Expectedly, buffering the oxidative stress effect with antioxidant *N*-acetylcysteine (NAC) effectively prevented the CPO-induced ROS generation, CHOP activation, and autophagic and apoptotic events as well as AMPKα phosphorylation. **Conclusions:** these results suggest that CPO exerted neurocytotoxicity via ROS-activated AMPK signal downstream-mediated CHOP-triggered autophagy-dependent apoptosis, ultimately leading to neuronal cell death. The regulation of ROS/AMPK/CHOP axis may be a promising intervention to against CPO-induced neurotoxicity.

4473 Chlorpyrifos-Induced Neurotoxicity in Zebrafish Embryos Is Mediated Through Synuclein and Autophagy

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Background and Purpose: Exposure to pesticides such as organophosphates is associated with an increased risk of Parkinson's disease (PD) but it is unclear if this association is causal and the mechanisms by which they might act are unknown. Using a zebrafish platform, we investigated the behavior, neurotoxicity, and molecular mechanisms of toxicity of the organophosphate pesticide chlorpyrifos. **Methods:** Transgenic zebrafish embryos were treated with chlorpyrifos at nanomolar concentrations after 24 hours post-fertilization. Behavioral testing was performed using the Viewpoint Imaging System. Neuronal loss and microglial activation were determined using immunostaining and imaged by confocal microscopy. Autophagic flux was determined using modulators of autophagy in GFP-LC3 transgenic zebrafish and Western blots. **Results:** Chlorpyrifos caused impairment of locomotor activity and selective loss of aminergic neurons. We also found an increase in apoptosis and microglial activation. Interestingly, dopamine neuron loss appeared to be at least partially dependent on γ1-synuclein (closest functional homolog to human α-synuclein) as neuronal loss did not occur in γ1-synuclein knockout zebrafish line. Live *in vivo* autophagic flux assay in zebrafish showed impaired turnover and lysotracker dye staining indicated an increase in lysosomal labeling. Chlorpyrifos treatment also led to elevated p62 levels consistent with impaired autophagic flux. **Conclusions:** Chlorpyrifos was selectively toxic to aminergic neurons *in vivo* while showing a variety of toxicity including behavioral deficit, neuron loss, apoptosis, neuroinflammation, and dysfunction in autophagy contributed to its neurotoxicity. These findings add biological plausibility to its epidemiological association with incident PD. These studies also support the induction of autophagy as a therapeutic strategy for disease modification in PD.

4474 Chronic memory impairments and decreased hippocampal spine density following occupational-like chlorpyrifos exposures in adult rats

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Background and Purpose: Exposure to organophosphates (OP) pesticides, such as chlorpyrifos (CPF), presents psychological and somatic baseline hazards. Epidemiological and laboratory research demonstrates the risk for dementia and cognitive decline as a result of sustained low-dose OP exposures such as those encountered occupationally or due to certain living conditions. Apart from civilian exposures, military service-related exposure to OP pesticides such as that experienced by soldiers during the First Gulf War deployment is thought to underlie mood and memory disturbances reported by the veterans of this War. While studies exist on the effects of CPF exposures on memory outcomes, research on long-term memory effects following occupational-like exposures in adult rats is not fully available. **Methods:** In this study, occupational-like exposures were first determined by identifying a dose and exposure paradigm that produced cholinesterase inhibitions similar to those experienced by humans during a typical agricultural dusting period, as understood by global studies on harvest cycles. CPF 10 mg/kg dose in peanut oil (VEH) was subsequently delivered via subcutaneous injection to adult male Sprague-Dawley rats once-daily for 21 consecutive days. Following a 12-week washout period, cholinesterase levels reverted to baseline, and the effects of CPF exposures on memory outcome were assessed using Barnes Maze (BMT) and Novel Object Recognition (NOR) tests. To evaluate CPF- induced changes to dendritic remodeling, we assessed hippocampal spine density using DiI staining. **Results:** On the BMT, CPF rats exhibited higher latency to escape and committed more errors than VEH- treated rats during the acquisition phase (day 1-3) but ultimately learned the task by day 4. A probe trial (day 5) assessed escape hole retention, a surrogate for short-term memory. VEH- treated rats made significantly more visits to the escape zone and spent significantly more time in the target quadrant compared to CPF rats (*p<0.05, n=5 rats, t-test). A recall trial (day 7) demonstrated that CPF- treated rats spent less time near the escape box compared to VEH- treated rats, suggesting deficits in long-term memory retention. On the NOR, CPF- treated rats significantly decreased their discrimination scores (ratio of time exploring the novel object over the total time spent exploring the two objects) compared to VEH rats, indicating deficits in recognition memory. The hippocampus is the primary brain region involved in forming and consolidating memories. Spines are neuronal protrusions and the primary recipients of excitatory signals. Spine morphology and density alterations profoundly affect neuronal plasticity and memory outcomes. At 3 months after CPF10 exposures, we observed a significant decrease in spine density in CPF-10 compared to vehicle-treated rats (*p<0.05, n= 10 neurons/ rat, 3 rats per group, t-test) . **Conclusions:** Occupational-like CPF exposures in adult rats produced significant chronic memory impairments. In addition, these repeated CPF exposures also produced pathological synaptic plasticity as evidenced by decreased hippocampal spine densities. Ongoing studies are exploring the expression of genes involved in the synaptic plasticity and cognitive processing in CPF- exposed rats. The distinct exposure paradigm of this study can be used to identify molecular mechanisms for CPF- contingent memory deficits and ultimately identify effective therapeutics for treating individuals experiencing OP-associated morbidities.

4475 Modeling Chemical Sensitivity: Prior Exposure to Stress and Pesticide Affects Neuroinflammatory Response to Subsequent Exposures in Mice

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Background and Purpose: Chemical sensitivity is a multi-symptom illness that results from sensitization to chemicals or mixtures following an initiating exposure and presents with symptoms including neurologic and cognitive dysfunction, depression, and anxiety, as well as respiratory and gastrointestinal issues. While many chemicals have been associated with development of chemical sensitivity, pesticides are one of the most common sensitizing agents. Previously, we have found that stress potentiates neuroinflammatory responses to organophosphate pesticides, such as chlorpyrifos and dichlorvos (DDVP), which is associated with long-term neuroimmune disorders such as Gulf War Illness (GWI). Interestingly, neuroinflammation is associated with the physiological and behavioral responses of "sickness behavior," whose symptoms share similarities with chemical sensitivity and long-term disorders like GWI. **Methods:** To evaluate the role of neuroinflammation in chemical sensitivity, adult male C57BL/6 mice were exposed corticosterone (CORT) for 7 days to mimic high physiological stress followed by exposure to DDVP; then, the mice were exposed to several other chemical and biological agents 7 days after the initial DDVP exposure, including DDVP, physostigmine, permethrin, and lipopolysaccharide. **Results:** The evaluation of inflammatory cytokine mRNA in the brain and peripheral tissues indicated that prior exposure to CORT DDVP exacerbated the expression of several cytokines compared to controls. **Conclusions:** These data suggest the potential involvement of neuroinflammation in the development of chemical sensitivity, which will be further investigated by future behavioral studies and evaluation of longer-term time points.

4476 Occupational Exposure to the Pesticides Malathion and Methyl Bromide Impacts Neuromuscular Junction Anatomy

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Background and Purpose: Pesticides are widely used and beneficial for pest and disease control in agriculture, aquaculture, forestry, and other industries as well as used to protect homes, businesses, and United States Service Members. According to the United States Geological Survey, 1 billion pounds of pesticides are used each year in the United States; however, numerous studies have demonstrated that these compounds can exert negative health effects. A spectrum of pathologies associated with pesticide exposure has been described, ranging from mild skin irritation to the development of progressive neurological diseases and cancer. Multiple chemicals and compounds that are used as pesticides are neurotoxicants with different mechanisms of action. Organophosphates, such as malathion (MAL), primarily inhibit acetylcholinesterase (AChE) activity at the neuromuscular junction (NMJ) which can lead to overstimulation and muscle paralysis. The workplace permissible exposure limit (PEL) for MAL established by the Occupational Safety and Health Administration (OSHA) is 15 mg/m3 for an eight-hour workday. On the other hand, methyl bromide (MB) is a volatile fumigant whose toxic mechanism of action is not fully understood but likely involves the methylation of nucleic acids, enzymes, and other cellular molecules. The PEL for MB established by OSHA is 20 parts per million (ppm) for an eight-hour workday. Although MAL and MB have different modes of action, locomotor effects have been reported from exposures to both pesticides in animals and humans. Overall, the effects from occupational exposures (repeated, low level) to these pesticides are understudied and, to our knowledge, no studies have examined the anatomical effects of these exposures on NMJs, the synaptic connections between motoneuron axon terminals and muscle fibers. We hypothesized that repeated occupational exposure to MAL or MB would cause differential effects in skeletal muscle NMJ anatomy. We expected

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