



Alcohol and inflammatory responses: Highlights of the 2015 Alcohol and Immunology Research Interest Group (AIRIG) meeting



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ABSTRACT

On September 27, 2015 the 20th annual Alcohol and Immunology Research Interest Group (AIRIG) meeting was held as a satellite symposium at the annual meeting of the Society for Leukocyte Biology in Raleigh, NC. The 2015 meeting focused broadly on adverse effects of alcohol and alcohol-use disorders in multiple organ systems. Divided into two plenary sessions, AIRIG opened with the topic of pulmonary inflammation as a result of alcohol consumption, which was followed by alcohol's effect on multiple organs, including the brain and liver. With presentations showing the diverse range of underlying pathology and mechanisms associated with multiple organs as a result of alcohol consumption, AIRIG emphasized the importance of continued alcohol research, as its detrimental consequences are not limited to one or even two organs, but rather extend to the entire host as a whole.

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Introduction

A study conducted by the Centers for Disease Control and Prevention reports approximately 1 in 10 deaths among working adults from the years 2006–2010 was due to excessive alcohol use (Centers for Disease Control and Prevention, 2014). Furthermore, alcohol-abuse mortalities remain one of the leading preventable deaths (Centers for Disease Control and Prevention, 2014). Acute or

chronic alcohol use can drastically increase patients' susceptibility to multiple co-morbidities, including asthma, lung injury, liver disease or injury, and neuronal dysfunctions (Crews, Zou, & Qin, 2011; Kim et al., 2001; Teng & Molina, 2014; Ware et al., 2007; Wyatt et al., 2012; Yeligar, Machida, Tsukamoto, & Kalra, 2009). Due to the critical importance of understanding these alcohol-attributed pathologies, the Alcohol and Immunology Research Interest Group (AIRIG) made these topics the basis of the 2015 meeting.

The AIRIG satellite symposium was divided into two plenary sessions, each with a distinct focus: the first on the effects of alcohol use on pulmonary inflammation and repair mechanisms following lung injury and the second on multiple-organ responses to alcohol

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exposure, including the brain and the liver. Fostering collaborative relationships and promoting scientific discourse among alcohol researchers remains critical to bridge gaps in knowledge in such an expansive field while opening new avenues for potentially unrecognized treatment options for patients suffering from exacerbated symptoms as a result of alcohol abuse. Only with symposia, such as the AIRIG satellite meeting at the Society for Leukocyte Biology's conference, can these important relationships not only be created but also more importantly sustained into the future.

Alcohol and the lung

Dr. Elizabeth J. Kovacs, formerly at Loyola University Chicago and now at the University of Colorado Denver, opened the 2015 AIRIG meeting with words of welcome, admiration, and respect for the many alcohol researchers present and ready to both share their own data and learn about new advancements in the field of alcohol research. This was followed by the first plenary session chaired by Dr. Brenda Curtis (formerly at Loyola University Chicago and now at the University of Colorado Denver) and Michael Price (University of Nebraska Medical Center), where researchers presented their work on the effects of alcohol on pulmonary inflammation in a variety of disease states. Dr. Daniel G. Remick of Boston University opened the session discussing how alcohol ingestion acts as an asthma trigger. Asthma affects 300 million people worldwide and, of those, 250,000 die each year from the disease ([World Health Organization, 2016](#)). Therefore, Dr. Remick and his group utilized a standard murine model of asthma using cockroach allergen (CRA), which requires an initial immunization of CRA followed by a challenge of CRA to induce the asthmatic disease state. Asthma induction was characterized histologically by an inflammatory infiltrate into the bronchoalveolar lavage (BAL) fluid and by symptomatically utilizing whole body plethysmography to show airway hyper-reactivity after CRA challenge ([Kim et al., 2001](#)). Interestingly, previous work showed that alcohol consumption actually suppresses pulmonary inflammation resulting from asthma or pneumonia ([Oldenburg, Poole, & Sisson, 2012](#)). However, this was found to be true only following episodes of chronic alcohol exposure. The CDC reported that alcohol is the most widely abused drug among the youth population in the United States, with most alcohol consumption occurring in a binge pattern ([Centers for Disease Control and Prevention, 2014](#)). Therefore, the question was posed whether binge alcohol drinking could act as an asthma trigger in CRA-sensitized mice. Dr. Remick reported that a binge alcohol paradigm given to CRA-sensitized mice acted as an asthmatic trigger, increasing mucus production in the lung, hyper-reactivity, BAL inflammatory cell infiltrates, and elevated cytokine levels of IL-5, IL-13, and IL-4 in lung tissue homogenates just 30 min after gavage with alcohol ([Bouchard et al., 2012](#)). Binge alcohol consumption triggering an asthmatic episode was not found to be due to mast cell degranulation, but rather was due to increased leukotriene production. Preliminary data suggested that a leukotriene receptor antagonist would decrease the asthma-like pulmonary inflammation induced by acute alcohol ingestion in CRA-sensitized mice.

Dr. Samantha Yeligar from Emory University presented her work focusing on alcohol abuse impairing lung function leading to increased risk of respiratory infection in mice. Phagocytic dysfunction of alveolar macrophages (AMs) and thus impaired bacterial clearance after chronic alcohol abuse is a consequence of AMs undergoing a feed-forward loop of oxidative stress, involving reactive oxygen species (ROS), TGF- β , and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases ([Mehta, Yeligar, Elon, Brown, & Guidot, 2013](#); [Yeligar et al., 2009](#)). However, down-regulation of the NADPH oxidases (Nox) 1, 2, and 4 via peroxisome proliferator-activated receptor (PPAR) γ ligands, such as

pioglitazone (PIO), reduce oxidative stress. Studies were performed in a mouse model of chronic alcohol consumption in which mice were given ethanol (20% weight/volume) in drinking water for 12 weeks. PIO (10 mg/kg/day) was given by oral gavage during week 12 to determine whether this PPAR- γ ligand attenuated alcohol-induced AM dysfunction by down-regulating Nox proteins and subsequently decreasing AM oxidative stress. Dr. Yeligar showed that PIO administration activated PPAR- γ , which acts to down-regulate alcohol-induced increases in Nox 1, 2, and 4. Down-regulation of the Nox proteins led to reversal of ethanol's detrimental effects in AMs by decreasing oxidative stress, increasing mitochondrial oxygen consumption rates, and increasing phagocytic capacity. Therefore, therapeutic intervention with PIO or other PPAR- γ ligands during chronic alcohol-use disorders could potentially reduce patient susceptibility to respiratory infections.

Lauren Poole, a graduate student from the laboratory of Dr. Gavin Arteel at the University of Louisville School of Medicine, shared her studies on the role of plasminogen activator inhibitor-1 (PAI-1) in alcohol-mediated acute lung injury (ALI). Alcohol use continues to be a major risk factor in the development of acute respiratory distress syndrome (ARDS), the most severe form of ALI. Previous studies have demonstrated that ARDS occurs 3.7 times more frequently in people meeting the diagnostic criteria for alcohol-use disorders ([Moss, Bucher, Moore, Moore, & Parsons, 1996](#); [Ritzenthaler, Roser-Page, Guidot, & Roman, 2013](#)). Excessive alcohol exposure can damage target organs via mechanisms including inflammation, oxidative stress, and/or tissue remodeling. Lauren's work focused on the role of pulmonary transitional tissue remodeling occurring after acute injury, specifically how PAI-1 is upregulated during this tissue remodeling phase of ALI. A previous study has shown that heightened concentrations of PAI-1 in circulation correlate with increased mortality after lung injury ([Ware et al., 2007](#)). PAI-1 was also associated with enhanced inflammation and fibrosis in other models of ALI ([Arndt, Young, & Worthen, 2005](#)). Utilizing a mouse model of endotoxemia-induced ALI, Lauren showed that chronic alcohol feeding enhanced ALI. Enhanced ALI after chronic alcohol consumption was accompanied by elevated chemokines, macrophage inflammatory protein-2 (MIP) 2, and keratinocyte chemoattractant (KC). Interestingly, knockout of PAI-1 attenuated both the pulmonary damage and exaggerated expression of chemokines seen in alcohol-exposed mice given liposaccharide. These results suggest that PAI-1 is critical in mediating the enhanced pulmonary damage seen in ALI following chronic alcohol exposure, which provides insight into the mechanisms behind which alcohol damages remote organs such as the lung.

Dr. Ellen L. Burnham, from the University of Colorado Denver, presented her work on the connection between acute respiratory distress syndrome (ARDS) and alcohol-use disorders. She showed that elevated activity of xanthine oxidoreductase (XOR) in the lung triggered pulmonary oxidative stress. XOR expressed in AMs produces ROS along with uric acid. Both ROS and uric acid work as a danger signal and can induce a strong inflammatory response leading to lung fibrosis ([Gasse et al., 2009](#); [Wright et al., 2004](#)). It has been suggested that alcohol metabolism contributes to oxidative stress via XOR activity. Dr. Burnham and her group were able to show that not only are there higher levels of uric acid in the BAL fluid from patients with an alcohol-use disorder (AUD), but also that the AMs obtained from the BAL fluid express more XOR protein. These observations accompanied data showing enhanced XOR activity in both BAL fluid and serum of patients with AUDs. To further expand upon the findings of elevated XOR activity in subjects with AUD, XOR activity was examined in patients with ARDS. Patients with ARDS demonstrated increased XOR activity in both BAL cells and serum compared with healthy controls. Additionally, when XOR activity in BAL fluid obtained from ARDS patients was

compared to that of healthy patients with AUDs, BAL cell XOR activity was similar between AUD subjects and ARDS patients, but substantially higher than in healthy controls. Together, these data point to a potential additive impact of AUDs on ARDS.

Ending the morning session, Dr. Todd A. Wyatt, from the University of Nebraska Medical Center, shared his work on the existent co-morbidity of impaired lung repair and function resulting from combined AUDs and cigarette smoking. Among AUD-positive subjects, 90–95% also smoke cigarettes (Patten, Martin, & Owen, 1996; Sapkota & Wyatt, 2015). Previous work has shown that the alcohol consumption combined with exposure to cigarette smoke resulted in decreased mucociliary clearance, increased detachment of ciliated cells, impaired wound healing, and enhanced lung inflammation (Elliott, Sisson, & Wyatt, 2007; Wyatt et al., 2012). Surprisingly, under the paradigm of combined alcohol and cigarette exposure, Dr. Wyatt and his group found that several anti-microbial and T-cell chemotactic cytokines in mouse whole-lung lavage were decreased when compared to that of either exposure alone. They utilized the Meadows-Cook *ad libitum* alcohol feeding model combined with the Teague whole-body smoke exposure system in their studies. Many chemokines (CXCL4, CCL17, CCL19, CCL24, CCL25, CCL27), cytokines (IL-4, IL-10), and some growth factors and hormones (3, IGFBP-5, IGFBP-6, leptin, SCF) were significantly reduced in lavage fluid of mice receiving combined insult of alcohol and cigarette smoke. Together, these data suggest that the combination of smoking cigarettes and drinking alcohol can alter the cytokine response, which then can modulate the lung repair processes that would otherwise occur in exposure to either alcohol or smoking alone.

Alcohol and multi-organ responses

The second plenary session was chaired by graduate students Tasha Barr, from the laboratory of Dr. Ilhem Messaoudi at the University of California Riverside, and Niya Morris, from the laboratory of Dr. Mashkooor Choudhry at the University of Loyola Chicago. In this session, the discussion shifted from the effects of alcohol on lung injury to that of alcohol's adverse effects on the liver, muscle, and brain. Dr. Patricia Molina of Louisiana State University Health Sciences Campus opened the session discussing alcohol–neuroimmune interactions in a model of traumatic brain injury (TBI) via lateral fluid percussion (LFPI), and how neuroinflammation-mediated changes in behavior can lead to increased alcohol consumption (Crews et al., 2011). Dr. Molina and her group found that, using a model of chronic intermittent alcohol vapor exposure (CIEV), acute alcohol intoxication at the time of TBI resulted in greater impairment of short-term outcomes from TBI, including apnea, respiratory rate, and righting reflexes when compared to TBI delivered in the absence of alcohol. Additionally, following TBI in the absence of alcohol there was increased expression of IL-6, TNF- α , IL-1 β , and MCP-1 mRNA in the ipsilateral cortex that resolved within 12 h, indicating short-term inflammation, whereas animals that were subjected to acute alcohol intoxication at the time of TBI displayed increased expression of these same proinflammatory cytokines 24 h post-injury suggesting that alcohol inhibited the resolution of the inflammation seen after TBI alone at the 24-h time point (Teng & Molina, 2014). In another set of studies, it was found that when CIEV was administered after TBI (as opposed to earlier studies when acute alcohol intoxication was produced pre-injury), there was impaired neurologic recovery following TBI, which persisted even after CIEV was discontinued. TBI is associated with increased numbers of both astrocytes and microglia at the site of injury. However, Dr. Molina and her group observed a more dramatic elevation in the activation of astroglia and microglia after the combined insult of CIEV and TBI.

Interestingly, the increase in neurological severity scores in animals exposed to CIEV after TBI positively correlated with increased neuroinflammation, suggesting a possible relationship between inflammation and behavioral changes. Neuroinflammation is now thought to be a correlate to many neurological and neurodegenerative diseases including Alzheimer's, Parkinson's, and depression/anxiety – diseases that are often associated with behavioral abnormalities. Because of this, it comes as no surprise that TBI, which results in sustained neuroinflammation, has also been associated with behavioral changes including increased alcohol and drug use. In a third set of studies, Dr. Molina and her group used a model of operant self-administration to examine changes in voluntary alcohol drinking following TBI. In these studies, it was observed that TBI caused escalated alcohol self-administration while maintaining increased astrogliosis and microglial activation. Finally, Dr. Molina and her group found that reducing neuroinflammation using an endocannabinoid degradation inhibitor (JZL184) administered once (16 mg/kg, 30 min post-TBI) could accelerate recovery from TBI by restoring the blood brain barrier, and limiting astrogliosis and microglial activation, and consequently improving behavioral outcomes. Collectively, these studies showed that alcohol exposure, whether acute at time of TBI or chronically following TBI, drastically increased neuroinflammation and impaired neurobehavioral recovery.

Kaku So-Armah, junior faculty at Boston University School of Medicine (mentored by Dr. Jeffrey Samet), shared his work investigating mechanisms of immunosenescence in a cohort of HIV-infected Russians with a recent history of heavy drinking prior to the initiation of antiretroviral therapy (ART). HIV-infected individuals may have a form of accelerated aging of the immune system (Deeks, 2011). Combined with HIV infection, the excessive alcohol use and viral hepatitis in this patient population could lead to poorer outcomes. Dr. So-Armah analyzed 250 ART-naive HIV-infected Russians with a recent history of heavy drinking to determine whether liver injury, as assessed by a high fibrosis-4 (FIB4) score, had levels of T-cell subsets consistent with immunosenescence, i.e., higher CD28-CD57+ and lower naive-to-memory T-cell ratios for CD8+ and CD4+ T cells. Patients with elevated FIB4 scores had higher HIV viremia and HCV levels when compared to patients with lower FIB4 scores. However, in ART-naive HIV-infected Russians with a recent history of heavy drinking, elevated FIB4 scores did not correlate with these T-cell phenotypes associated with immunosenescence.

Trinidad Cisneros, a graduate student at Stanford University from the laboratory of Dr. Olivia Martinez, discussed the use of stem cell-derived hepatoblasts (SC-DH) as a potential alternative to treat alcoholic liver disease. The presentation highlighted a novel system for generating SC-DH from murine embryonic and induced pluripotent dual-reporter transgene+ stem cells, which has the added benefit of facilitating *in vivo* fate tracking and post-mortem evaluation. Both morphological and functional features of the hepatic lineage are present in SC-DH cells 13 days post-differentiation. Finally, following transplantation, the hepatoblasts survived and could be monitored by bioluminescent imaging. Together, these data provide evidence that stem cell-derived hepatoblasts could serve as a potential treatment for chronic alcoholic liver disease.

Dr. Guoshun Wang, from Louisiana State University Health Sciences Center in New Orleans, LA, shared his work on Glucocorticoid-Induced Leucine Zipper (GILZ) activation as a potential mechanism behind the immunosuppression seen following alcohol intoxication. GILZ acts as a glucocorticoid- (GC) responsive gene, which mediates anti-inflammatory and immunosuppressive processes. It is well documented that alcohol abuse suppresses immunity, which allows for increased susceptibility to infection (Keshavarzian et al., 1999; Wang et al., 2014; Wood et al.,

2013). Acute alcohol exposure at a binge-drinking level (50 mM or 100 mM) for 24 h induced GILZ expression in multiple cell types, including primary human airway epithelial cells, human umbilical vein endothelial cells (HUVEC), human peripheral blood monocytes, A549 cells, and BEAS-2B cells. The alcohol-upregulation of GILZ was through a non-canonical activation of glucocorticoid receptor signaling, which involved no glucocorticoids. Considering downstream effects of GILZ induced by alcohol, Dr. Wang went on to discuss how the elevated levels of the pro-inflammatory cytokine TNF- α in LPS-stimulated Mono-mac-6 cells, a human monocyte cell line, was suppressed after exposure to alcohol. Depletion of GILZ via small RNA interference abolished the alcohol suppression of TNF- α production, suggesting that alcohol suppression of the monocyte response to LPS is mediated through induction of GILZ via non-canonical activation of the glucocorticoid receptor signaling.

Dr. Charles Lang of the Penn State College of Medicine rounded out the afternoon session, sharing his work on the effects of alcohol on the central nervous system (CNS), and how such effects regulate peripheral muscle metabolism. Chronic alcohol abuse leads to various biochemical and functional myopathies, and although the etiology remains unclear, data from the Lang lab clearly demonstrate the central role played by the inhibition of mechanistic target of rapamycin (mTOR)-kinase activity following both acute and chronic alcohol exposure. To assess the direct effects of alcohol on the CNS, alcohol was administered via intracerebroventricular (ICV) injection. Dr. Lang and his group showed that ICV alcohol exposure decreased skeletal muscle protein synthesis, and that this was a direct CNS effect of alcohol and not a result of alcohol metabolites. This was demonstrated using a non-metabolizable alcohol, *t*-butanol, and by inhibiting catalase, the enzyme responsible for metabolizing alcohol in the brain, which failed to trigger an alcohol-mediated decrease in skeletal muscle protein synthesis. The normal anabolic response of muscle protein synthesis to the amino acid leucine was also blunted in rats given ICV infusion of alcohol, and again the mechanism for this alcohol effect was mTOR-dependent. Since protein balance requires both *de novo* synthesis and protein degradation, Dr. Lang and his group examined effects of ICV alcohol infusion on muscle proteolysis and found an increased in proteolysis and proteosomal activity. The mechanism by which ICV alcohol infusion produces long-term changes in muscle protein synthesis did not involve continued stimulation of the hypothalamic-pituitary-adrenal axis, as adrenocorticotropic hormone levels were only transiently elevated. It was found, however, that ICV alcohol infusion selectively stimulated muscle sympathetic nerve activity. The neuronal mechanism regulating the protein synthesis and degradation after ICV alcohol exposure still needs to be fully elucidated, but these data suggest that alcohol, through its effects on the CNS, has the ability to regulate the metabolism of peripheral organs in general and to stimulate muscle protein wasting in particular.

Summary

The 2015 AIRIG satellite symposium allowed presenters to share their novel data regarding how alcohol potentiates adverse pathophysiologies in the lung, brain, muscle, and liver. Experimental data shared at the meeting demonstrated that alcohol increases the severity of respiratory syndromes, such as asthma-like symptoms and acute respiratory distress syndrome, and the susceptibility to lung infection, while it limits normal lung repair mechanisms following injury. Moreover, alcohol induced excessive neuroinflammation and had a negative impact on TBI. Additionally, alcohol exposure can lead to immunosuppression, which can increase susceptibility to infection in the liver and other organ systems. Together, these data not only demonstrate

the widespread adverse effects of alcohol on disease progression, but also show the continued need for the inclusion of both acute and chronic alcohol models, as many questions remain unanswered.

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