from exposure to heavy metals such as manganese and lead. Experiments to block senescent pathways in dopaminergic neurons to preserve autophagy and limit αSyn accumulation are currently ongoing in our lab.

3910 Bisphenol A Single and Repeated Treatment Increases HDAC2, Leading to Cholinergic Neurotransmission Dysfunction and SN56 Cholinergic Apoptotic Cell Death through AChE Variants Overexpression and NGF/TrkA/P75^{NTR}-Signaling Disruption

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Bisphenol-A (BPA), a widely used plasticizer, induces cognitive dysfunctions following single and repeated exposure. Several studies, developed in hippocampus and cortex, tried to find the mechanisms that trigger and mediate these dysfunctions, but those are still not well known. Basal forebrain cholinergic neurons (BFCN) innervate hippocampus and cortex, regulating cognitive function, and their loss or the induction of cholinergic neurotransmission dysfunction leads to cognitive disabilities. However, no studies were performed in BFCN. We treated wild type or histone deacetylase (HDAC2), P75^{NTR} or acetylcholinesterase (AChE) silenced SN56 cholinergic cells from BF with BPA (0.001 μM-100 μM) with or without recombinant nerve growth factor (NGF) and with or without acetylcholine (ACh) for one- and fourteen days in order to elucidate the mechanisms underlying these effects. BPA induced cholinergic neurotransmission disruption through reduction of ChAT activity, and produced apoptotic cell death, mediated partially through AChE-S overexpression and NGF/TrkA/P75^{NTR} signaling dysfunction, independently of cholinergic neurotransmission disruption, following one- and fourteen days of treatment. BPA mediates these alterations, in part, through HDAC2 overexpression. These data are relevant since they may help to elucidate the neurotoxic mechanisms that trigger the cognitive disabilities induced by BPA exposure, providing a new therapeutic approach.

3911 Olfactory and Central Neurotoxicity of Occupationally Relevant Inhaled Aerosols

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Fine and ultrafine particles generated at the workplace can aerosolize and thus inhalation exposure is a major occupational concern. Aerosolized particles deposited in nose and/or lung can reach the brain via retrograde transport across the olfactory sensory neurons (OSNs) or through the systemic circulation. The OSNs extend into the brain from the air-interface in the nose and thus have direct access to airborne pollutants and toxic chemicals. Indeed, environmental air pollutants are known to cause nasal pathology, neuroinflammation, and neurodegenerative changes, both in humans and animals. Toxicant-mediated olfactory damage often manifests as loss of olfaction, which precedes the hallmark clinical signs of neurodegeneration seen in Parkinson's (PD) and Alzheimer's diseases. Our recent experimental data suggest that olfactory and central neurotoxicity is elicited by a variety of chemicals and particulate aerosols. Here, we present evidence of neurotoxicity associated with exposure to two occupationally-relevant agents, welding fumes (WF) and diesel exhaust (DE). Welding generates fumes with high concentrations of fine and ultrafine metal aerosols composed of iron, manganese, chromium, and nickel, besides gaseous agents. There is growing concern that inhalation of WF causes PD-like manifestation, thus warranting extensive characterization of the neurotoxic potential of WF. Rats (male Sprague-Dawley; ~3 m old) were exposed to fumes generated by gas metal arc-stainless steel welding (GMA-SS / WF; 15 mg/m^3; 3 h/d × 10 d) and humanely euthanized after 7 d for neurotoxicity assessments. WF increased serotonin (5-HT; 43 %) levels in the olfactory bulb (OB), while reducing tyrosine hydroxylase protein (TH; 39 %) and glial fibrillary acidic protein (GFAP; 45 %). In the striatum (STR) and midbrain, brain regions typically affected in PD, WF reduced dopamine levels by 33 % and 14 %, respectively. A concordant reduction (22 - 33 %) in TH, alpha-synuclein (SNCA), and ubiquitin C-terminal hydrolase L1 (UCHL1 / PARK5) proteins was also seen in the STR, suggesting that a short-term repeated exposure to WF causes dopaminergic neurotoxicity. DE is a complex mixture of particulates and gases. The particulate fraction mainly consists of an insoluble elemental carbon core and an organic solvent soluble coating adsorbed on the carbon core that make up the bulk of the particulate matter in DE. The gaseous components primarily include oxides of carbon, nitrogen, and sulfur, as well as some low molecular weight hydrocarbons. Rats (male Sprague-Dawley; ~3 m old) were exposed to DE from a tier 2 engine (1 mg/m^3 particulate; 6 h/d × 4 d) and humanely euthanized after 1 d for neurotoxicity assessments. DE caused upregulation (3 to 5-fold) of mRNA transcripts for matrix metalloproteinase 9 (*Mmp9*), claudins (*Cldn1* and *Cldn2*), and *Gfap* (1.6-fold) in the OB, suggestive of altered blood-brain barrier integrity and reactive gliosis. A reduction (20 %) in olfactory marker protein was also evident. In the hippocampus, DE caused a robust increase in 5-HT (1000 %), tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon (YWHAE / 14-3-3-ε; 130 %), and GFAP protein (63 %). Activation of serotonergic receptors by 5-HT is known to inhibit hippocampal pyramidal neurons, which in turn is linked to cognitive impairment and cognitive dysfunction. Further, increased YWHAE is indicative of injury/damage to neural cells. Collectively, our findings show that occupationally-relevant incidental aerosols can elicit olfactory and central neurotoxicity and calls for extensive investigation of the long-term effects to assess progressive neurodegeneration and neurobehavioral outcomes, if any.

3912 Unraveling Neurotoxic Pathways of Manganese-Induced Parkinsonism *In Vivo*: Insights from High-Coverage Global Metabolomics Profiling

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disease and the most common among motor disorders. PD cases over age 65 are largely sporadic, with new studies suggesting a predominance of environmental risk factors over genetics in PD etiology. Chronic exposure to manganese (Mn) from occupational or environmental settings has been widely linked to PD, as indicated, for example, by higher PD prevalence found in welder/miner populations. Mn toxicity itself manifests as a disease termed manganism, sharing strikingly common hallmark features of neurodegeneration for which the molecular underpinnings remain to be elucidated. In this study, we leveraged an *in vivo* model of Mn toxicity, reproduced in it the behavioral and pathological hallmarks of PD, and conducted high-resolution global metabolomic analyses to illuminate Mn-induced neurotoxic effects and biochemical pathways. Importantly, in a dose-dependent manner, Mn-exposed *Drosophila melanogaster* experienced reduced lifespan, displayed deficits in climbing and locomotor activities, and supported by histological data, underwent loss of neurons. On live fly brains, LysoTracker assay further confirmed Mn-enhanced autophagic defects, and both Seahorse assay and MitoTracker assay demonstrated dysregulated mitochondrial dynamics under Mn exposure. In light of model relevance to PD, upon the completed dose scheme, heads and bodies were extracted and subjected to a liquid chromatography quadrupole-orbitrap mass spectrometry analysis for global metabolomic profiling. Raw MS1 fullscan data were processed to yield alignment tables; dose-specific pattern was discerned through multivariate partial least square discriminant analysis (PLS-DA). Welch's *t*-test and analysis of variance (ANOVA) were performed to single out statistically significant molecular features between groups, and tandem mass spectra were acquired for these features using pooled extracts. A streamlined high-coverage cheminformatic pipeline was applied, yielding a realm of unique structures owing to Mn-induced Parkinsonism including 234 and 405 respectively altered in head and body. The perturbed metabolomes embraced a vast chemical space, spanning for brain from lipids (e.g., acylcarnitines, sphingolipids, ceramides, lysophospholipids, fatty acids), amino acid neurotransmitters (e.g., arginine, glutamine/glutamate), purines (e.g., adenine), to vitamins (e.g., B family), etc. Quantitative pathway enrichment analyses (qMSEA) of brain metabolites identified 35 significantly metabolic pathways adjusted for false discovery rates (Holm-Bonferroni procedures), as represented by arginine biosynthesis, pantothenate and CoA biosynthesis, and nicotinate and nicotinamide metabolism. Combining PD-mimicking *Drosophila* model of Mn toxicity and untargeted high-coverage metabolomics, this study may be of use to future research seeking therapeutic countermeasures against PD as well as toward a better understanding of the basic cellular pathways that regulate Mn-induced neurotoxicity.

3913 Heterocyclic Aromatic Amines (HAAs) Target Mitochondrial Physiology

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Heterocyclic aromatic amines (HAAs) are classified as mutagens and potential human possible carcinogens. HAAs are toxicants that can be found naturally in plants or produced in a heat-dependent reaction between amino acids and sugars, producing pyridine, pyrimidine, or pyrazine, which reacts with creatine during high-temperature meat cooking. HAAs represent widespread exposure. HAAs exposure produces Alzheimer's disease (AD) and Parkinson's disease (PD) relevant neurotoxicity in cellular and animal models; data from our laboratory and others have shown that dopaminergic neurons are especially sensitive to HAA exposures, while other neuronal populations such as cholinergic neurons may also be affected. Biochemical mechanisms of neurotoxicity implicate elevated oxidative stress and mitochondrial toxicity. Notably, these mechanisms are critical to both AD and PD pathogenesis. There are many gaps in the literature with respect to the mechanism of neurotoxicity of HAAs that need to be addressed. We hypothesized that HAAs would target mitochondrial respiration as a key mechanism of neurotoxicity. Thus, we tested the effect of common HAAs harmane, harmine, norharmane (0-150 μM), PhIP (0-100 μM), and HONH-PhIP (0-10 μM) on mitochondrial physiology, a key pathogenic target in AD and PD. Upon assessing the parameters of mitochondrial function by measuring the oxygen consumption rate of cells, we observed a significant reduction in mitochondrial bioenergetics in primary cortical neurons exposed to HAAs for 24h, indicating that HAA negatively impacts mitochondrial respiration. Studies on specific mitochondrial complexes of the electron transport chain showed that β-carboline subclass compounds (harmane, harmine, and norharmane) inhibit mitochondrial complex I enzyme activity. Aminoimidazoaazarenes

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