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Alcohol and Inflammation & Immune Responses:

Summary of the 2006 Alcohol and Immunology Research Interest Group (AIRIG) meeting

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Abstract

The 11th annual meeting of the Alcohol and Immunology Research Interest Group (AIRIG) was held at Loyola University Medical Center, Maywood, Illinois on November 17, 2006. The AIRIG meeting is held annually to exchange new findings and ideas that arise from ongoing research examining the effects of alcohol intake on the immune system. The event consisted of five sessions, two of which featured plenary talks from invited speakers, two with oral presentations from selected abstracts, and a final poster session. Participants presented new data on a variety of topics including the effects of ethanol on key cells of the immune system (neutrophils, dendritic cells, NK cells), B cell responses, the capacity to clear infectious agents, and the barrier functions of skin, lung and intestine.

Keywords

Alcohol; Inflammation; Lung immunology; Skin immunology; Intestinal immunology

Introduction

It is well documented that excess alcohol intake results in compromised immunity and increased risk of infectious disease (Cook, 1998; Happel and Nelson, 2005; MacGregor and Louria, 1997; Messingham et al., 2002; Nelson and Kolls, 2002; Szabo, 1999). Not only have multiple deficiencies been associated with innate immunity, but with sufficient time on alcohol, clear dysfunction within the adaptive immune system has also been demonstrated. With these immune lesions well documented, research is increasingly focusing on ethanol-induced defects in specific functions, cells and molecules of both innate and adaptive immunity. In addition, studies are testing immune competence of organs outside the primary and secondary lymphoid organs after alcohol ingestion, and examining sites such as skin, lung and intestine. Importantly, investigators are coupling knowledge gained from these experiments with model systems exploring immune responses to specific infectious agents that typically cause disease in human alcoholics.

Many of these issues were addressed at the 11th meeting of the Alcohol and Immunology Research Interest Group (AIRIG) held at Loyola University Medical Center on November 17,

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2006. The meeting was supported by an R13 grant from the National Institute on Alcohol Abuse and Alcoholism (AA016751) and by funds from the Department of Surgery at Loyola University Medical Center. The meeting was organized by Dr. Elizabeth J. Kovacs (Loyola University Medical Center), Dr. Luisa A. DiPietro (University of Illinois, Chicago), Dr. Lou Ann S. Brown (Emory University School of Medicine), Dr. Robert T. Cook (University of Iowa College of Medicine), Dr. Thomas R. Jerrells (University of Nebraska Medical Center) and Dr. Thomas J. Waldschmidt (University of Iowa College of Medicine). The day consisted of four sets of oral presentations and a poster session. Two of the oral sessions featured invited speakers and two consisted of presentations from selected abstracts. Abstracts for all oral and poster presentations were previously published in this journal (*Alcohol* 39, 112-117).

Alcohol and Immunity

The first plenary session, chaired by Drs. Lou Ann Brown and Robert Cook, featured presentations that explored the effects of alcohol on basic mechanisms of innate and adaptive immunity. Dr. Carl Waltenbaugh, Northwestern University School of Medicine, summarized a number of studies from his laboratory detailing how short-term ethanol exposure (1-2 weeks) compromises T helper cell 1 (Th1) driven delayed type hypersensitivity (DTH) reactions in mice (Heinz and Waltenbaugh, 2007; Latif et al., 2002; Wang et al., 2001). This was demonstrated using both an ear swelling model as well as graft rejection to a minor (HY) antigen. Dr. Waltenbaugh presented further data showing a 2-3 fold increase in total serum IgE after a similar schedule of alcohol feeding. The increase in IgE was independent of immunization and shown to be generated by conventional (B2) B cells. Further experiments suggested that diminished DTH activity and increased IgE levels after ethanol consumption may derive from the impaired ability of CD11c⁺CD8α⁺ dendritic cells (DC) to support Th1 cell formation (Heinz and Waltenbaugh, 2007). DC dysfunction was proposed to arise from glutathione depletion and resulting oxidative stress.

Dr. Gary Meadows from Washington State University provided an overview of his work exploring the effects of chronic ethanol intake on NK cell maintenance in mice. Using a model whereby alcohol is provided in the drinking water for extended periods of time (Meadows et al., 1989; Meadows et al., 1992; Spitzer and Meadows, 1999; Zhang and Meadows, 2005), mice were shown to progressively lose NK cell numbers in the spleen while maintaining normal or elevated levels in the bone marrow. In order to understand the basis for this loss, experiments assessed production and expansion of NK cells in the bone marrow and spleen. *In vivo* BrdU incorporation studies demonstrated normal numbers of labeled NK cells in both organs of ethanol drinking mice; however, one month after BrdU cessation animals provided alcohol exhibited lower numbers of residual BrdU⁺ NK cells in the spleen. This finding suggested a failure to maintain NK cells and further studies indicated increased rates of apoptosis to account for this observation. Given the importance of IL-15 in NK cell homeostasis (Ma et al., 2006), Dr. Meadows documented a decrease of IL-15 expressing cells in the spleens of chronic ethanol mice. Final studies explored whether delivery of IL-15 (in combination with IL-15 receptor alpha chain) to alcohol drinking mice would restore NK cell numbers. IL-15 supplementation did indeed provide benefit, as NK cell values were returned to normal and elevated rates of apoptosis in this population were reversed.

Michael Shey from the University of Iowa College of Medicine also presented data on NK cell recovery and function using the same mouse model of ethanol consumption. When examining mice after relatively short periods on ethanol (1-2 weeks) splenic NK cell numbers were found to be depressed. This drop in numbers directly correlated with NK cell function *in vitro*, as both IL-2 and CpG treated cells exhibited lower lytic activity compared with splenocytes obtained from control (water only) mice. Of interest, splenic NK cell numbers and functional activity recovered after 4-8 weeks of alcohol treatment. There appears therefore, to be a biphasic

response to ethanol intake in mice with diminished splenic NK cell number and activity early after initiation of alcohol drinking followed by recovery at intermediate time points.

The last presentation in this session was given by Audrey Lau, University of Pittsburgh Medical Center. Using the ethanol in water chronic model, previous studies from this group demonstrated splenic DC from alcohol mice to exhibit poor induction of co-stimulatory molecules after CpG activation along with a reduced capacity to stimulate T cells (Lau et al., 2006). This was not found with activated hepatic DC after extended ethanol consumption, as these cells displayed normal levels of co-stimulatory markers and enhanced T cell stimulatory ability. To further these observations, studies were performed to explore the migratory capacity of splenic and hepatic DC taken from mice after 8 weeks of ethanol intake (Lau et al., 2007). DC were thus isolated, labeled with CFSE and injected into the footpad of naïve recipient mice. Donor DC were enumerated in draining lymph nodes 24 hours later. Of interest, chronic ethanol exposure increased the migratory capacity of hepatic DC compared with DC from water control mice. This held true whether the DC were freshly obtained or activated with CpG prior to injection.

Ethanol had no effect on splenic DC in the same assay. Additional experiments demonstrated the enhanced migratory ability of hepatic DC to be independent of CD11a or CCR7 expression. Consistent with the differential effects of alcohol consumption on hepatic and splenic DC, final studies showed ethanol to lower expression of CD209 (DC-SIGN) on splenic DC (both baseline and activated) but to have no effect on DC obtained from the liver. Taken together, these studies document different functional effects of chronic ethanol intake on splenic and hepatic DC, with the former being impaired by alcohol and the latter largely resistant.

Alcohol and Injury & Infection

The second plenary session was chaired by Drs. DiPietro and Jerrells and centered on heightened susceptibility to infectious disease after ethanol exposure, with a focus on pneumonia. The first presentation was given by Dr. Gregory Bagby from Louisiana State University Health Sciences Center and focused on impaired innate lung responses to bacterial infection after alcohol consumption. Using a rat model, studies demonstrated an acute dose of ethanol to impair neutrophil recruitment to the lung after intratracheal bacterial challenge (Boe et al., 2001; Boe et al., 2003; Quinton et al., 2005). The defective granulocytic response was accompanied by reduced pro-inflammatory cytokine production in alcohol dosed rats as evidenced by diminished levels of TNF- α , CXC chemokines [cytokine-induced neutrophil chemoattractant (CINC) and MIP-2], IL-12, IL-17 and IL-23 in bronchoalveolar lavage fluid after bacterial exposure (Boe et al., 2001; Boe et al., 2003; Quinton et al., 2005). In an attempt to counter the effects of ethanol, experiments were performed whereby G-CSF, IFN- γ , or CINC/MIP-2 (Quinton et al., 2005) was delivered either systemically or intratracheally followed by bacterial challenge. G-CSF and CXC chemokine therapy variably restored neutrophil recruitment and IFN- γ intervention normalized the pro-inflammatory response also leading to enhanced neutrophil migration. Dr. Bagby further summarized data from another model in which mice ingesting ethanol for 5 weeks were given a bolus injection of alcohol (binge after chronic exposure). Shortly after bolus injection, mice were challenged intratracheally with *S. pneumoniae*. Whereas control mice respond to bacterial challenge with increased G-CSF release, production of bone marrow neutrophils and recruitment of these cells to the lung, mice provided ethanol exhibited a much lower response resulting in significantly fewer neutrophils in the lung. Collectively, these findings underscore the marked negative effect ethanol consumption has on neutrophil recruitment during pulmonary bacterial infection.

Dr. David Guidot, Emory University, presented work exploring the basis of lung macrophage dysfunction induced by long-term ethanol consumption. Examining alveolar macrophages

from rats after 6 weeks of alcohol intake, Dr. Guidot and co-workers demonstrated these cells to be functionally immature as measured by phagocytic activity as well as cytokine and chemokine production after LPS treatment (Brown et al., 2007; Joshi et al., 2005). Of interest, these investigators found lower expression levels of GM-CSF receptors on alveolar macrophages from ethanol consuming rats (Joshi et al., 2005). Since GM-CSF mediated signals are critical for functional competence of macrophages, further studies examined endogenous levels of PU.1, a transcription factor central in mediating GM-CSF driven activities. Consistent with poor macrophage function and lower GM-CSF receptor levels, PU.1 levels and activity were diminished within alveolar macrophages from ethanol fed rats (Joshi et al., 2005). To assess whether administration of GM-CSF to ethanol fed rats might reverse these defects, rGM-CSF was given via the upper airway to rats after extend time on alcohol. rGM-CSF treatment enhanced GM-CSF receptor levels and PU.1 activity, and importantly, helped restore the functional competence of alveolar macrophages (Joshi et al., 2005). In addition to affecting macrophage GM-CSF receptors and PU.1 activity, ethanol was found to reduce levels of these molecules in airway epithelium as well (Joshi et al., 2006). Although the reason for lower GM-CSF mediated activity in the lung after ethanol intake is unclear, a model was proposed whereby alcohol elevates angiotensin II leading to chronic oxidative stress, reduced glutathione levels and interestingly, increased production of TGF- β 1. Excess TGF- β 1 activity appears to downregulate GM-CSF receptors leading to the compromised state of lung macrophages and epithelial cells (Joshi et al., 2007).

The next talk was given by Dr. Martha Gentry-Nielsen from Creighton University and summarized results from a rat model testing the combined effects of ethanol and smoke on innate immune responses in the lung. Since most patients who abuse alcohol also smoke, this model was established to ask whether smoking exacerbates the deleterious effects of chronic alcohol on immune function (Gentry-Nielsen et al., 2006). Rats were therefore exposed to smoke twice daily for a total of 8 weeks and provided ethanol in a liquid diet during the last 7 days of the smoking regimen. At the end of 8 weeks, mice were given a dose of LPS intratracheally to induce neutrophil recruitment, followed five hours later by intratracheal challenge with *Streptococcus pneumoniae* (Vander Top et al., 2006). Short term alcohol intake, alone or with smoking, did not alter the ability of LPS to recruit neutrophils into the lung, nor did either treatment affect the ability of neutrophils to phagocytize bacteria. When examining the capacity of recruited neutrophils to kill bacteria, ethanol consumption alone resulted in a significant loss of bactericidal activity in the lung, a defect that was reversed when alcohol was provided along with smoking. To understand the basis for this observation, further studies assessed chemokine levels in both lung and serum. The results demonstrated that exposure to both smoking and ethanol increased lung and serum CINC compared to rats given alcohol alone. Although the mechanism by which this occurs is unclear, the combination of smoking and ethanol apparently enhances local chemokine production in the lung thereby facilitating neutrophil activity and reversing the immune deficit caused by alcohol alone (Vander Top et al., 2006).

The last speaker in this session was Dr. Michael Sander from Charite University Medicine Berlin in Germany. Dr. Sander summarized a number of studies examining outcomes and immune parameters in alcoholic and non-alcoholic patients after major surgery. Previous work from this group established that chronic alcoholics have longer hospital (intensive care unit) stays and increased rates of post-operative infection, especially pneumonia (Sander et al., 2002; Sander et al., 2005; Spies et al., 2004). These studies also showed alcoholic patients to have reduced ratios of CD4⁺ Th1 to Th2 cells, CD8⁺ Tc1 to Tc2 cells and pro-inflammatory (IL-6 and IFN- γ) to anti-inflammatory (IL-10) cytokines. In addition to altered immune function, they further demonstrated chronic alcoholics undergoing surgery to exhibit elevated post-operative cortisol levels compared with non-alcoholic patients (Sander et al., 2005; Spies et al., 2004). The combined effect of skewed immune responses (towards an anti-inflammatory

bias) and hypercortisolism in alcoholics clearly has an impact on immune competence and likely accounts for the significantly higher rates of infection and longer hospital stays. In order to achieve better outcomes, Dr. Sander and colleagues treated alcoholics with agents known to affect the hypothalamus-pituitary-adrenal axis with the goal of reducing the post-operative cortisol spike (Spies et al., 2006). Whether using low dose ethanol, morphine or ketoconazole, alcoholic patients had lower cortisol levels and tended towards a pro-inflammatory immune profile after surgery. Importantly, these patients had lower infection rates and shorter stays in the intensive care unit (Spies et al., 2006). Finally, Dr. Sander summarized data from a mouse model of ethanol exposure designed to explore some of the same issues in mice (Lanzke et al., 2007). Animals were provided daily injections of ethanol for a week, after which they were challenged intranasally with *Klebsiella pneumoniae*. Alcohol exposed mice infected with *K. pneumoniae* exhibited altered frequencies of cytokine producing splenic CD4⁺ and CD8⁺ T cells compared with infected animals that did not receive ethanol. Specifically, T cells from alcohol injected and *K. pneumoniae* challenged mice produced lower levels of IFN- γ but higher amounts of TNF- α again demonstrating the ability of ethanol exposure to alter cytokine responses after infection.

Short presentations

As a complement to the plenary speakers, two sessions were organized to feature podium presentations selected from a number of abstracts submitted by meeting participants. These talks covered a range of topics exploring dysfunction in innate and adaptive immunity after ethanol exposure. The first session was chaired by Dr. Elizabeth Kovacs and was led off by Dr. Kevin Legge from the University of Iowa. Dr. Legge presented work examining the ability of mice to respond to infection with influenza A after long term ethanol intake. Whereas low dose (0.01LD₅₀) intranasal challenge with influenza virus minimally affected control mice, infection of animals after 4 or 8 weeks of alcohol intake (ethanol in water regimen) resulted in significant morbidity (weight loss) and mortality (up to 50%). Examination of the pulmonary immune system revealed lower numbers of influenza-specific CD8⁺ T cells, as measured by either tetramer or intracellular IFN- γ staining, as well as compromised migration of respiratory dendritic cells to the draining lymph nodes after infection. These results clearly indicate that chronic ethanol exposure weakens the pulmonary immune system and predisposes towards severe disease after influenza infection. Rhonda Brand, Evanston Northwestern Hospital, summarized her research testing the effect of ethanol consumption on the barrier function of the skin. Rats were provided ethanol either acutely by gavage (Brand et al., 2006) or chronically (up to 12 weeks) using a liquid diet (Brand et al., 2004) and subsequently tested for transdermal penetration of xenobiotics. Both chronic and acute exposure to alcohol resulted in increased penetration of chemicals such as paraquat, N,N-diethyl-m-toluamide (DEET), dimethyl formamide and 2,4-Dichlorophenoxyacetic acid (2,4-D). In order to reveal the means by which ethanol compromises skin barrier integrity, Dr. Brand measured dermal blood flow and transepidermal water loss after alcohol exposure (Brand et al., 2007). Both acute and chronic ethanol administration increased dermal blood flow whereas only chronic intake increased transepidermal water loss. As the latter is a measure of lipid integrity within the stratum corneum, further studies examined the level of lipid peroxidation in the skin. A modest increase in lipid peroxidation was observed, suggesting ethanol to damage lipid structure by way of oxidative stress. Final studies indicated alcohol-induced damage in the skin to persist for a period of time after ethanol was withdrawn.

The second session was chaired by Dr. Thomas Waldschmidt and featured three short presentations examining altered innate immunity after alcohol exposure in rodents. Dr. Ping Zhang from Louisiana State University Health Sciences Center discussed his work exploring the mechanism by which ethanol suppresses neutrophil recruitment to the lung after pulmonary infection with bacteria. These studies utilized the same model described by Dr. Bagby (see

above in summary of the second plenary session), in which mice were provided ethanol by liquid diet for 5 weeks, given a bolus injection of alcohol (acute after chronic exposure) and challenged intratracheally with *S.pneumoniae*. To understand the basis for poor recruitment of neutrophils to the lung in these mice after bacterial challenge, Dr. Zhang examined the G-CSF signaling pathway in bone marrow cells. Lung infection typically generates systemic G-CSF which increases production and release of bone marrow derived neutrophils. In addition to promoting myelopoiesis, G-CSF can also diminish proliferation by activating (via phosphorylation) STAT3 which in turn increases transcription of p27^{Kip1} (de Koning et al., 2000). The latter is known to cause G1 arrest and hence aids in determining the balance between differentiation and proliferation of myeloid cells. Importantly, levels of phosphorylated STAT3 and p27^{Kip1} were found to be elevated in bone marrow cells obtained from infected mice exposed to ethanol. This result suggests that alcohol intake alters the biochemical response to G-CSF leading to poor expansion of neutrophil precursors. Eva Murdoch from Loyola University Medical Center presented findings examining the combined effect of acute alcohol and burn injury on susceptibility to pulmonary infection. Using a mouse model, animals were given a bolus injection of ethanol followed by burn injury (approximately 15% of body area). Mice were then challenged with *Pseudomonas aeruginosa* intratracheally and examined 48 hours later. Although more than half the group that received burn injury alone survived the infection, greater than 80% mortality was observed in those animals receiving both alcohol and burn injury. Consistent with this outcome, lungs obtained from ethanol and burn injury treated mice harbored greater numbers of bacteria than those infected after burn injury alone. In addition, histologic assessment of lung tissue from infected mice after both alcohol and burn injury treatment revealed significant infiltrate, with neutrophils comprising a large proportion of the inflammatory cells. These data clearly show that ethanol intake proximal to burn injury predisposes towards increased susceptibility to bacterial infection. The final presentation in this session was given by Dr. Xiaoling Li from the University of Alabama at Birmingham. Dr. Li also examined the combined effects of ethanol and burn injury on immunity integrity, with a focus on the intestinal tract. In these studies, rats were provided acute alcohol by gavage followed by burn injury (25% of body area). Intestinal tissue was harvested 4 and 24 hours later, and edema, myeloperoxidase activity [MPO (as a measure of neutrophil content)] and IL-18 levels determined (Li et al., 2006; Rana et al., 2005). Compared with burn injury alone, the combined effects of acute ethanol and burn resulted in increased levels of tissue edema, MPO and IL-18 at both time points. Based on these results, it was hypothesized that alcohol and burn injury treatment results in elevated IL-18 in the intestine leading to neutrophil retention. The prolonged presence of neutrophils in this organ is believed to initiate tissue damage and edema. To test this hypothesis, ethanol and burn injury treated rats were administered an IL-18 inhibitor followed by assessment of intestinal MPO and tissue edema. IL-18 blockade resulted in reduced MPO and edema, suggesting this cytokine to be a key mediator of intestinal injury after the combination of acute alcohol and burn injury (Li et al., 2006; Rana et al., 2005).

In addition to the scientific presentations, Dr. Sam Zakhari from the National Institute for Alcohol Abuse and Alcoholism (NIAAA) gave an overview of scientific areas being targeted for funding by the NIAAA, as well as granting vehicles for young investigators. Dr. Zakhari focused on the Institute's interest in the effect of alcohol on epigenetic regulation. Further discussion centered on opportunities for trainees (F30, F31 and F32) and for young investigators (K99/00 and K award programs).

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