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

Abigail R. Cannon [a,b], Niya L. Morris [a,b], Adam M. Hammer [a,b], Brenda Curtis [a], Daniel G. Remick [d], Samantha M. Yeligar [e], Lauren Poole [f], Ellen L. Burnham [g], Todd A. Wyatt [h,i], Patricia E. Molina [j], Kaku So-Armah [k], Trinidad Cisneros [l], Guoshun Wang [m], Charles H. Lang [n], Pranoti Mandrekar [o], Elizabeth J. Kovacs [a,b,c], Mashkoor A. Choudhry [a,b,c,*]

[a] Department of Surgery, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA
[b] Integrative Cell Biology Program, Loyola University Chicago Health Sciences Division, Maywood, IL, USA
[c] Department of Microbiology and Immunology, Loyola University Chicago Health Sciences Division, Maywood, IL, USA
[d] Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA, USA
[e] Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Atlanta Veterans Affairs and Emory University Medical Centers, Decatur, GA, USA
[f] Department of Pharmacology and Toxicology, University of Louisville School of Medicine, Louisville, KY, USA
[g] Department of Medicine, University of Colorado, Aurora, CO, USA
[h] Division of Pulmonary, Critical Care, Sleep and Allergy, University of Nebraska Medical Center, Omaha, NE, USA
[i] Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, NE, USA
[j] Department of Physiology, Louisiana State University Health Science Center, New Orleans, LA, USA
[k] Department of Medicine, Boston University School of Medicine, Boston, MA, USA
[l] Department of Surgery, Stanford University, Stanford, CA, USA
[m] Department of Microbiology and Immunology, Louisiana State University Health Sciences Center, New Orleans, LA, USA
[n] Department of Cellular and Molecular Physiology, Pennsylvania State College of Medicine, 500 University Drive, Hershey, PA, USA
[o] Department of Medicine, University of Massachusetts Medical Center, Worcester, MA, USA

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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.

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

* Corresponding author. Department of Surgery, Burn & Shock Trauma Research Institute, Loyola University Chicago Health Sciences Division, 2160 South First Ave., Maywood, IL 60153, USA. Fax: +1 708 327 2813.
E-mail address: mchoudhry@luc.edu (M.A. Choudhry).

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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 give 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- (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 lipopolysaccharide. 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