1858 The Effect of Circadian Disruption on Hepatic Inflammation and Cancer Formation

N. D. Carrillo, M. T. Walcheck, P. B. Schwartz, and S. Ronnekleiv-Kelly. *University of Wisconsin–Madison, Madison, WI.*

Incidence of hepatocellular carcinoma (HCC) has steadily increased over the last several decades and has proven to be one of the least responsive to current therapeutic options. Recently, circadian disruption has been shown to induce non-alcoholic steatohepatitis that often progresses to HCC. Circadian rhythms are normal biologic processes that coordinate cell and organ function with a 24-hour period. The disruption of these rhythms has been shown to promote inflammation and cancer development, but the effect on HCC development is largely unknown. To investigate a potential pathway for development of liver inflammation and HCC, we began by evaluating C57BL6/J (WT) mice under normal circadian (WT_N) and circadian disrupted (WT_D) conditions and compared transcriptomic profiles between the groups. A total of 144 mice were divided into 2 age-matched, cage-matched groups comprised of equal representation of male and female mice. At 4 weeks of age, the WT_N group was kept on a standard 12:12, light-dark cycle to establish a "normal" circadian rhythm and the WT_D group began a jet-lag protocol consisting of a 4-hour time shift every 2 days for 4 weeks to induce circadian disruption. At 8 weeks of age, 6 WT_N and 6 WT_D of equal males and females were sacrificed every 4 hours over a 48-hours window. Hepatic mRNA was immediately isolated from the 12 time-points in order to illustrate gene expression throughout the day. Core Clock Genes (CCGs) were analyzed with real time quantitative polymerase chain reaction (RT-qPCR). We found that the jet-lag protocol did not have a major impact on the relative expression of Nuclear Receptor subfamily 1 group D member 1 (NR1D1) and Cryptochrome Circadian Regulator 2 (*Cry2*). Opposingly, Cryptochrome Circadian Regulator 1 (*Cry1*) and Nuclear Factor Interleukin 3 (*Nfil3*) were significantly disrupted experiencing rhythm loss and phase shift respectively. The time point 22:00 was identified as the most sensitive time point with significant fold change and max peak heights for both *Cry1* and *Nfil3*. This study identifies CCGs and select inflammatory regulators were disrupted in the liver. This information is crucial to establish a baseline for circadian disruption in the liver, guiding future studies into the development of HCC in inducible transgenic mouse models.

1859 Ampakine CX546 Ameliorates Gulf War Agents Exposure and Stress-Induced Exosomal HMGB1 That Causes Neurological Ailment in Experimental Gulf War Illness

R. K. Seth[1], D. Bose[1], P. Saha[1], D. Kimono[1], S. Sarkar[1], A. Mondal[1], M. S. Albadrani[1], P. Janulewicz Lloyd[2], R. D. Horner[1], J. P. O'Callaghan[3], K. Sullivan[2], and S. Chatterjee[1]. *[1]University of South Carolina, Columbia, SC; [2]Boston University School of Public Health, Boston, MA; and [3]NIOSH, Morgantown, WV.*

Gulf War Illness (GWI) is a medically unexplained, multisymptomatic condition that includes chronic pain, gastrointestinal and neuroinflammation, and cognitive difficulties. Exposure to Gulf War (GW) agents pyridostigmine bromide (PB) and permethrin (Per), and war theater stress were key contributors to the etiology of GWI post-deployment to the Persian GW. In this study, we examined the role of circulatory exosomal high mobility group box-1 (HMGB1) protein in neuroinflammation, neuroimmunotoxicity, and neuroplasticity in the mouse model of GWI. Here, we used an established mouse model of GWI. The C57BL/6 mice were exposed to GW agents (PB+Per) along with restraint stress for one week. Results show that GW agent exposure along with stress causes exosomal biogenesis and HMGB1 expression in the small intestine and concurrently increase circulatory exosome loaded with HMGB1. Data also show decrease Zonal Occludin-1 (ZO1) and Claudin-1 mRNA expression, and serum albumin accumulation in frontal cortex suggests blood-brain barrier (BBB) integrity loss that enables entry of circulatory exosomal HMGB1 in the brain. Increase HMGB1 in both the frontal cortex and hippocampus activate microglia (M1 phenotype), thus induces an inflammatory response. We observed that HMGB1 induced neuroinflammation suppress brain-derived neurotropic factor (BDNF) and thus causing neuroplastic and cognitive impairment. The GW agents exposed mice co-treated with exosome inhibitor (Nexinhib20), or glutamate activator (ampakine, CX546) show improvement in BBB integrity, neuroinflammation, neuroplasticity, and cognitive function. In summary, our findings suggest that the circulatory exosomal HMGB1 plays a key role in GWI pathogenesis, and Nexinhib 20 and CX546 might be promising therapeutics in GWI. *This study was supported by W81XWH1810374 and VA merit award I01 CX001923-01 to Saurabh Chatterjee.*

1860 The Effects of Age, Sex, and Genotype on LPS-Induced Neuroinflammation in Humanized Targeted Replacement APOE Mice

I. Mhatre[1,2], A. Eid[1], Y. Han[1], and J. R. Richardson[1]. *[1]Florida International University, Miami, FL; and [2]Kent State University, Kent, OH.*

Neuroinflammation is implicated in the progression and pathogenesis of several neurodegenerative diseases including Alzheimer's disease (AD). While AD presents differently in individual patients, advancing age and the presence of the strongest known genetic risk factor, Apolipoprotein E4 genotype, have been shown to contribute greatly to the increased risk of AD. In addition, females have an increased risk of developing AD at a younger age when compared to males and this risk is modified by the Apolipoprotein E (APOE) genotype. Here, we sought to determine age, sex and APOE genotype susceptibility to neuroinflammation following administration of lipopolysaccharide (LPS; 0.5 mg/kg for 4 hours) in humanized targeted replacement APOE3 and APOE4 mice. Using quantitative PCR, we evaluated the proinflammatory cytokines Il1b and Tnfa in the cortex and hippocampus. LPS caused a higher induction of pro-inflammatory cytokines, Il1b and Tnfa mRNA expression in both the frontal cortex and hippocampus of young (3-month-old) and aged (16-month-old) APOE4 mice compared to APOE3. Il1b mRNA levels were increased in the frontal cortex by ~30-fold in aged APOE4 males and ~17-fold in APOE4 females. In contrast, Il1b expression only increased ~5-fold and ~7-fold in APOE3 males and females, respectively. In the hippocampus, there were no differences by genotype in the young mice, but aged APOE4 males and females exhibited a higher Il1b response than the young mice. Similar effects were observed for Tnfa expression in both regions, with differences apparent at 16 months for both APOE4 males (~9-10-fold increase in both, the frontal cortex and hippocampus) and females (~10-fold in both, the frontal cortex and hippocampus). These data indicate that a peripheral LPS challenge induces a higher increase in pro-inflammatory cytokine mRNA expression in older APOE4 targeted replacement mice compared to APOE3 and this effect appears to be sex-specific at different age groups. *Supported in part by NIH R01ES026057.*

1861 Redox-Associated Modulation of O-GlcNAcylation Signaling Ameliorates Liver Injury Induced by Co-exposure to Ethanol and Lipopolysaccharide in Mice

F. Wan[1,2], D. Orlicky[3], V. Vasiliou[1], and Y. Chen[1]. *[1]Yale School of Public Health, New Haven, CT; [2]Guangxi Medical University, Nanning, China; and [3]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Both alcohol consumption and endotoxin [lipopolysaccharide (LPS)] exposure can induce oxidative liver injury, the synergetic effect of which is hypothesized to contribute significantly to the deleterious progression of alcoholic liver disease (ALD). O-GlcNAcylation of protein is an emerging form of post-translational modification, where a single O-linked N-acetylglucosamine moiety is added to Ser and Thr residues of nuclear, cytoplasmic and mitochondrial proteins. This process is controlled by a pair of enzymes, O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA). O-GlcNAcylation of protein is increasingly recognized as playing an important role in stress sensing and fine-tuning of inflammatory response. To date, little is known about the role of O-GlcNAcylation in ALD pathogenesis. In the current study, we investigated the impact of binge alcohol drinking in combination with LPS exposure on hepatic O-GlcNAcylation pathway in a mouse model of chronic glutathione (GSH) deficiency. Female wild-type (WT) and GSH-deficient *Gclm*-null (KO) mice received ethanol for 3 consecutive days (5 g/kg i.g. per day), followed by a single LPS administration (10 mg/kg i.p.). At 0, 6,12 and 24 hr post LPS treatment, liver injury, expressions of inflammatory genes and the O-GlcNAcylation pathway in the liver were examined. Compared to WT mice, KO mice had a lower injury score at 24 hr post LPS treatment. The expression profile of inflammatory genes and O-GlcNAcylation-related genes revealed differential changes between WT and KO livers at 12 and 24 hr post LPS treatment. There was an overall increase of O-GlcNAcylation of liver proteins in KO mice by ethanol binge feeding alone and by ethanol-LPS co-treatment at 24 hr. In conclusion, GSH-deficient mice display a partial protection against liver injuries caused by acute ethanol-LPS co-exposure. We speculate that modulation of O-GlcNAcylation signaling by low GSH may serve as a protective mechanism. *This work was supported, in part, by NIH grants K01AA025093, P30DK034989, R24AA022057 and International Communication of Guangxi Medical University Graduate Education.*

SOT 2020

59th Annual Meeting & ToxExpo

Anaheim, California • March 15–19

The Toxicologist

Supplement to *Toxicological Sciences*

Toxicological Sciences

ISSN 1096-6080
Volume 174, Issue 1
March 2020

The Official Journal of the Society of Toxicology

OXFORD UNIVERSITY PRESS

SOT | Society of Toxicology

www.academic.oup.com/toxsci

Publication Date: February 21, 2020

Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and Scientific Sessions of the 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. If a number is missing in the numerical sequence, the abstract assigned to the missing number was withdrawn by the author(s). Author names that are underlined in the author block indicate that the author is a member of the Society of Toxicology. For example, J. Smith. SOT members may sponsor abstracts that do not include an author with SOT membership. Authors who are members of designated organizations could serve as the sponsor of the abstract if an SOT member was not a co-author; these types of sponsorships are displayed with an organization name after the sponsor name (e.g., Sponsor: A. Smith, EUROTOX).

Scientific Session Types:

- CE Continuing Education Courses
- EC Education-Career Development Sessions
- IS Informational Sessions
- PL Platform Sessions
- PS Poster Sessions
- RI Regional Interest Sessions
- R Roundtable Sessions
- S Symposium Sessions
- W Workshop Sessions

The 2020 SOT Event App and Online Planner

The Event App is available via the SOT Annual Meeting website and app marketplaces. The Event App, alongside the Online Planner available on the SOT Annual Meeting website, enables attendees to engage with organizers, exhibitors, and each other and to manage their time and maximize their experience during the Annual Meeting. ePosters also can be accessed electronically via the Event App until May 15, 2020.

To cite a 2020 SOT Annual Meeting abstract, please format as follows: *The Toxicologist*, Supplement to *Toxicological Sciences*, 174 (1), abstract #__, 2020, Title, First Author.

Society of Toxicology
11190 Sunrise Valley Drive, Suite 300, Reston, VA 20191

www.toxicology.org