How does your fat affect your liver when you drink?

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Commentary

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How does your fat affect your liver when you drink?

Seonghwan Hwang and Bin Gao
Laboratory of Liver Diseases, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA.

White adipose tissue (WAT) dysfunction is generally thought to promote the development of alcoholic liver disease (ALD) in alcoholics by releasing free fatty acids and inflammatory mediators. This explains, at least in part, the synergistic or additive effects of alcohol and obesity on liver disease progression. In this issue of the JCI, Shen et al. establish a previously unrecognized concept that brain alcohol sensing enhances thermogenesis of brown adipose tissue (BAT) through sympathetic nerve activation. BAT functions as hepatoprotective machinery to counteract the development of ALD, implying a therapeutic potential of BAT activity modulation for the treatment of ALD.

Adipose tissue in alcoholic liver disease
Alcoholic liver disease (ALD) is a leading cause of chronic liver diseases that ranges from fatty liver to steatohepatitis, cirrhosis, and liver cancer (1). There are no FDA-approved medications for ALD, necessitating the extension of our understanding of its pathogenic mechanisms as well as identification of potent therapeutic targets. Many mechanisms underlying ALD pathogenesis have been identified (1), with recent attention on adipose tissue, which likely plays a more important role in modulating ALD in the modern age than in the past due to the global obesity epidemic (2). Numerous clinical and experimental studies have documented the synergistic or additive effects of alcohol and obesity on liver disease progression well (see review in ref. 2 and references therein). Accumulating data suggest that adipose tissue dysfunction promotes the development of ALD in alcoholics by releasing free fatty acids (FFAs) and inflammatory mediators (2); however, precisely how adipose tissue affects the pathogenesis of ALD still remains largely unknown.

The classical view of adipose tissue as an inert organ for energy storage has been challenged by recent studies providing evidence that adipose tissue is an endocrine organ that actively participates in the regulation of energy metabolism and the immune system by secreting various factors, such as adipokines, cytokines, and chemokines. Accordingly, the dysregulation of adipose tissue biology has been highlighted as a crucial player in the development of inflammatory and metabolic diseases, such as diabetes, nonalcoholic fatty liver disease (NAFLD), and ALD (2, 3). Adipocyte death, which is significantly increased during obesity (4) and alcohol drinking (5), has been recognized as an important initiator for inducing infiltration of macrophages in adipose tissues. Infiltrated macrophages subsequently produce a variety of inflammatory cytokines, such as TNF-α and IL-6, and chemokines, such as CCL2, which exacerbate insulin resistance in adipocytes and further recruit immune cells to the inflamed adipocytes (6, 7). Adipocyte death has also been shown to induce hepatic fat accumulation and injury, as demonstrated by the observation that reduction of adipocyte death via adipocyte-specific deletion of the Fas gene attenuated fatty liver in high-fat diet-fed (HFD-fed) mice (8), whereas induction of adipocyte death via adipocyte-specific deletion of the Snap23 gene exacerbated hepatic steatosis (9). Recently, by using a model of acute and specific adipocyte death, we extensively characterized how adipocyte death causes liver injury and inflammation, demonstrating the importance of CCR2-dependent macrophage infiltration and lipolysis in the development of liver injury and inflammation after adipocyte death (10).

Role of white adipose tissue in alcoholic liver disease
The adipose-tissue pool in rodents and humans consists of white adipose tissue (WAT) and brown adipose tissue (BAT)/beige fat. Traditionally, both white and brown adipocytes were believed to be able to store fat; however, there is now a consensus that these two cell types are morphologically and functionally different. While white adipocytes have unilocular structure and act primarily to store energy in the form of triglycerides, brown adipocytes have multilocular structure and are rich in mitochondria for fatty acid oxidation and thermogenesis. Alcohol first gained attention as an insult that causes white adipocyte dysfunction. Several previous studies suggest that chronic alcohol intake activates the lipolysis of white adipocytes, diminishes insulin-dependent glucose uptake, and dysregulates secretion of adipokines and cytokines, thereby inducing systemic insulin resistance, inflammation, and steatosis in rodents (see reviews in refs. 2, 11, and references therein) (Figure 1). Additionally, the Nagy laboratory extensively characterized the effects of chronic alcohol feeding on white adipocyte death in mice, demonstrating that chronic alcohol feeding elevates TNF-α– and Bid-mediated apoptosis of adipocytes, which creates an inflammatory environment in adipose tissue and is also believed to contribute to ALD pathogenesis (5).

Role of BAT in alcoholic liver disease
BAT maintains metabolic homeostasis against body weight gain and development
journal of metabolic syndrome through thermogenesis mediated by mechanisms involving activation of uncoupling protein 1 (UCP1), a protein that is specifically expressed in brown and beige adipocytes. UCP1 uncouples fatty acid oxidation from ATP synthesis in the mitochondria and dissipates energy in the form of heat. Active BAT was originally thought to exist only in infants and rodents, whereas later studies suggest BAT is also present in adult healthy humans, but is less frequently observed in metabolically unhealthy individuals (12–14). The importance of UCP1 and thermogenic activity of BAT in the regulation of energy metabolism was confirmed by the ensuing studies showing that deletion of the Ucp1 gene induced obesity at thermoneutrality (15) and that activation of BAT conferred resistance to obesity and metabolic dysfunction in HFD-fed mice (16, 17). Additionally, recent studies also suggest a negative correlation between BAT activity and NAFLD development in both humans (18) and rodents (19).

Although BAT has been in the spotlight as a modulator of energy metabolism and potential therapeutic target of NAFLD (20), the association between BAT and ALD has been elusive. Indeed, the influence of alcohol on BAT physiology (e.g., organ mass, thermogenic activity, and lipolysis) has been reported to be inconsistent between studies and thus appears to be contingent on experimental conditions (11). In this issue, Shen et al. extensively investigated the influence of BAT thermogenesis on ALD development by utilizing thermoneutral environment and Ucp1-knockout mice (21). For years, it was not explained why Ucp1 ablation failed to cause obesity in mice, as opposed to the observation that genetic obesity was associated with reduced BAT capacity and activity. This question was solved by an elegant study by Feldmann et al. (15), who performed experiments at thermoneutrality (at 30°C) in which thermal stress was removed, BAT activity was minimized, and thus physiological responses to the alteration in BAT thermogenesis could be better analyzed. This condition is indeed more physiologically relevant, as humans in developed countries do not suffer from metabolic cold stress today (due to clothes and housing) (15). Shen et al. demonstrated that, at thermoneutrality, alcohol feeding significantly elevated the levels of UCP1 expression and mitochondrial respiration complexes, indicating that ethanol intake enhances BAT activity. This notion was further supported by their findings that energy expenditure was elevated and body weight was reduced when mice were fed an alcohol-diet at thermoneutrality. Furthermore, pathological aspects of ALD, such as steatosis, oxidative stress, hepatocyte death, and liver inflammation, were more prominent in Ucp1-deficient mice exposed to alcohol as compared to the wild-type controls. In contrast, cold-induced BAT activation diminished alcohol-induced steatosis, oxidative stress, and liver injury. These collectively suggest that alcohol-induced activation of UCP1 and thermogenesis in BAT is a defensive mechanism that counteracts the development of ALD. In contrast with the study by Shen et al., the majority of the other stud-
Conclusions
Collectively, the data from Shen et al. suggest that BAT protects against ALD by activating thermogenesis, producing hepatoprotective adipokines (e.g., adiponectin), and removing circulating FFAs. Several approaches have been under investigation for the pharmacological activation of BAT (e.g., adrenergic receptor agonists, transient receptor potential channel agonists, and thyroid hormones), mostly in the context of the treatment of metabolic syndrome (25). Continuous effort toward the development of BAT activators may also open new avenues for the therapeutic intervention of ALD, beyond the hitherto well-studied obesity and metabolic syndrome.

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Address correspondence to: Bin Gao, Laboratory of Liver Diseases, NIAAA/NIH, 5625 Fishers Lane, Bethesda, Maryland 20892, USA; Phone: 301.443.3998; Email: bgao@mail.nih.gov.