Published in final edited form as:

Alcohol Clin Exp Res. 2017 May ; 41(5): 880–882. doi:10.1111/acer.13370.

Alcoholic Liver Disease on the Rise: Interorgan Cross Talk Driving Liver Injury

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Abstract

Advanced alcoholic liver disease (ALD) represents a substantial public health burden, threatening the lives of more than ten million people in the United States. Although the direct harmful effects of alcohol in the liver are nearly universally recognized, emerging evidence suggests alcohol also adversely affects other organs such as the intestine, skeletal muscle, adipose tissue, and likely many other tissues. In fact, the extrahepatic effects of alcohol clearly converge to impact the morbidity and mortality associated with chronic alcohol abuse. In the intestine alcohol consumption can profoundly impact both gut barrier function as well as reorganizing intestinal microbial communities. In the skeletal muscle, chronic alcohol consumption promotes sarcopenia by altering protein homeostasis or proteostasis. In parallel, alcohol can impact the normal endocrine and metabolic function of adipose tissue. Collectively, chronic alcohol abuse sustains an interorgan cross talk that provides the multiple hits necessary for progression to end stage liver disease. Here we briefly highlight several recent examples of interorgan cross talk underlying the morbidity and mortality associated with alcohol abuse, and discuss how these recent advances have the potential to impact therapeutic strategies for those suffering with ALD.

Keywords

microbiota; adipose; muscle; circadian

Alcoholic Liver Disease (ALD) poses a significant public health burden worldwide. It is clear that the direct effects of alcohol and its metabolites on the liver are key drivers of ALD-associated morbidity and mortality. However, several recent advances in the field of ALD research suggest that alcohol's effects outside of the liver are also very important in ALD outcomes. In addition to alcohol's effects in the liver, there is mounting evidence that chronic alcohol abuse initiates a number of pathological events in many other organs including the intestine, lymphatic system, skeletal muscle, central nervous system, adipose tissue, kidney, and likely many other organ systems. In fact, alcohol abuse initiates an

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Author Contributions: S.D. and J.M.B. worked equally together to conceptualize, organize, and write this commentary.

Conflict of Interest: Both authors declare no conflict of interest.

interorgan cross talk that provides the multiple hits necessary for progression to end stage liver disease. Here we briefly highlight several recent examples of alcohol's effect outside of the liver that contribute substantially to the progression of ALD. These recent paradigm shifting insights have the potential to change the way we treat those suffering from alcohol abuse disorders.

Ald on The Rise: Epidemiology Of Alcohol-Induced Liver Injury

Even though the adverse effects of alcohol use disorders on the liver are nearly universally recognized, there are a number of other more frequent causes of liver disease including viral hepatitis (specifically HCV and HBV) and non-alcoholic fatty liver disease. Advances in screening techniques, vaccination and novel therapies have significantly reduced the prevalence of hepatitis B. Novel therapies are likely to reduce the burden of HCV and estimates suggest that in the next 2 decades, HCV will be a rare disease. With the increasing prevalence of obesity, the associated nonalcoholic fatty liver disease is becoming one of the most frequent causes of liver disease. Newer therapies including vitamin E, pioglitazone and obeticholic acid have been identified to be effective in improving hepatic histology. These and other emerging therapies in combination with measures targeting obesity are likely to result in a reduction in prevalence of NAFLD related cirrhosis. In contrast, despite extensive studies and therapeutic trials, there are no effective therapies for alcoholic hepatitis or alcohol use disorders. A recent study modeled the published data on the prevalence of alcoholic liver disease and alcohol use disorders, and estimated that unless novel, effective therapies are developed, alcoholic liver disease is likely to be the major cause of liver disease in the United States (Giurgius et al., 2015). Since the effects of alcohol abuse affect organs beyond the liver, including skeletal muscle, intestine, and adipose tissue, these clinical consequences are also likely to become more prevalent in the next few decades.

Alcohol Effects In The Intestine: Setting The Clock For Pathogenic Microbe-Host Interactions

Importantly, not all alcohol abusers develop ALD, indicating that a combination of associated genetic or environmental risk factors induce a “second hit” to promote disease progression. Recent evidence suggest that commensal bacteria in the intestine may serve as an important “second hit”. There is now substantial evidence that excessive alcohol consumption can promote abnormal intestinal permeability or “leakiness” allowing for constituents of the microbial cell wall such as lipopolysaccharide (LPS) to enter into the portal circulation to drive ALD (Hartman et al., 2015). Microbe-associated molecular patterns (MAMPs) such as LPS are sensed by hepatic pattern recognition receptors (PRR) such as toll like receptor 4 (TLR4) to drive hepatic injury. Although there is a wealth of evidence supporting gut permeability as a major driven of ALD, recent findings have shown that microbe-host interactions in ALD are not quite as simple as LPS-TLR4 signaling. Seminal work by Chen and colleagues recently showed that mice housed in germ-free conditions actually show significantly greater ethanol-induced liver injury and hepatic steatosis (Chen et al., 2015). Interestingly, germ-free mice have increased hepatic expression ethanol metabolizing enzymes, which is associated with rapid clearance of ethanol (Chen et

al., 2015). These results provocatively demonstrate that commensal bacteria play important roles in ethanol metabolism and ethanol-induced liver injury, and also remind the field that microbe-host interactions go well beyond the canonical LPS-TLR4 signaling axis.

In addition to altering the classic LPS-TLR4 signaling axis, alcohol has been shown to alter intestinal microbial community structure. In fact, this ethanol-induced intestinal dysbiosis is thought to be an important driver of ALD progression (Hartmann et al., 2015). In another important recent study, Voigt and colleagues uncovered an unexpected cross talk between ethanol consumption, the circadian clock system, and intestinal dysbiosis (Voigt et al., 2015). This discovery came about by studying ethanol-induced dysbiosis in mice lacking the normal circadian clock system (i.e. mice expressing the dominant-negative *Per1* allele of the Clock gene). Employing this approach Voigt and colleagues discovered that disruption of the circadian clock results in shifts in gut microbial communities, and this clock-driven shift can be exacerbated by ethanol feeding (Voigt et al., 2015). This study provides the first evidence that ethanol abuse may synergize with the circadian clock to promote intestinal dysbiosis pathogenesis in the host. These findings are particularly exciting, given other recent reports demonstrating that the host circadian system is a central regulator of diurnal oscillations in intestinal microbe-driven metabolic reprogramming in the host (Thais et al., 2016; Liang et al., 2015). These recent studies provide strong evidence that bi-directional cross talk between gut microbial communities and the host circadian clock system may represent a new therapeutic target in ALD.

In another recent example of intestinal effects of alcohol, Tang and colleagues identified a novel signaling axis involving micro-RNA 212 (miR-212) and inducible nitric oxide synthase (iNOS) that regulates gut permeability (Tang et al., 2015). Given the strong links between oxidative stress and ALD, Tang and colleagues examined the potential role for iNOS and miR-212 in intestinal barrier function. This work has uncovered a novel pathway whereby iNOS-driven oxidative stress promotes the overexpression of miR-212 to promote the loss of intestinal tight junctions (Tang et al., 2015). Identification of this iNOS-miR-212 signaling axis provides a new potential therapeutic target to attenuate alcohol-induced gut hyperpermeability. Collectively, these recent studies advance the concept that intestinal dysbiosis and gut permeability play an important role in the development of ALD, and identify targets for potential therapeutic intervention.

Alcohol Effects on The Structure and Function of Skeletal Muscle

One of the dominant effects of ethanol in the liver is an increase in lobular fibrosis with activation of the stellate cells to myofibroblasts. In addition to the liver, muscle is another major target of ethanol-induced toxicity. Extensive physiological, molecular and metabolic studies have helped shed light on the potential mechanisms of perturbations in proteostasis or protein homeostasis with loss of muscle mass. Impaired protein synthesis due to reduced mTORC1 signaling has been identified and consistently, autophagy is increased (Thapaliya et al., 2014). Unlike those in the liver, there have been few studies on skeletal muscle fibrosis and Lang's group in Hershey has performed seminal work in this area using a complementary genetic and functional approach to show that ethanol has a context specific effect on tissue fibrosis in the heart and skeletal muscle (Steiner et al., 2015). An increase in

muscle profibrotic genes and collagen have the potential to adversely affect both the metabolic and contractile function with consequent impaired functional activity. The unbiased approach taken by these investigators showed that mRNA of specific extracellular matrix proteins were upregulated in the skeletal muscle along with myofibroblast activation and increased deposition of distinct collagen subtypes. Interestingly, in contrast to the robust induction of TGF β , a classical activator of fibrosis, in myotubes in response to ethanol, this pathway was not activated in the gastrocnemius muscle of ethanol fed rats. Similarly, despite significant upregulation of a number of distinct extracellular matrix protein mRNA, these genes were not upregulated in the cardiac muscle from ethanol fed rat. These interesting observations show that ethanol effects *in vivo* are context and concentration dependent and contribute to skeletal muscle dysfunction in alcohol abuse. This important work adds to a growing body of literature demonstrating that alcohol abuse reprograms skeletal and cardiac muscle to negatively impact contractility and promote muscle wasting.

Alcohol Effects on Adipose Tissue and Lymphatics

In addition to effects in the intestine, and muscle there is a growing body of literature linking alcohol abuse to pathogenic remodeling of adipose tissue. Excessive alcohol use has been linked to alterations in the normal metabolic and endocrine function of adipose tissue (Kama et al., 2015). A recent study has provided new insight linking intestinal effects of alcohol to adipose tissue dysfunction. In this important paper Souza-Smith and colleagues examined the effects of intragastric infusion of ethanol on lymphatic and peri-lymphatic structure in rats, and discovered that acute alcohol administration increases mesenteric lymphatic permeability. Interestingly, acute alcohol administration was also associated with the recruitment of mast cells and neutrophils into perilymphatic adipose tissue and reduced adiponectin levels (Souza-Smith et al., 2015). This work suggests that hyperpermeability of intestinal lymphatics may promote perilymphatic adipose tissue dysfunction, which provides yet another potential therapeutic target for ALD.

Conclusions

Given its central role in ethanol metabolism, the liver is uniquely positioned for alcohol-induced tissue injury. However, emerging evidence suggests that the extrahepatic effects of ethanol are also important for providing the additional hits necessary for progression of ALD towards end stage liver disease. There is now little doubt that intestinal effects of alcohol including microbial dysbiosis, gut “leakiness”, and lymphatic hyperpermeability are key players in the progression of ALD. In parallel, the effects of alcohol on skeletal muscle wasting also plays a major role in ALD morbidity and mortality. Here we have highlighted a few seminal new discoveries that put forth potentially paradigm shifting ideas. These studies clearly suggest that studying the deleterious effects on alcohol abuse outside of the liver has great promise to lead to effective therapies for those suffering from ALD.

Acknowledgments

This work was supported several grant from the National Institutes of Health (NIH) including the NIAAA-funded Northern Ohio Alcohol Center grant P50-AA024333 (S.D. and J.M.B), U01AA021893 (S.D.), R21 AA022742 (S.D.), R01 DK83414 (S.D.), and R01 HL122283.

References

- Chen P, Miyamoto Y, Mazagova M, Lee KC, Eckmann L, Schnabl B. Microbiota protects mice against acute alcohol-induced liver injury. *Alcohol Clin Exp Res*. 2015; 39:2313–2323. [PubMed: 26556636]
- Guirguis J, Chhatwal J, Dasarathy J, Rivas J, McMichael D, Nagy LE, McCullough AJ, Dasarathy S. Clinical impact of alcohol-related cirrhosis in the next decade: estimates based on current epidemiological trends in the United States. *Alcohol Clin Exp Res*. 2015; 39:2085–2094. [PubMed: 26500036]
- Hartman P, Seebauer CT, Schabl B. Alcoholic liver disease: the gut microbiome and liver cross talk. *Alcohol Clin Exp Res*. 2015; 39:763–775. [PubMed: 25872593]
- Kama VH, Mojerla NR, Khan I, Mandal P. Effect of alcohol on adipose tissue: a review on ethanol mediated adipose tissue injury. *Adipocyte*. 2015; 4:225–231. [PubMed: 26451277]
- Liang X, Bushman FD, Fitzgerald GA. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. *Proc Natl Acad Sci USA*. 2015; 112:10479–10484. [PubMed: 26240359]
- Souza-Smith FM, Siggins RW, Molina PE. Mesenteric lymphatic-perilymphatic adipose crosstalk: role in alcohol-induced perilymphatic adipose tissue inflammation. *Alcohol Clin Exp Res*. 2015; 39:1380–1387. [PubMed: 26147204]
- Steiner JL, Pruznak AM, Navaratnarajah M, Lang CH. Alcohol differentially alters extracellular matrix and adhesion molecular expression in skeletal muscle and heart. *Alcohol Clin Exp Res*. 2015; 39:1330–1340. [PubMed: 26108259]
- Tang Y, Zhang L, Forsyth CB, Shaikh M, Song S, Keshavarzian A. The role of miR-212 and iNOS in alcohol-induced intestinal barrier dysfunction and steatohepatitis. *Alcohol Clin Exp Res*. 2015; 39:1632–1641. [PubMed: 26207424]
- Thaiss CA, Levy M, Korem T, Dohnalova L, Shaprio H, Jaitin DA, David E, Winter DR, Gury-BenAri M, Tatrovsky E, Tuganbaev T, Federici S, Zmora N, Zeevi D, Dori-Bachash M, Pevsner-Fischer M, Kartvelishvili E, Brandis A, Harmelin A, Shibolet O, Halpern Z, Honda K, Amit I, Segal E, Elinav E. Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell*. 2016; 67:1495–1510.
- Thapaliya S, Runkana A, McMullen MR, Nagy LE, McDonald C, Naga Prasad SV, Dasarathy S. Alcohol-induced autophagy contributes to loss in skeletal muscle mass. *Autophagy*. 2014; 10:677–690. [PubMed: 24492484]
- Voigt RM, Summa KC, Forsyth CB, Green SJ, Engen P, Naqib A, Vitaterna MH, Turek FW, Keshavarzian A. The circadian clock mutation promotes intestinal dysbiosis. *Alcohol Clin Exp Res*. 2016; 40:335–347. [PubMed: 26842252]