by HD carry an expansion of 36 or more repeats in one copy. While HD is predominately inherited, some cases, up to 4% or more, arise through sporadic CAG expansion. Environmental exposures may cause CAG repeat expansions, yet it is unknown which exposures contribute to repeat instability in trinucleotide repeat disorders such as HD. We previously demonstrated that pyraclostrobin, a prevalent oxidative stress-inducing fungicide, evokes gene expression signatures of HD in cultured embryonic mouse cortical cells. The objective of the current study was to determine if exposure to pyraclostrobin is capable of expanding CAG repeat length. Pyraclostrobin or a vehicle control was administered to an immortalized CAG-GFP reporter cell line as well as primary cortical cells and fibroblasts from the Q175 knockin mouse model of HD. Distributions of CAG repeat numbers were then measured using molecular fragment analysis. In addition to obtaining the main CAG repeat allele, an instability index (Lee et al., PMID: 20302627) was computed to investigate the occurrence of mosaic expansions existing in subsets of cells in each culture. The index can express either a widening or narrowing of the distribution of variability of CAG repeats around the main peak allele, and may thus be a more sensitive indicator of repeat instability compared to measuring the main CAG allele alone. We demonstrated that exposure to pyraclostrobin caused repeat expansion in the CAG-GFP reporter cell line and modestly increased the instability index. In contrast, mixed cortical cells from knockin mice did not show repeat expansion or altered instability upon pyraclostrobin treatment. Our results suggest that cell lines might be more prone to mitochondrial superoxide-induced trinucleotide repeat expansion compared to primary neuronal enriched cultures. Application of the instability index may prove to be a critical tool in understanding CAG repeat instability resulting from xenobiotic exposures.

PS 3094 Investigating the Influence of CHD8 Haploinsufficiency on Pyrethroid-Induced Developmental Neurotoxicity

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The considerable plasticity of the developing brain renders it exceptionally vulnerable to genetic and environmental perturbations. Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder with a strong but complex genetic component associated with key molecular pathways early in development. Yet, genetic risk factors seem insufficient to explain an increase in ASD prevalence over the past 15 years, raising the possibility that nonheritable risk factors are also at play. Exposure to exogenous agents during a critical developmental period has been suggested to contribute to ASD etiology. However, given the evidence on ASD heritability, environmental factors that play a role in ASD development likely influence mechanisms also involving some element of genetic susceptibility. Thus, there is an urgent need to identify mechanisms by which nonheritable factors may interact with susceptibility genes. In this study we investigate how haploinsufficiency in one of the most high confidence ASD risk genes, Chromatin Helicase DNA Binding Protein 8 (CHD8), influences pesticide-induced neurotoxicity. We report that *Chd8* mutant mice demonstrate several abnormal phenotypes, including increased anxiety-like behavior in an elevated plus maze, decreased rearing movements in the open field, and hyper-sociability in a three-chamber test. These behaviors were altered in mice developmentally exposed to deltamethrin, an insecticide that functions by inhibiting sodium channel function. Using immunohistochemistry, we investigate differences in neuronal proliferation and neuronal maturation indicative of altered brain structures following developmental deltamethrin exposure. Further, we assess alterations in gene expression that may be responsible for the observed behavioral changes in *Chd8* mutant mice with bulk RNA-sequencing of cortical tissue from postnatal day 5 mice and 1 year old mice exposed to deltamethrin.

PS 3095 Prior Exposure to Stress Hormone Exacerbates the Neuroinflammatory Response to the Nerve Agent Sarin and Pesticide Dichlorvos in a Mouse Model of Gulf War Illness

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Ongoing research into the underlying cause of Gulf War Illness (GWI) has repeatedly indicated a role for persistent aberrant neuroinflammatory signaling associated with neurotoxicant exposure; veterans with GWI had the potential for exposure to several neurotoxicants in theater. Our prior research using a GWI animal model has indicated that exposure to organophosphate acetylcholinesterase inhibitors (OP AChEIs), such as the sarin surrogate diisopropyl fluorophosphate (DFP) or the pesticide chlorpyrifos, following administration of exogenous corticosterone (CORT) to mimic high physiological stress experienced in theater, results in robust neuroinflammation. In our effort to expand upon these results, we investigated if: 1) our DFP results were representative of nerve agent exposure; 2) CORT priming affected another OP AChEI pesticide, dichlorvos (DDVP). In this study, mice were given CORT (200 mg/L) in the drinking water for 7 days followed by exposure to sarin (LD20=100 µg/kg, s.c.) or DDVP (20 mg/kg, i.p.). Cytokine expression was evaluated in the brain by qPCR (sarin and DDVP) and serum by multiplex ELISA (sarin) at 6 hours post-exposure. Like DFP and chlorpyrifos, exposure to sarin or DDVP following CORT resulted in a significant increase in brain cytokine mRNA. However, CORT + sarin only significantly increased three (IL-6, IL-12, and IL-17) of the 16 serum cytokines, compared to all other conditions. These data indicate that every known OP AChEI that veterans with GWI may have encountered in theater carries the potential to produce exacerbated neuroinflammation. The parallels between our observations with DFP and sarin validates the use of DFP as a surrogate to nerve agent in animal models. While these experiments focus on an acute exposure paradigm, the neuroinflammatory profile observed here has been demonstrated to align with the aberrant neuroimmune state associated with GWI and has been shown to facilitate detrimental responses to future inflammatory challenges. This suggests that exposure to any OP AChEIs under conditions of high physiological stress was likely to cause or contribute to the development of GWI and warrants continued investigation regarding their long-term effects as it pertains to GWI.

PS 3096 Comparative Analysis of the Mechanisms of Organophosphorus Pesticide Developmental Neurotoxicity in Freshwater Planarians

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Organophosphorus pesticides (OPs) are a chemically diverse class of commonly used insecticides. Epidemiological studies suggest that low dose chronic prenatal and infant exposures can lead to life-long neurological damage and behavioral disorders. Inhibition of acetylcholinesterase (AChE) as the shared mechanism of acute OP neurotoxicity is well studied and used as the biomarker for OP exposure. However, OP-induced developmental neurotoxicity (DNT) can occur in the absence of significant AChE inhibition, suggesting alternative targets. Moreover, while different OPs can cause different adverse outcomes, most studies have focused on the most abundant OP, chlorpyrifos. Thus, it is unclear whether different OPs act through different mechanisms. We hypothesized that differences of OP DNT are due to differential effects on alternative targets. To test this, a comparative high-throughput screen of 7 OPs (acephate, chlorpyrifos, dichlorvos, diazinon, malathion, parathion and profenofos) across 10 concentrations in quarter-log steps was performed to investigate potential differential effects of different OPs on the adult and developing brain. Asexual freshwater planarians were used for this screen because this invertebrate system uniquely allows for testing of adult and developing specimen in parallel on an automated system. Neurotoxicity was evaluated using quantitative morphological and behavioral readouts. Twenty-two "mechanistic control compounds" known to target pathways suggested in the literature to be affected by OPs (cholinergic neurotransmission, serotonin neurotransmission, endocannabinoid system, cytoskeleton, adenyl cyclase and oxidative stress) and assay negative and positive controls were also tested. Comparison of the holistic toxicological profile for each compound demonstrated that different OPs caused differential DNT phenotypes. Moreover, when compared with the mechanistic control compounds, the different OPs separated into distinct mechanistic clusters. Interestingly, the phenotypic profiles of adult versus regenerating planarians exposed to the OPs clustered differently, suggesting some developmental-specific mechanisms. Thus, this study provides new insight into how OPs differentially damage the developing brain. *Supported by NIH grant R15 ES031354.*

PS 3097 Chlorpyrifos and $^{\Delta 9}$Tetrahydrocannabinol Exposure and Effects on Parameters Associated with Obesity

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The use of medicinal and recreational cannabis (main component $^{\Delta 9}$Tetrahydrocannabinol: $^{\Delta 9}$THC) has increased globally by 60% from 2010-2019 (>200 million in the US smoke cannabis: 2019). Obesity in the US has also rapidly increased to 42% in adults (2017-2018) with 20% prevalence in adolescents (2019). Further, chlorpyrifos (CPF), a neurotoxic organophosphate pesticide is used on cannabis plants. Both CPF and $^{\Delta 9}$THC affect the endocannabinoid system (ECS), critical to regulation of appetite, energy balance, metabolism, and gut microbiota, which, if disrupted, could lead to increased risk for obesity and related diseases. CPF inhibits EC breakdown at neural

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