioned, lipid homeostasis is usually tightly controlled by expression, substrate supply, oxidation and secretion that keeps hepatic lipid poolsrelatively constant. However, perturbations of any of these processes can lead to lipid accumulation in the liver. Although it is thought that these responses are hepatic arms of the ‘thrifty genome’, they are maladaptive in the context of chronic fatty liver diseases.[181,182] Ethanol is likely unique among toxins, in that it perturbs almost all aspects of hepatic lipid metabolism. This complex response is due in part to the large metabolic demand placed on the organ by alcohol metabolism, but also appears to involve more nuanced changes in expression and substrate supply. The net effect is that steatosis is a rapid response to alcohol abuse. Although transient steatosis is largely an inert pathology, the chronicity of ALD seems to require steatosis. Better and more specific understanding of the mechanisms by which alcohol causes steatosis may therefore translate into targeted therapies to treat ALD and/or prevent its progression.

Supplementary Material

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Financial support

Supported, in part, by grants (AA021978, AA013623 and AA015951) and centers (P50 AA024333 P50 AA024337) funded by National Institute of Alcohol Abuse and Alcoholism (NIAAA, USA).

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Key point

The initial hepatic change caused by excessive alcohol consumption is steatosis, which occurs in almost all patients who consume harmful levels of alcohol.

Key point

There is evidence that stimulation of fatty acid transporters, particularly CD36/FAT, has an important role in alcoholic fatty liver disease.

Key point

Ethanol activates *de novo* lipogenesis via a number of processes, leading to lipid accumulation in the liver.

Key point

The net effect of ethanol is to inhibit mitochondrial β-oxidation, even in the context of increased fatty acid supply, reducing the utilisation of lipid.

Key point

A number of emerging research areas deserve further investigation in the context of alcohol and steatosis, including long noncoding RNAs, pre-mRNA splicing and gut microbiota.

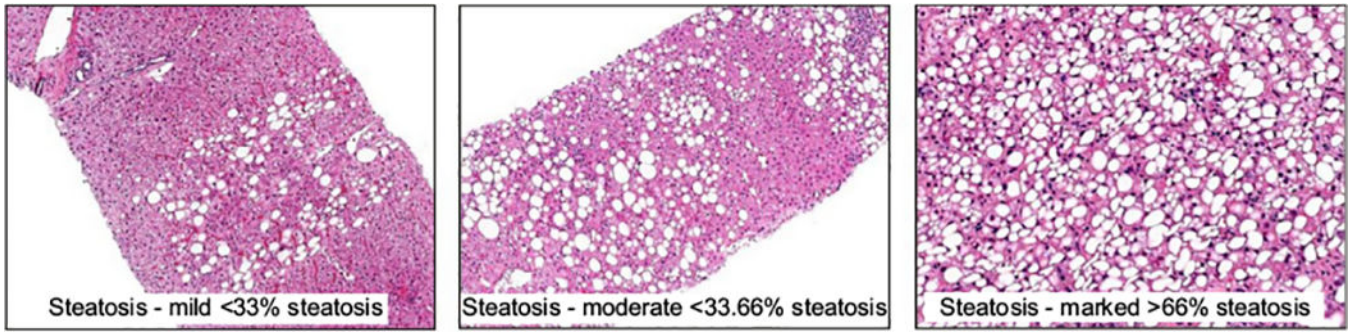

Fig. 1. Steatosis in alcohol-related liver disease.

Representative pictures of liver biopsies from patients with ALD and different degrees of steatosis. In all cases macro- and microsteatosis are present. Photomicrographs courtesy of Dr. John Woosley, University of North Carolina at Chapel Hill.

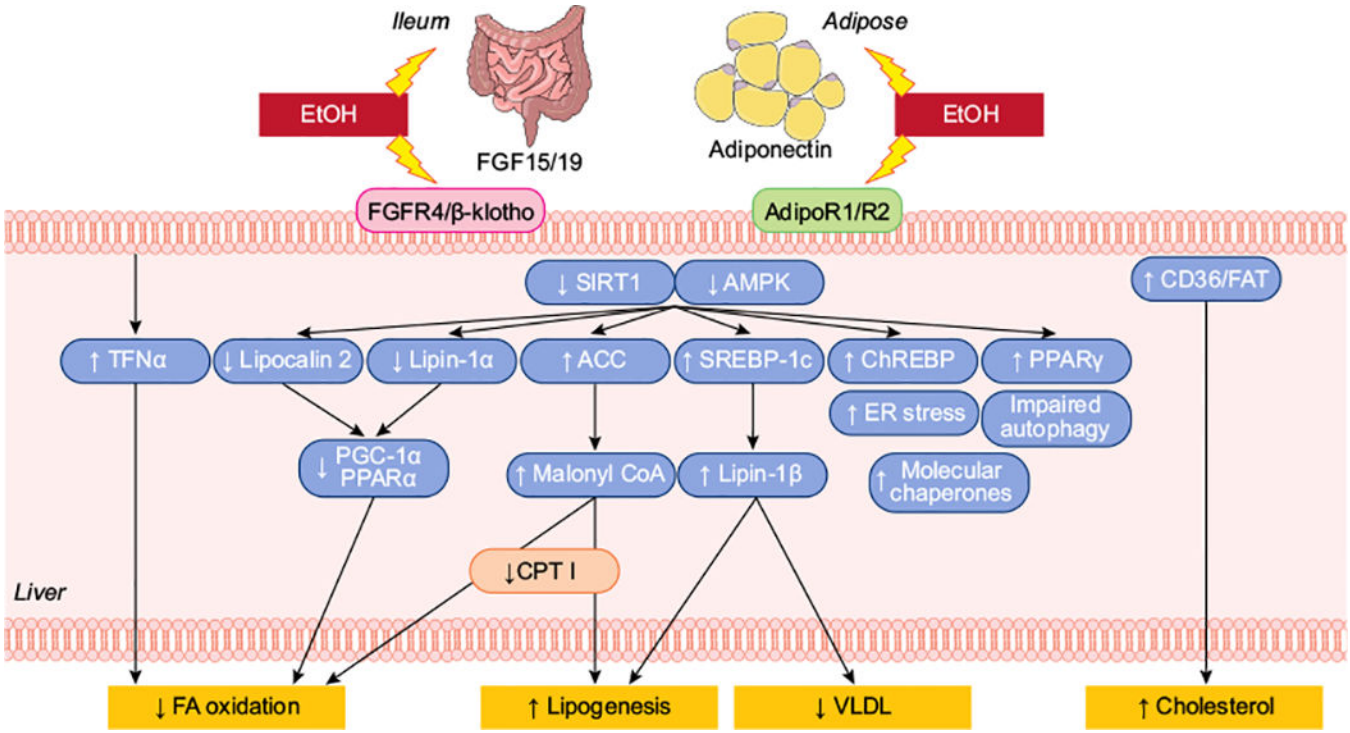

Fig. 2. Intricate regulation of lipid metabolism, and the impact of ethanol exposure.

The liver plays a central role in lipid metabolism for the entire organism. Hepatic free FAs are not only directly synthesised (lipogenesis), but are also actively taken up by the liver. This pool of FAs can either be used for energy (FA oxidation), membrane synthesis or for esterification into triglycerides by hepatocytes. Triglycerides are subsequently packaged as VLDLs to be secreted. There is intricate cross-talk between these systems and hepatic lipid metabolism is controlled by a complex interplay of hormones, nuclear receptors, intracellular signalling pathways and transcription factors. Alcohol directly and indirectly impacts numerous aspects of hepatic lipid flux that ultimately leads to lipid accumulation. FA, fatty acid; VLDL, very low-density lipoprotein.