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Alcohol and Trauma: A Summary of the Satellite Symposium at the 30th Annual Meeting of the Shock Society

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Abstract

This article highlights the research presented at the Alcohol and Trauma Satellite Symposium at the 30th Annual Shock Society Annual Meeting. The satellite meeting was held on June 8th and 9th in Baltimore, MD. Its purpose was to discuss recent findings in the areas of alcohol and injury, including the effect of alcohol use on patients in the trauma unit of hospitals. The meeting consisted of three sessions, with plenary talks by invited speakers, short talks from selected abstracts, and a poster session. Participants presented data on the effects of alcohol on organ function, healing, and immune processes after a variety of injuries including burn, hemorrhagic shock, sepsis, and ischemia-reperfusion.

Keywords

alcohol; immune response; trauma-hemorrhage; injury; inflammation

Introduction

Alcohol consumption is a major risk factor for all types of injuries, such as falls, fires, drowning, assaults, suicides, and motor vehicle collisions (Driscoll et al., 2004; Hingson, 2004; McDonald et al., 2004). Almost half of alcohol-related deaths are due to injuries, with injuries resulting from motor vehicle collisions being the leading cause of death in alcohol-related incidents (Mokdad et al., 2004; Schermer, 2006). Additionally, excessive alcohol consumption is the third leading cause of preventable death in the United States (Mokdad et al., 2004). Alcohol is known to cause changes in the physiological response following trauma leading to increased complications and mortality (Jones et al., 1991; Jurkovich et al., 1993; Madan et al., 1999; Spies et al., 1996; von Heymann et al., 2002). Alcohol also affects the immune system as numerous studies have demonstrated the detrimental effect of ethanol on immune function including decreased lymphocyte activation following antigen-stimulation, decreased neutrophil infiltration and phagocytic capability, and altered cytokine production by both T

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cells and macrophages (Cook, 1998; Jerrells et al., 1990; Kawakami et al., 1990; Messingham et al., 2002; Sibley et al., 2001; Szabo et al., 1998).

This meeting was designed to promote discussion and interaction among researchers studying the effect of alcohol on immune and physiological responses following trauma. It was sponsored by the Shock Society, the Society of Leukocyte Biology, the Alcohol Research Program, the Burn and Shock Trauma Institute, and the Department of Surgery at Loyola Medical Center in Maywood IL, the Alcohol Research Center and Department of Physiology at Louisiana State University Health Sciences Center in New Orleans, LA, and the Center for Surgical Research and Department of Surgery at University of Alabama at Birmingham in Birmingham, AL. Meeting co-organizers were Drs. Elizabeth Kovacs, Patricia Molina, and Mashkoor Choudhry. There were three plenary sessions with two presentations per session by invited speakers and several short talks from selected abstracts. Additionally a poster session was held on the second day to allow for further discussion between participants.

Alcohol and post-injury responses

Impact of binge ethanol on counter-regulatory mechanisms after hemorrhage shock

Patricia Molina, Louisiana State University Health Science Center—Acute alcohol intoxication is a frequent underlying condition associated with traumatic injury. The pathophysiology of traumatic-hemorrhagic injury involves hypovolemia- and hypoperfusion-mediated signaling to central cardiovascular centers involved in activation of descending autonomic neuro-endocrine pathways aimed at restoring hemodynamic stability (Molina, 2005). Acute alcohol intoxication also impairs the hemodynamic counter-regulatory response to hemorrhagic shock. A conscious rodent model of intragastric alcohol administration followed by fixed-pressure hemorrhagic shock (60 min at ~40 mmHg) and fluid resuscitation demonstrated that alcohol-treated animals had lower initial mean arterial blood pressure (MABP), showed a greater decrease in blood pressure in response to a given blood loss, and had a blunted pressor response to fluid resuscitation when compared to time-matched controls (Mathis et al., 2006; Phelan et al., 2002). It was hypothesized that this impaired hemodynamic response was the result of blunted hemorrhage-induced rise in catecholamines (epinephrine and norepinephrine), and arginine vasopressin; or alternatively due to impaired pressor response to these vasoactive substances in the alcohol-intoxicated host. Moreover, it was shown that alcohol intoxication accentuates the rise in alanine transaminase (ALT) and base deficit during trauma/hemorrhage suggesting an accentuation of tissue injury most likely resulting from the marked hypotension seen in alcohol-intoxicated animals (Phelan et al., 2002). Alcohol-intoxication was also shown to modulate the immediate pro-inflammatory cytokine response to hemorrhage (Phelan et al., 2002). Marked upregulation of hemorrhage-induced tissue pro-inflammatory cytokine expression immediately post fluid resuscitation with increased neutrophil apoptosis, attenuated phagocytic activity and oxidative burst, and impaired neuromodulation of stimulated cytokine release was observed after ethanol treatment (Molina et al., Alcohol 2004). These alterations in markers of host defense are associated with a marked increase in the morbidity and mortality resulting from *Klebsiella pneumoniae* during the recovery period (Greiffenstein et al., 2007; Zambell et al., 2004) that improved hemodynamic homeostasis of alcohol-intoxicated hemorrhaged animals should improve organ function, prevent tissue injury, and decrease susceptibility to infections and its associated morbidity.

Central choline-mediated sympathetic outflow does not attenuate hypotensive response to blood loss in acute alcohol-intoxicated rodents

Keisa Mathis, Louisiana State University Health Science Center—As described above, hemodynamic instability was observed following alcohol intoxication and trauma

which may be caused by suppressed sympathetic nervous system activation (Phelan et al., 2002; Zambell et al., 2004). Using a rat model of trauma-hemorrhage, animals given high doses of ethanol intragastrically prior to hemorrhage were shown to have decreased mean arterial blood pressure and increased hypotension. In order to counteract the suppressed neuroendocrine response, rats were given intracerebroventricular (ICV) choline prior to saline or ethanol and hemorrhage. ICV choline was observed to increase basal arterial blood pressure as well as levels of epinephrine and norepinephrine in control animals. While basic catecholamine levels were not disturbed, ethanol suppressed these choline-induced increases. These results suggested that choline increases mean arterial blood pressure in early stages of hemorrhagic shock but also that this increase is short-lived. Therefore, sustained central acetylcholine may be required for enhanced sensory nervous system activation during dramatic blood loss and for amelioration of alcohol-induced hypotension.

Alcohol-induced derangement of vascular responsiveness, impact on recovery from trauma-hemorrhage

Kathleen H. McDonough, Louisiana State University Health Science Center—

Animals given ethanol prior to trauma-hemorrhage have a delayed recovery of blood pressure compared to control animals, which may be due to an inability of the vascular smooth muscle to respond to vasoconstrictor signals from the sympathetic nervous system. To examine this possibility, rats were either given ethanol or isocaloric dextrose control for four days in a model of binge drinking. Additionally, one group of animals was given a bolus of ethanol on day 4. Aortas were then stimulated with the vasoconstrictor, phenylephrine, and the responses were measured by force transducers.

Vasodilation was also measured after peak contraction. Aortas from ethanol rats demonstrated a heightened response to phenylephrine and an attenuated response to acetylcholine suggesting an alteration in endothelial function. In contrast, rats exposed to four days of ethanol but no bolus showed the opposite trend with an attenuated response to phenylephrine and a greater dilation response to acetylcholine. These data suggest a possible temporal effect of ethanol on endothelial vessel function and that binge drinking may impair responsiveness to vasoconstrictor agents.

Alcohol impairs recovery of muscle mass resulting from disuse atrophy

Charles Lang, Pennsylvania State College of Medicine—Following traumatic injury, many patients are immobilized and suffer from muscle disuse atrophy. In a study examining ethanol's ability to increase the risk of muscle tissue injury and disrupt muscle protein balance, immobilized rats who consumed ethanol demonstrated a depressed ability for muscle mass and protein recovery. Additionally, ethanol-fed animals had increased levels of E3 ligase mRNA which is involved in the ubiquitin protein degradation pathway. Decreases in phosphorylation of 4E-BP1 and S6 were observed suggesting a decrease in translational control of protein synthesis in the ethanol animals (Vargas and Lang, 2008). The ethanol-fed animals also had a 2-fold increase in phosphorylation of 5'AMP-activated protein kinase (AMPK). These data suggest that chronic ethanol exposure blunts the normal repletion of muscle protein observed during recovery from disuse by increasing proteolysis and decreasing protein synthesis and these changes may be mediated by activation of AMPK (Vargas and Lang, 2008).

Alcohol and immunity after trauma

Alcohol and Toll-like receptor signaling

Gongyi Szabo, University of Massachusetts Medical School—Most pathogens express ligands that interact with multiple Toll-like receptors (TLRs) that share common signaling pathways. Ethanol was observed to exert effects on inflammatory pathways by TLR2

and/or TLR4 ligands. In human monocytes, ethanol decreased TLR4 but not TLR2-induced TNF- α protein and mRNA levels (Oak et al., 2006). Additionally, NF κ B activation was attenuated by ethanol after culture with TLR4 ligands. In contrast, when both TLR2 and TLR4 ligands were present, acute ethanol increased TNF- α production. Interleukin-1 receptor associated kinase-1 (IRAK-1) expression was reduced by ethanol in TLR4 stimulated cells but up-regulated in cells given both TLR2 and TLR4 stimulation. IRAK-M, an inhibitor of IRAK-1, was increased in TLR4-stimulated cells and decreased in cells given both ligands in the presence of ethanol. This is consistent with data showing lower levels of binding of IRAK-1 to Tumor Necrosis Factor Receptor Associated Factor 6 (TRAF-6) in the TLR4 stimulated cells but normal levels of IRAK-1:TRAF6 complexes in cells stimulated with both TLR2 and TLR4 ligands and ethanol (Oak et al., 2006). Increased phosphorylation of c-Jun NH2-terminal kinase (JNK) and AP-1 nuclear binding were also augmented by acute ethanol in the presence of combined TLR4 and TLR3 ligands. Consistently, a JNK inhibitor prevented the ethanol-induced elevation in TNF- α production. These data suggest that acute ethanol dampens the TLR4-induced inflammation via inhibition of IRAK-1 and ERK kinases as well as increased in IRAK-M levels in human monocytes. In contrast, acute ethanol enhanced the inflammatory response in the presence of TLR2 and TLR4 ligands via IRAK-1 activation and JNK phosphorylation (Oak et al., 2006). Therefore, the number and complexity of TLR4 signals may determine what effect acute ethanol has on the inflammatory response.

Severe alcohol intoxication changes cytokine profiles of trauma patients

Valerie Schaeffer, Harborview Medical Center, Seattle, WA—Clinical data from a multi-center prospective cohort study examining outcomes of severely injured adult patients with blunt hemorrhagic shock demonstrates significant alterations in patients with high blood alcohol concentrations. In particular, significantly elevated levels of IL-18 were observed. Ethanol appeared to suppress TNF- α production in these severely intoxicated patients. These results were consistent with IL-6 being a predictor of multiple organ dysfunction syndrome (MODS) since patients with high blood alcohol levels had the highest plasma levels of IL-6. While this was a limited study, it demonstrates that alcohol modulates the cytokine response following injury and increases the risk of morbidity and mortality.

Inflammation after acute ethanol and burn injury

Elizabeth Kovacs, Loyola University Medical Center—Using a mouse model acute ethanol and burn injury, significant increases in mortality and inflammatory response were observed following topical and intratracheal infection with *Pseudomonas aeruginosa* (Murdoch et al., 2008). Increased levels of proinflammatory cytokines, such as IL-6 and TNF- α , as well as increased leukocyte infiltration, were observed in the lungs of mice following ethanol, burn, and infection (Murdoch et al., 2008). The overproduction of chemokines, possibly resulting from signaling through toll-like receptors (TLRs) or the interleukin-1/interleukin-18 (IL-1/IL-18) receptor, may be responsible for the aberrant accumulation of leukocytes in the lung. However, it was also suggested that expression of adhesion molecules or the leakiness of the vasculature may also play a role of increased cellular infiltrate in the lungs after alcohol and burn injury.

Intratracheal infection after ethanol exposure and burn results in excessive pulmonary neutrophil accumulation

Eva Murdoch, Loyola University Medical Center—It was previously established that ethanol increases mortality of mice exposed to a topical infection after burn injury (Faunce et al., 1997). Further studies were undertaken to examine the effect of ethanol and burn injury on bacterial clearance in the lung. After acute ethanol and burn injury, mice given *Pseudomonas aeruginosa* have significantly decreased bacterial clearance and survival than mice given burn

or ethanol alone (Murdoch et al., 2008; Murdoch, 2008). Regardless of ethanol exposure, at 24 hours post infection, there is an increase in leukocyte accumulation in the lungs of burn-injured mice compared to control mice. This inflammation was greatly exaggerated in mice treated with burn and ethanol at 48 hours, whereas mice given burn alone showed only small foci of inflammatory cells (Murdoch et al., 2008). Flow cytometric analysis revealed these infiltrating cells to mainly be Gr-1 positive neutrophils. Therefore, the inability of mice given ethanol and burn to clear a bacterial infection does not appear to be due to a lack of infiltrating inflammatory cells, but may be due to a loss of effector function in these cells.

Hemeoxygenase-1 plays a critical role in the release of neutrophil superoxide anion following ethanol and burn injury

Xiaoling Li, University of Alabama, Birmingham—Hemeoxygenase-1 (HO-1) was shown to be an antioxidant and to provide protection against tissue damage (Soares et al., 2004). Following ethanol and burn injury, intestinal and pulmonary damage, as well as increased neutrophil superoxide production, has been observed (Choudhry et al., 2004; Haycock et al., 1997; Till et al., 1985). To test the hypothesis that decreased HO-1 lead to superoxide production and subsequent tissue damage, rats were given ethanol and burn or sham injury. Twenty-four hours later, neutrophils were isolated from peripheral blood and HO-1 and superoxide levels were measured. Interestingly, ethanol alone did not alter HO-1 expression in neutrophils (Li et al., 2008). However, the combined insult of acute ethanol and burn injury decreased HO-1 expression while accompanied by an increase in neutrophil superoxide production. Furthermore, treatment of animals with Cobalt protoporphyrin IX chloride (Copp), a HO-1 activator, restored HO-1 expression in neutrophils and prevented the increase in superoxide production (Li et al., 2008). These results suggest that the combined insult of ethanol and burn injury decreases the antioxidant, HO-1, resulting in increased superoxide production and possibly subsequent tissue damage.

T cell-mediated-intestinal immune defense in alcohol and burn injury

Mashkoo Choudhry, University of Alabama, Birmingham—The effects of acute ethanol intoxication and burn injury on the intestinal immune response were examined in a rat model. T cell effector responses (proliferation and cytokine production) were measured in the Peyer's patches and mesenteric lymph nodes after ethanol and burn injury. The combined insult produced a significant decrease in T cell produced IL-2 and interferon- γ (IFN- γ) along with an increase in bacterial translocation from the gut lumen to the mesenteric lymph nodes at 24 hours post-injury (Li et al., 2005; Li et al., 2006). The decrease in IL-2 and IFN- γ production was accompanied by an increase in IL-18 and a decrease in IL-12 production. The role of these cytokines was further investigated by culturing T cells from ethanol-exposed and burn-injured animals in the presence of recombinant IL-12 or neutralizing antibodies to IL-18. Addition of recombinant IL-12 prevented the suppression of IL-2 and IFN- γ production in response to anti-CD3. However, anti-IL-18 antibodies did not influence T cell cytokine production suggesting that decreased IL-12 and not increased IL-18 following the combined insult may be responsible for the suppressed T cell function in the intestine. More studies are being conducted to further investigate this T cell suppression and its consequence on morbidity and mortality after ethanol and burn injury.

Synergistic effect of ethanol and shock insults on gut cytokine production and barrier dysfunction

Parth Amin, Wayne State University—Both ethanol and gut-ischemia-reperfusion are known to impair the intestinal barrier function and increase the occurrence of sepsis following trauma (Diebel et al., 2002; Osborne et al., 1994). However, the combined effects of ethanol and ischemia-reperfusion on epithelial function are unknown. In this study, Caco2 cells were

cultured with either ethanol and/or *Escherichia coli* (*E. coli*) under normal (21% O₂) or hypoxic (5% O₂) conditions followed by reoxygenation. Apical and basal production of TNF- α and IL-6 was then analyzed by ELISA. Cellular integrity was also measured by an index of apoptosis and monolayer permeability. Production of TNF- α and IL-6 was elevated in both the apical and basal compartments following ethanol and *E. coli*, after ethanol and hypoxia/reoxygenation conditions, as well as all three conditions together (Amin et al., 2008). In addition, ethanol and hypoxia had an additive effect on apoptosis. Monolayer permeability was greatest in cells receiving ethanol, *E. coli*, and hypoxia (Amin et al., 2008). These data suggest that ethanol and ischemia-reperfusion may have a synergistic effect on cytokine production and barrier dysfunction following injury.

Consequences of alcohol and trauma

The epidemiology of alcohol abuse and ARDS

Marc Moss, University of Colorado at Denver—Historically, alcohol abuse has been associated with increased incidence and severity of Acute respiratory distress syndrome (ARDS) in critically ill patients (Moss et al., 1999). Looking at two different epidemiological studies conducted with ICU patients, it was observed that alcohol abuse was a significant comorbid variable that increased the incidence of ARDS almost three-fold. Additionally, 50% of all ARDS patients had a significant history of alcohol abuse, making it a common association in this population (Esper et al., 2006). Both clinical and animal model studies of chronic alcohol use demonstrate significant changes in the lungs including epithelial and endothelial cell function, surfactant synthesis and secretion, and barrier function. Decreased glutathione in the epithelial lining fluid was also observed. Importantly, the decreased levels of glutathione observed in chronic alcoholic patients did not significantly increase even after abstaining for one week. Barrier function in these patients appeared to be disrupted as based on increased protein levels in the epithelial lining fluid. This research has implications for proper treatment of acute lung injury in alcoholics and may lead to discovery of novel therapeutics.

The nuts and bolts of brief alcohol interventions for trauma patients

Carol Schermer, Loyola University Medical Center—Problem or at-risk drinkers were linked with increases in risk and severity of traumatic injury. Since most people change behaviors without the aid of professional help, studies were conducted on the efficacy of brief interventions given by trained health professionals to at-risk drinkers, who were hospitalized after traumatic injury. Brief interventions are short patient-centered counseling sessions that were shown to decrease alcohol use and recurrent arrest for driving under the influence of alcohol (Schermer, 2006). The sessions were shown to be effective with traumatically-injured patients and did not have to be given by a mental health professional meaning that trauma surgeons, social workers, nurses, or residents could be trained to give brief interventions effectively.

In a prospective study conducted in Seattle, Dr. Gentilello and colleagues found that 46% of a total of 2,524 trauma patients met criteria for an alcohol use disorder. These patients were then randomly assigned to groups to receive a 30-minute brief intervention or standard care. Patients receiving brief intervention counseling had a significant reduction in alcohol use as well as recurrent injury (as determined by re-admittance to a trauma center) in the following three years compared to patients receiving standard care. Additionally, a cost-analysis study of brief interventions was performed. The cost of screening, wages for staff to provide the brief interventions, administrative costs, and the money saved by decreased injury recurrence were included in the analysis. Compared to standard care, brief intervention counseling actually saved the hospital \$3.81 in direct health care costs for every dollar invested. This marginal cost

is so low that interventions with even marginal success are indeed cost-effective (Gentilello et al., 2005).

Summary

This satellite meeting focused on the effects of alcohol on organ systems following trauma or injury and is summarized in Figure 1. Both acute and chronic alcohol exposure lead to immunosuppression of the innate and adaptive arms of the immune response resulting in increased susceptibility to pathogens. Ethanol affected multiple signaling pathways including pathways involved in oxidative stress, toll-like receptor signaling, and cytokine production. In addition to the immune system, ethanol disrupted hemodynamic stability after trauma-hemorrhage, prevented muscle protein synthesis and recovery after injury, as well as endothelial cell function and epithelial barrier function. Studies in animal models were also observed in the clinic, and it is apparent that strategies of brief interventions with patients may be beneficial in decreasing ethanol-associated complications after injury.

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Highlights of the Alcohol and Trauma Satellite Meeting

Effects of Ethanol after Injury on:

<u>Burn</u>	<u>Trauma-Hemorrhage</u>	<u>Signaling</u>
<ul style="list-style-type: none">◆Increased proinflammatory mediators◆Increased number of leukocytes in tissues◆Suppressed T cell response◆Decreased pathogen clearance◆Increased tissue permeability and damage	<ul style="list-style-type: none">◆Increased proinflammatory mediators◆Increased susceptibility to pathogens◆Decreased sympathetic nervous system response◆Decreased hemodynamic stability	<ul style="list-style-type: none">◆Decreased muscle protein synthesis during muscle disuse atrophy◆Increased tissue permeability after ischemia◆Disruption of Toll-like receptor signaling◆Decreased antioxidant expression

Figure 1.

A brief and general overview of the effects of ethanol after traumatic injury including effects on the immune response, tissue damage, and signaling.