mental effects are likely indicative of size-and oxidation-dependent toxicity and reveals the importance of identifying structure-specific toxicity which is particularly relevant in biomedical applications of GOs.

3667 Striatal Astrocytic REST Plays a Critical Role against Manganese-Induced Neurotoxicity in Mice

E. Pajarillo[1], A. Digman[1], I. Nyarko-Danquah[1], M. Aschner[2], and E. Lee[1]. [1]*Florida A&M University, Tallahassee, FL; and* [2]*Albert Einstein College of Medicine, New York, NY.*

Chronic manganese (Mn) overexposure causes a neurological disorder, referred to as manganism, exhibiting symptoms similar to parkinsonism. Dysfunction of the repressor element-1 silencing transcription factor (REST) is associated with various neurodegenerative diseases including Mn-induced neurotoxicity. Although neuronal REST showed neuroprotection in several neurological diseases, the role of astrocytic REST in neuroprotection remains to be studied. We investigated if astrocytic REST in the brain striatal region where Mn preferentially accumulates plays a role in Mn-induced neurotoxicity. Striatal astrocytic REST was deleted by infusion of adeno-associated viral vectors (AAV) containing sequences of the glial fibrillary acidic protein (GFAP) promoter-driven Cre recombinase into the striatum of $REST^{flox/flox}$ mice for 3 weeks, followed by Mn exposure (30 mg/kg, daily, intranasally) for an additional 3 weeks. Striatal astrocytic REST deletion exacerbated Mn-induced impairment of locomotor function, motor coordination, and cognitive function Moreover, this deletion further decreased Mn-reduced tyrosine hydroxylase (TH) expression and glutamate transporter 1 (GLT-1) in the striatum. REST deletion also exacerbated Mn-induced proinflammatory cytokines, such as TNF-α, and COX-2 in the striatum as well as human H4 astrocyte cultures. To confirm these changes are from astrocytic REST in the mouse brain, we used an *in vitro* astrocytes and neuronal cultures. Incubation with conditioned media from Mn-treated astrocytes with DN-REST for REST inhibition led to exacerbated oxidative stress and cytotoxicity in Cath.-a-differentiated (CAD) neuronal cultures compared to CAD cells exposed to media from control astrocytes. But CAD cells exposed to conditioned media from Mn-exposed astrocytes with REST overexpression showed lower ROS levels and increased cell viability compared to those from Mn-treated astrocytes with DN-REST or control vector. REST overexpression attenuated Mn-reduced GLT-1, while its inhibition exacerbated Mn-reduced GLT-1 in astrocytes. These findings indicate that astrocytic REST plays a critical role against Mn-induced neurotoxicity, at least in part, by modulating proinflammatory cytokines and GLT-1.

3668 Changes in Fecal and Cecal Microbiota in Male and Female Offspring Exposed Prenatally and Postnatally to Silver and Palladium Nanoparticles

S. E. Woodman, J. Pedersen, and P. L. Durham. *Missouri State University, Springfield, MO.* Sponsor: P. L. Durham, American Association for the Advancement of Science

Heavy metal nanoparticles are increasingly being used in cosmetics, agriculture, biomedical applications, and food and beverage products. Acid rain can cause leaching of heavy metals into water systems, which can then be ingested and depending on the concentration may lead to pathology in the digestive system. A growing body of evidence points to the crucial role of the gut microbiome in maintaining a healthy immune system and in helping to prevent development of various chronic diseases, including IBD, obesity, diabetes, and various allergies. However, the impact of nanoparticle exposure on the gut microbiome is not yet fully understood, especially when exposure occurs early in life, as most studies in mammalian models have focused primarily on adult organs and tissues. Additionally, nanoparticles ingested by the mother may be passed down to their offspring through breast milk. To investigate the impact of nanoparticles on the gut microbiome, male and female rats were exposed to palladium (15 nm; 2 mg/L) and silver (20 nm; 0.1 mg/L) nanoparticles in their drinking water during mating. Nanoparticle exposure continued throughout gestation and postpartum. Control rats were given deionized water to drink throughout the study. Fecal and cecal samples were collected from pups that had been exposed to prenatal and postnatal nanoparticles and from control rats at day 21 after birth. DNA was extracted from samples using a QIAamp DNA Stool Mini Kit, and bacterial tag encoded FLX titanium amplicon pyrosequencing (bTEFAP) Illumina sequencing of the 16s ribosomal DNA was used to determine the bacterial types present in the samples. Decreases in the Firmicutes to Bacteroidetes ratios, an indication of gut dysbiosis, were observed in both fecal and cecal samples of male and female animals exposed to silver or palladium when compared to control animals. Also, a decrease in diversity was observed in the silver and palladium exposed offspring. Changes were seen in bacterial abundance across all taxonomic levels, including a decrease in Verrucomicrobiae, Spirochaetia, and Clostridiales and an increase in Bacteroidetes and Eacteroidales within both fecal and cecal samples in both sexes. Additionally, Ruminococcaceae and Akkermansiaceae decreased in male and female fecal samples, but not in cecal samples. These results provide the first evidence to our knowledge that exposure to silver and palladium nanoparticles during development and early life can promote gut dysbiosis. Since gut dysbiosis is a risk factor for irritable bowel disease (IBD), chronic exposure to nanoparticles could result in development of IBD.

3669 Orally Administered Cellulose Nanofibrils Impact Cardiac Performance, Neurotransmitters, and Metabolite Profile in Male and Female Rat Pups in an Age- and Sex-Related Manner

N. P. Mortensen[1], M. M. Moreno Caffaro[1], W. Pathmasiri[2], R. W. Snyder[1], S. L. Watson[1], P. R. Patel[1], S. J. Sumner[2], and T. R. Fennell[1]. [1]*RTI International, Research Triangle Park, NC; and* [2]*University of North Carolina at Chapel Hill, Chapel Hill, NC.*

The potential applications of cellulose nanofibrils (CNFs) as food additives or in food packaging, present a possible source of human ingestion. Little is known about biological responses to CNFs exposure during infancy when both the intestinal tract and brain are still undergoing considerable development. In the study presented here male and female rat pups received four daily oral doses of 10 mg/kg CNFs between postnatal day (PND) 7-10 or 17-20 and were sacrificed at PND 21. Basic neurobehavioral (acoustic startle response, locomotor activity, and rotarod) and cardiac assessments were performed at PND 20. Six neurotransmitters/metabolites were quantified in brain by UPLC with electrochemical detection. Plasma metabolites (n = 186) were quantified using AbsoluteIDQ® p180Kits (Biocrates) analyzed by LC-MS. Pups dosed between PND 7-10 had significantly ($P<0.05$) increased neurotransmitters/metabolites in brain tissue (male: dopamine, norepinephrine, and serotonin, female: dopamine and serotonin). The plasma ratio serotonin/tryptophan was found to have a significantly increased fold change (FC, male: 1.29, female: 1.42), tryptophan is a biosynthetic precursor for serotonin. No changes in the neurobehavioral assessment were observed following dosing between PND 7-10. However, female pups dosed between PND 17-20 had a significantly increased response time in the acoustic startle test. While no significant changes in neurotransmitters/metabolites were found in the brain for female pups orally administered CNF between PND 17-20, 16 amino acids had a decreased FC in plasma, including glutamate (FC: 0.75) and aspartate (FC: 0.67). Also, the FC for the sums of essential, non-essential, branch-chain, and aromatic acids were decreased. Amino acids are important for proper neurotransmission, having specific, but interconnected, roles. Metabolomic analysis of plasma showed that 23-48 individual metabolites were important for discrimination of CNF dose groups from control, and that largest class of metabolites was amino acids for all dosing groups with between 7-16 individual amino acids. Our results show that the biological responses to orally dosed CNF in early life happen in an age- and sex-related manner. Our data suggests that CNF may impact neurobehavioral, neurotransmitter/metabolite concentrations in brain, as well as the metabolite profile in plasma.

3670 CNC-Exposed Paternal Reproductive Toxicity Affects the Placenta

I. Shrivastava[1], L. Campagnolo[2], N. Yanamala[3], A. Pietroiusti[4], G. Somma[2], E. R. Kisin[1], V. E. Kagan[5], and A. A. Shvedova[1]. [1]*NIOSH, Morgantown, WV;* [2]*Università degli Studi di Roma Tor Vergata, Rome, Italy;* [3]*Rutgers Robert Wood Johnson Medical School, Newark, NJ;* [4]*UniCamillus—Saint Camillus International University of Health Sciences, Rome, Italy; and* [5]*University of Pittsburgh, Pittsburgh, PA.*

Exposure of mice to nanocellulose crystals (CNC) is known to affect male reproductivity caused by alterations in sperm properties such as concentration, motility, morphology and DNA integrity. Mechanisms driving these malfunctioning reproductive responses to CNC exposure are unclear. Published results support the idea that epigenetic changes contributing to male infertility have the potential for transgenerational transfer. We explored if epigenetic changes in testis affect both male reproductive function and gene/protein expression in placental tissue of unexposed females impregnated by CNC exposed males. A group of C57/BL6J male mice was sub-chronically exposed to CNC (40µg/mouse/twice a week/3 weeks) by pharyngeal aspiration; the control group was exposed to the vehicle (USP grade water). Three months post exposure, mice were mated with naïve females and the testis and placenta tissues (exposed and control) were evaluated for gene-expression data. The CNC-exposed mice showed a significant difference in sperm cell counts, motility and immotile spermatozoa compared to non-exposed control mice. Post-weaning, 8 pups from CNC-exposed fathers died, while no death was observed in the litters from unexposed fathers, suggesting a higher fragility of pups from the CNC-exposed fathers. Differentially expressed genes (DEGs) that overlap between exposed testis and placenta of mice plugged by the exposed males was identified, resulting in a gene-set of 63 DEGs. Hierarchical clustering identified EIF3A, FXR1, LUZP1 in testis and EIF3A, TGFBR3 in placenta as significantly upregulated. The top enriched pathways and network using IPA for the same gene-set was PTEN-Signaling and Organismal Injury and Abnormalities, respectively. In conclusion, our data support the hypothesis that paternal exposure to CNC reflects adverse effects on the progeny, probably via placental mediated pathways. *Disclaimer: The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.*

SOT 61ST ANNUAL MEETING & TOXEXPO • SAN DIEGO, CA MARCH 27–31, 2022

The Toxicologist

Supplement to *Toxicological Sciences*

SOT | Society of Toxicology

Toxicological Sciences
The Official Journal of the Society of Toxicology
www.academic.oup.com/toxsci

OXFORD UNIVERSITY PRESS

ISSN 1096-6080 Volume 186, Issue S1 March 2022

Publication Date: March 23, 2022