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Mechanisms Involved in Disruption of Adipose Tissue Mass Resulting from Chronic Unhealthy Alcohol Consumption

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Abstract

Chronic heavy alcohol consumption leads to loss in adipose tissue mass. The mechanisms involved are not fully known and most of our understanding has been derived from animal studies. The study by Crowell et al. (2016) investigated the impact of chronic alcohol feeding on white adipose tissue (WAT) protein synthesis. Their detailed analysis of the signaling mechanisms that regulate protein synthesis reveals tissue-specific alterations resulting from chronic alcohol feeding. The focus on protein synthesis as a possible mechanism of loss of WAT following chronic alcohol feeding is interesting. But the study provides additional insight into what could possibly be a more relevant mechanism for loss of adipose mass in chronic alcohol-consuming animals and humans; that is, the delicate balance between lipolysis and lipogenesis and the potential contribution of alcohol-mediated inflammation to their disruption. Their study highlights the importance of continued research on the metabolic alterations resulting from chronic alcohol consumption and the potential impact of those metabolic alterations on development of comorbid conditions, from obesity to lipodystrophy.

Keywords

Adipose; Lipolysis; Lipogenesis; Alcohol; Ethanol

The effects of chronic alcohol consumption on the mechanisms underlying development of fatty liver are well studied. However, the effects of chronic heavy alcohol consumption on extra-hepatic adipose tissue, in particular the effects involved in loss of white adipose tissue (WAT), are not well understood. The impact of chronic heavy alcohol consumption on extra-hepatic adipose mass remains of interest due to the relevance of WAT mass in the pathophysiological mechanisms underlying hepatic triglyceride (TG) accumulation (Syn et al., 2009). Several studies have stressed the importance of adipose tissue lipolysis in the development of hepatic steatosis (Ress and Kaser, 2016). Investigators have proposed that altered WAT storage may promote excess fatty acid (FA) influx into the liver, leading to steatosis (Sozio et al., 2010). Hepatic steatosis results from an imbalance between hepatic fatty acid uptake, lipid synthesis, lipid oxidation, and lipid export via very low density

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Conflicts of Interest

The author declares no conflicts of interest.

lipoprotein (VLDL) particles. The importance of balanced adipose tissue lipolysis and lipogenesis is supported by reports of hepatic steatosis in leptin-deficient lipodystrophic patients ([Petersen et al., 2002](#)) and in subjects with mutations of perilipin-1 ([Agarwal and Garg, 2006](#)), a critical protein involved in both pro- and antilipolytic effects of hormones and catecholamines.

The study by Crowell et al. ([2016](#)) tested the hypothesis that the reduction in WAT mass resulting from chronic alcohol consumption is associated with a decreased protein synthesis mediated by impaired function of mTOR complex 1 (mTORC1). The group's previous work on skeletal muscle has provided a wealth of information on the mechanisms involved in decreased skeletal muscle protein synthesis that contribute to decreased lean body mass in chronic alcohol-fed rodents ([Steiner and Lang, 2015](#)). The approach employed in the present study was similar to that used for the study of muscle protein synthesis to investigate the impact of alcohol on WAT protein synthesis. The results showed progressive accretion of whole-body fat mass in control animals, which was abolished after 12 weeks of alcohol feeding, resulting in an overall decrease in whole-body fat mass after 18 weeks of alcohol feeding. Contrary to their prediction, the alcohol-induced decrease in whole-body fat mass seen in their study was associated with increased protein synthesis and activity of ribosomal protein S6 kinase beta-1 (S6K1). Protein accounts for less than 5% of fat mass, thus even if protein synthesis had been shown to be decreased in alcohol-fed animals, it is unlikely that it would have accounted for the decrease in adipose mass seen in their study. Thus, decreased adipose mass must have resulted from an altered balance between lipogenesis and lipolysis ([Saponaro et al., 2015](#)). Lipogenesis, the process of FA storage as triglycerides, requires activity of lipoprotein lipase (LPL), which releases FAs by intravascular endothelial surface hydrolysis of very low density lipoproteins or chylomicrons. Most of the FAs used in lipogenesis are derived from the diet, with minimal contribution from FAs synthesized in liver (<5%) and adipose tissue (<2%). FAs enter adipocytes by traversing lipid bilayers, or by CD-36, fatty acid transport proteins (FATPs), and structural proteins like caveolin. TG synthesis requires the availability of glycerol phosphate which is derived from glucose or glyceroneogenesis. Lipolysis involves the hydrolysis of triglycerides and release of FAs and glycerol from adipocytes into the systemic circulation. Several pathways are involved in activation of lipolysis, including activation of β -adrenergic receptors leading to increased cAMP-mediated activation of protein kinase A (PKA) pathway; the 5'-AMP-activated protein kinase pathway; the extracellular-signal-regulated kinase pathway (ERK); and growth hormone and cytokine signaling pathways. In addition, natriuretic peptide-mediated activation of guanyl cyclase, and the cyclic guanosine monophosphate (cGMP)-mediated activation of protein kinase G has also been shown to result in activation of TG hydrolyzing enzymes. Overall, beta adrenergic receptor stimulation is the principal stimulus for lipolysis; and hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) are the two principal and best-characterized enzymes sequentially involved in beta adrenergic mediated lipolysis ([Kolditz and Langin, 2010](#)). ATGL catalyzes the initial removal of the first FA from triacylglycerides (TGs), producing diacylglycerides (DAGs) which are subsequently hydrolyzed by HSL leading to the generation of an additional FA and monoacylglycerides (MAGs). The final conversion of MAGs into FA and glycerol is catalyzed by monoglycerol lipase (MGL). While activation of HSL is known to be mediated by cAMP-mediated PKA

phosphorylation that leads to its translocation from the cytosol to the surface of the lipid droplet, the mechanisms involved in ATGL activation are not completely understood. Additionally, phosphorylation of perilipin-1, a lipid droplet surface protein, has been shown to play a key role in facilitating translocation of HSL to the surface of the lipid droplet, facilitating lipolysis (Tansey et al., 2004). In contrast, under basal non-hormone-stimulated conditions, perilipin protects the lipid droplet from lipolysis. Previously, loss of adipose tissue mass as a result of chronic alcohol consumption was shown to result in part from an increase in triglyceride turnover without significant alteration in triglyceride synthesis in mice (Kang et al., 2007a, Zhong et al., 2012). In the present study by Crowell et al. (2016), chronic alcohol feeding resulted in a decrease in PPAR γ and C/EBP α , key regulators of lipogenesis, which supports alcohol-mediated suppression of lipogenesis. In addition, Crowell et al. (2016) showed significant increases in ATGL and phosphorylated HSL in adipose tissue of alcohol-fed animals, suggesting a contribution of lipolysis to the decreased fat mass seen in their studies. Clearly, there are multiple sites where chronic alcohol consumption can interact with either the lipogenic or lipolytic process, and additional studies are warranted to fully explore the alcohol-sensitive mechanisms that contribute to decreased fat mass. Although beta adrenergic receptor stimulation is a principal mechanism underlying lipolysis (Nielsen et al., 2014), the contribution of this pathway to alcohol-mediated lipolysis does not appear to be significant. Reports in the literature indicate that chronic alcohol feeding suppressed beta-adrenergic receptor-stimulated lipolysis in vivo and ex vivo. The lipolytic effects of beta adrenergic agonists are opposed by the antilipolytic effects of insulin. Studies suggest that this may be a pathway with greater sensitivity to alcohol-mediated effects, as shown by impaired insulin-mediated suppression of lipolysis during a hyperinsulinemic-euglycemic clamp in conscious rats chronically fed an alcohol diet, and in adipocytes isolated from epididymal and subcutaneous adipose tissue. Crowell et al. (2016) did not examine the role of insulin or catecholamines in the alcohol-associated decrease in adipose mass. However, their results show that chronic alcohol feeding increased mRNA expression of TNF- α and IL-1 β , which suggests that local inflammation may contribute to decreased adipose mass caused by chronic alcohol consumption in their model. Chronic alcohol consumption results in an overall tissue proinflammatory milieu that includes adipose tissue (Kang et al., 2007b). TNF- α , a prominent inflammatory cytokine upregulated in tissues following chronic alcohol consumption, is a major factor implicated in alterations in adipose tissue metabolism (Coppack, 2001) through stimulation of HSL expression (increase lipolysis), and decreased LPL activity (decreasing fat accumulation). In addition, by reducing insulin receptor tyrosine phosphorylation and increasing phosphorylation of insulin receptor substrate-1 at serine residues, TNF- α may lead to an insulin-resistant state. Similar anti-insulin actions have been reported for IL-1 β (Grant and Stephens, 2015). Crowell et al. (2016) did not find evidence to support the contribution of the “inflammasome,” a multiprotein complex of NLRP3 (nucleotide-binding domain and leucine-rich repeat protein 3), ASC (apoptosis-associated speck-like protein containing a CARD), and procaspase-1 in loss of adipose mass (Benetti et al., 2013). It is possible that this mechanism may be relevant under longer alcohol feeding protocols or in combination with a high fat diet, reflecting a more common pattern of alcohol and diet intake in humans.

Adipose tissue is composed of adipose stem cells, adipocytes, vascular smooth muscle, endothelial cells, and neuronal cells and is a dynamic organ initiating its development in utero and continuing its growth and remodeling throughout the lifespan. Adipose tissue is located in discrete depots throughout the body and for functional purposes can be categorized as intra-abdominal or visceral and subcutaneous. These depots differ in gene expression (subcutaneous fat depots have higher leptin, angiotensinogen, and glycogen synthase expression compared with visceral fat; while visceral fat expresses increased levels of insulin receptor, 11 β hydroxysteroid dehydrogenase (HSD) and interleukin 6 (IL6)). These differences are likely to affect responsiveness of different adipose depots to regulators of lipolysis and lipogenesis and, consequently, susceptibility to alcohol-mediated alterations in fat mass. The results from Crowell et al. (2016), suggest that the effects of alcohol were generalized to all depots. The results show an approximate 40% decrease in total body and gonadal fat in alcohol-fed animals compared to pair-fed controls. In addition to adipose mass being a determinant of the metabolic state of adipose tissue and its contribution to overall metabolic regulation, adipocyte phenotype is also considered relevant. Impaired maturation of small adipocytes into fully functional adipocytes leads to lipid accumulation in peripheral tissues including the liver, muscle, and pancreas, thus contributing to alterations in hepatic glucose production, pancreatic insulin release, and muscle response to insulin. Adipocyte differentiation and maturation involves transcriptional regulation of TG storage, lipolytic capacity, and adipokine release. While Crowell et al. (2016), did not report differences in adipocyte size, others have reported smaller adipocyte size in chronic alcohol-fed animals (Zhong et al., 2012).

Finally, in addition to serving as fuel storage, adipose tissue functions as an endocrine organ, releasing not only FA, but adipokines and cytokines. Thus, it is quite possible that in addition to its likely contribution to the pathophysiology of alcohol-associated hepatic steatosis, adipose tissue may also play a role in alcohol-related pathological effects on other organ systems such as the bone system and the reproductive system. Moreover, our improved understanding of the metabolic, endocrine, and inflammatory mechanisms that regulate adipose tissue function calls for renewed attention to studies focused on the response of these mechanisms to chronic alcohol consumption and the biomedical consequences of their derangement.

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