iNOS, and nitrite levels were also dependent on PKR. Hemin pretreatment induced a greater expression of HO-1 mRNA and protein than PolyIC alone, while hemin inhibited polyIC-induced PKR, iNOS, CAT2, IL-10, and nitrites. Pretreatment with ZnPP induced PKR formation over polyIC alone, and did not inhibit nitrite formation. We conclude that dsRNA caused a PKR-mediated induction of genes of oxidative stress (iNOS, CAT2) as well as cytoprotective genes (HO-1, IL-10), and that the induced HO-1 activity provided a braking mechanism to subsequently downregulate PKR, CAT2, and iNOS. Therefore, in concert with HO-1, PKR can control cytoprotective responses to foreign dsRNA as well as apoptotic and inflammatory responses.

809.13

Apolipoprotein E Isoforms Differentially Regulate iNOS Activity in Male Targeted Replacement Mice

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Immunomodulatory functions for apolipoprotein E (apoE) protein isoforms have been described but the underlying mechanisms are poorly understood. Peritoneal macrophages from homozygous APOE targeted replacement (APOETR) mice expressing only human APOE3 alleles or APOE4 alleles were utilized as mouse models to investigate the role of apoE isoforms and gender in the regulation of oxidative and nitrosative stress. Stimulated peritoneal macrophages from male APOE4/4TR mice produced higher levels of nitric oxide (NO) than APOE3/3TR mice ($p<0.01$), while peritoneal macrophages from female mice did not. ELISA measurement of apoE protein levels and inhibition of apoE receptors with 500nM RAP, did not alter NO release between APOE genotypes. However, macrophages treated with 5μM 1400W, an inducible nitric oxide synthase (iNOS) inhibitor, completely abolished all NO production, but iNOS mRNA and protein levels did not display any isoform differences. Conversely, enzymatic activity assays revealed that male APOE4/4TR macrophages display higher iNOS activity levels than APOE3/3TR macrophages ($p<0.01$), suggesting that APOE4/4 modulates iNOS activity at the post-translational level. These data support a potentially novel mechanism for apoE isoform-dependent immune responses critical for the progression of inflammatory diseases in the central nervous system and the periphery. *Supported by NIH/NIA and NSF.*

809.14

NF-kappaB activity and iNOS protein expression are upregulated in skeletal muscle of mdx mice

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Duchenne muscular dystrophy (DMD) is the most common and severe type of muscular dystrophy. DMD is caused by a mutation in the dystrophin gene, resulting in progressive wasting and weakness of skeletal muscle. Recent data indicate that DMD is accompanied by large inflammation and oxidative stress, where oxidant production overwhelms the protective antioxidant system. However, the cellular mechanisms by which oxidative stress and inflammation contribute to muscle wasting with DMD remains unknown. We hypothesized that activity of the pro-inflammatory transcription factor nuclear factor kappaB (NF-kappaB) and protein expression of inducible nitric oxide synthase (iNOS) would both be upregulated in mdx skeletal muscle, a mouse model of DMD. Four week old C57BL/10 *mdx* mice (n=10) and C57BL/10 wild-type mice controls (n=10) were used for this study. Gastrocnemius muscle samples were extracted, weighed, quickly frozen in liquid nitrogen and stored at –80°C until analyses. NF-kappaB activity was quantified using an ELISA technique, and iNOS protein expression was determined using Western blot analysis. Mean NF-kappaB activity was 33% higher in mdx mice when compared to wild type mice. iNOS protein expression was also higher (194 %) in mdx mice than wild type mice. These results support the hypothesis that pro-inflammatory signaling involving NF-kappaB and iNOS protein expression is upregulated in skeletal muscle from mdx mice.

809.15

Protection of DNA and Cellular Membranes from Reactive Oxygen Species Mediated Damage by Uric Acid

Beth Stinefelt[1], Stephen S Leonard[2], Kenneth P Blemings[1], Xianglin Shi[2], Hillar Klandorf[1]. [1]Animal and Veterinary Sci., West Virginia University, P.O. Box 6108, Morgantown, WV 26506, [2]Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, West Virginia

The objective of the present study was to investigate the quenching effect of uric acid on specific ROS and determine the ability of UA to protect DNA and cellular membranes from ROS mediated damage. Hydroxyl ($^{\cdot}OH$) and superoxide ($O_2^{\cdot-}$) radicals were detected with electron spin resonance (ESR). $^{\cdot}OH$ radicals generated via the Fenton reaction and $O_2^{\cdot-}$ radicals were created using xanthine and xanthine oxidase. Hydroxyl and superoxide radical ESR signals were both reduced by addition of uric acid in a concentration dependent manner ($P < .05$). The ability of uric acid to protect DNA from hydroxyl damage was determined by exposure of λ Hind III DNA fragments to the Fenton reaction. Uric acid inhibited hydroxyl mediated DNA damage, indicated by the presence of intact bands of λ Hind III DNA after agarose gel electrophoresis and ethidium bromide staining. Lipid peroxidation, a marker of cellular injury by ROS, was induced in RAW 264.7 cells by exposure to Minn-U-Sil, a silica based stimulant of ROS production. Peroxidation of cellular membranes, detected using spectroscopy, was less ($P < .015$) with addition of 1mM uric acid to the cell incubation mixture. The results of these studies demonstrate uric acid's ability to scavenge hydroxyl and superoxide radicals, thus protecting against both DNA damage and lipid peroxidation. Support: WV Ag. For. Expt. Sta. H393 (HK).

809.16

Protective effects of 17-β estradiol and 4-hydroxytamoxifen on reactive oxygen species-mediated DNA damage

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The Women's Health Initiative study of the benefits and risks of estrogen therapy is continuing, and use of tamoxifen (T) as a therapeutic agent for hormone-dependent breast cancer is controversial due to the risk for endometrial cancer. Studies indicate that 17-β estradiol (E2) and 4-hydroxytamoxifen (4HT), an active metabolite of T, protect lipoprotein from damage by reactive oxygen species (ROS). This study examines the ability of E2 and 4HT to protect DNA from ROS-mediated strand breaks. Supercoiled ϕX-174 RF I DNA (0.2 μg) was incubated for 60 minutes (37° C) with H_2O_2 (50 μM) and Cu II (30 μM), in the presence and absence of E2 (25, 50 or 100 μM) or 4HT (25, 50 or 100 μM) or vehicle (ethanol), in PBS (pH = 7.4) at a final volume of 24 μl (in 1.5 ml centrifuge tubes). Control supercoiled ϕX-174 RF I DNA was incubated in PBS in the absence of any added agents. Following incubation, samples and marker DNA (Lambda DNA-Hind III digest) were loaded in a 0.8% agarose E-Gel (pre-cast with ethidium bromide) and electrophoresed at 57 volts for 30 minutes. Gels were then photographed under UV light. Linear form of the DNA, indicative of DNA damage, was produced by the H_2O_2 /Cu *in vitro* system, and ethanol (hydroxyl radical scavenger) did reduce DNA damage. E2 and 4HT appear to modify a reaction path involving ROS and protect DNA from oxidative damage. (Supported by BES Research Funds).

809.17

Monocytic Cells Differentially Express MKP-1 Based on the Level of Intracellular H_2O_2

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Macrophages are critical in initiating immune and inflammatory responses in the lung. We have shown that the p38 MAPK regulates cytokine gene expression. MKP-1 is a phosphatase that regulates the activation of the p38 MAPK, and H2O2 has been shown to oxidize cysteine residues within the phosphatase that are essential for its catalytic activity. Since monocytes and macrophages differentially express p38 MAPK when stimulated with asbestos and H2O2 is

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Protection of DNA and Cellular Membranes from Reactive Oxygen Species Mediated Damage by Uric Acid

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ABSTRACTS

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