levels after their expression. Ectopic expression of HIF and EGR family proteins increased both PK2 mRNA and protein levels in dopaminergic cells. Collectively, our results demonstrate that HIF and EGR families of transcription factors play a role in PK2 upregulation and its compensatory response during early stages of neurotoxic insults (NIH grants NS78247and ES10586).

PS 1527 Farnesoid X Receptor Deficiency in Mice Enhances MPTP-Induced Neuroinflammatory Response

E. E. Beier[1], M. M. Hossain[1], B. Kong[2], G. Guo[2] and J. R. Richardson[1]. *[1]Department of Environmental and Occupational Medicine, Rutgers University, Piscataway, NJ and [2]Department of Pharmacology and Toxicology, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ.*

Neuroinflammation is a prominent feature of several neurodegenerative disorders including Parkinson's disease. The nuclear factor κB (NF-κB) pathway is present in a wide variety of neuronal cells including microglia, astrocytes, and neurons, and plays a predominant role in the activation and regulation of key inflammatory molecules. The farnesoid -x receptor is a transcription factor and a bile acid receptor predominantly expressed in liver and intestine that was previously reported to regulate NF-κB activity in the liver. Fxr deficiency was associated with increased hepatotoxicity following challenge with lipopolysaccharide, suggesting that Fxr mitigates the inflammatory response. Here, we report that Fxr is also expressed in mouse brain and that Fxr knockout mice exhibited enhanced levels of neuroinflammation, as evidenced by an 94% increase in tumor necrosis factor-alpha (Tnf-α) and an 57% increase in cyclooxygenase 2 (Cox2) protein levels. Following striatal injury with repeated administration of the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), we found that Fxr KO mice exhibited an exaggerated inflammatory response. Specifically, compared to control saline, MPTP increased Tnf-α (44%) and Cox2 (86%) in the striatum of wild-type mice, whereas MPTP administration to Fxr KO mice resulted in a combined 127% increase in Tnf-α and a combined 121% increase in Cox2. This was accompanied by an 11% greater striatal dopamine depletion, and greater reduction of tyrosine hydroxylase protein (-12%) and dopamine transporter (-28%) in Fxr KO mice following MPTP. Our findings suggest that FXR may play an important role in the regulation of basal and toxicant-induced neuroinflammation. Supported in part by NIH T32ES, P30ES005022, R01ES021800, and GM104037.

PS 1528 Systems Genetics Analysis of MPTP Neurotoxicity

G. Alam[1], D. B. Miller[2], J. P. O'Callaghan[2], L. Lu[3], R. W. Williams[3] and B. C. Jones[3, 1]. *[1]Biobehavioral Health, The Pennsylvania State University, University Park, PA, [2]CDC-NIOSH, Morgantown, WV and [3]Genetics, Genomics and Informatics, University of Tennessee Health Science Center, Memphis, TN.*

Heavy metals, and pesticides herbicides are suspected risk factors for neurological disorders including Parkinson's disease (PD). Nevertheless, their role is not clear-cut, as there are inconsistencies in epidemiological and preclinical research. One reason may be related to individual differences in susceptibility, differences that can be traced to the genetic constitution of humans and animals so exposed. Newer epidemiological and animal methods address the role of genes, the environment and their interaction as key. We recently reported on neurotoxicity of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in male BXD recombinant inbred mice. In the current study, we examined the effect of MPTP neurotoxicity in females from 9 of the same strains of BXD RI mice. The mice received 12.5 mg/kg MPTP s.c. (vs. saline) and 48 h later brains were taken for biochemical analyses. Striatal dopamine (DA) and its metabolites, DOPAC and HVA, and serotonin and its metabolite, 5-HIAAA, were analyzed by HPLC. DA turnover was assessed using DOPAC/DA and HVA/DA ratios. Striatal tyrosine hydroxylase (TH), glial fibrilary acidic protein (GFAP), and iron content in ventral midbrain were quantified. All dopamine measures, as well as TH and GFAP, demonstrated wide, genotype-dependent differences in response to MPTP. Moreover, strong positive correlations were seen between the sexes for DA, TH, and GFAP. This systemic approach to the study of environmental neurotoxicants in genetic reference populations of mice is likely to elucidate genetic factors underlying individual differences in developing neurodegenerative diseases such as PD. Supported in part by USPHS Grant R01 ES02261

PS 1529 Molecular Mechanisms of Rotenone and MPP+ Damage to Dopaminergic Neurons in a Human Neuronal 3D Model

G. A. Harris, J. Delp, J. Smith, D. Pamies, H. T. Hogberg, T. Hartung and L. Smirnova. *Center for Alternatives to Animal Testing, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.*

Increasing evidence suggests a major role of mitochondria-mediated cellular signaling in response to environmental stress, such as toxicant exposure. Mitochondria-mediated cellular perturbations include response to ROS, perturbation in ATP production, DNA damage, histone modifications and altered DNA methylation. The development of cellular models and experimental approaches reflecting mitochondrial intra-cellular crosstalk are of high importance, since they will lead to more comprehensive understanding of early cellular events, including cellular defense mechanism prior to apoptosis activation. A variety of toxicants induce mitochondrial respiratory chain perturbations that lead subsequently to apoptosis. This work takes advantage of our recently characterized 3D LUHMES dopaminergic neuronal model to test two known mitochondrial neurotoxicants (MPP+ and rotenone) and identify early events which lead to toxicity. Cell viability, mitochondria dysfunction, neurite outgrowth and arborization, and perturbations in gene expression were measured after short-term (24 and 48h) exposures. We were able to see changes in expression for energy metabolism and stress response genes (ATF4, ASS1, CBS, CTH, MLF1IP, SHMT and TYMS) at non-cytotoxic concentrations (0.1μM rotenone, 10μM MPP+) as well as a dose-dependent decrease in mitochondria functionality using MitoTracker®. We also recorded changes in expression of mitochondria/apoptosis-related miRNAs (miRs 30a, 34c, 15, 338, and 210). We visualized toxicant-induced changes in neuronal morphology by confocal microscopy of co-cultures of wild type and RFP-expressing LUHMES. In the next steps we will study the expression of oxidative stress response genes (NFE2L2, KEAP1 and SOD1) and identify metabolic changes using metabolomics. The 3D model mimics the *in vivo* physiology more closely than existing 2D *in vitro* models therefore can be used to identify molecular and cellular effects of neurotoxic compounds.

PS 1530 Biochemical and Gene Expression Changes in Mice Exposed to Polychlorinated Biphenyls during Early Brain Development

S. Hampton[1], M. Kromme[1, 2], M. Stegman[1, 2], C. Bates[1], A. Lopez[2] and C. P. Curran[1]. *[1]Biological Sciences, Northern Kentucky University, Highland Heights, KY and [2]Cincinnati Children's Medical Center, Cincinnati, OH.*

Polychlorinated biphenyls (PCBs) are neurotoxicants that have been banned for decades, but are still a continuing public health concern. The primary route of human exposure is through contaminated food. Recently, PCBs have been linked with an increased risk of Parkinson's disease in highly exposed humans. Interestingly, PCBs have long been known to deplete dopamine levels in the brain. Our previous studies in mice showed that variations in the aryl hydrocarbon receptor (AHR) and cytochrome P450 1A2 (CYP1A2) affect PCB neurotoxicity when assessing learning and memory and motor function. In our current studies, we used immunohistochemistry and quantitative real-time PCR to assess gene expression, enzyme-linked immunoassays to look at thyroid hormone levels, and HPLC to measure neurotransmitters. Pregnant dams were treated with PCBs or corn oil-soaked fruit loops daily from gestational day 0 (GD0) to postnatal day 25 (PND 25) when the pups were weaned. We collected tissues from offspring at P30 and following motor function tests (~P120). We confirmed AHR activation through qPCR of liver tissue only in high-affinity Ahrb mice. There were no significant differences in thyroid hormone levels in adults although PCB-treated *Ahr^{b}Cyp1a2(-/-)* mice had the lowest plasma levels (4.77± 0.76 ng/dl) compared with the most resistant *Ahr^{b}Cyp1a2(+/+)* mice (5.91± 0.46 ng/dl). Although we found no significant differences in striatal dopamine, there was a significant difference in the metabolite DOPAC. PCB-treated mice with a high-affinity *Ahr^b* genotype both had depleted DOPAC compared with the corn oil-treated controls ($P < 0.05$). There was also a significant main effect of genotype with *Cyp1a2(-/-)* mice having lower DOPAC compared to the wild type mice ($P < 0.05$). Supported by ES020053 and GM103436.

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