neurons in the *Substantia nigra*, leading to movement disorders. The pathological hallmark of PD is presence of Lewy bodies, which are intracellular inclusions consisting of primarily of α-synuclein. Although essentially all cases of PD are of unknown etiology, two point mutations (A53T and A30P) in the α-synuclein gene have been identified in familial early-onset PD. Previous reports have shown that mutant α-synuclein may form fibrils more rapidly than wild-type (WT) protein. In order to determine the underlying molecular basis for enhanced fibrillation of mutants, structural properties, responses to environmental changes and propensity to aggregates of WT, A30P and A53T α-synucleins were systematically investigated. A variety of biophysical methods, including far-UV circular dichrosim, FTIR, small-angle X-ray scattering, and light scattering, were employed. Neither the natively unfolded, nor the partially-folded intermediate conformations, are affected by the mutations. However, both mutants underwent self-association more readily than the WT. We attribute this effect to increased propensity of their partially-folded intermediates to aggregate, which would account for the correlation of these mutations with PD.

68 SC ***Post-Doctoral Student***

OBESITY AS A POTENTIAL RISK FACTOR FOR DOPAMINERGIC NEUROTOXICITY. Krishnan Sriram, James P. O'Callaghan. *Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV*

Obesity is a major risk factor associated with a variety of human disorders. While its involvement in disorders such as diabetes, coronary heart disease and cancer have been well characterized; it remains to be determined if obesity has a detrimental effect on the nervous system. Due to the limited regenerative capability of the CNS and the specific vulnerability of certain cell types to disease and chemical injury, obesity may confer an added risk of damage to the brain as it does to other organ systems. To address this possibility we sought to determine whether obesity can mediate/modify the brain's response to neurotoxic insult. To that end we examined the effects of the neurotoxin methamphetamine (METH), which is known to mimic some key features associated with the pathogenesis of Parkinson's disease (PD), in an experimental animal model of obesity, the leptin-deficient (*ob*/*ob*) mouse. Epidemiological studies provide evidence to show that low calorie intake decreases the risk of PD, while a converse situation, high calorie intake and a lack of exercise may be associated with the development of PD. Administration of METH resulted in mortality among *ob*/*ob* mice but not among their lean littermates. While METH caused dopaminergic nerve terminal degeneration as indicated by decreased striatal dopamine (49%) and tyrosine hydroxylase protein (TH, 68%), and increased glial fibrillary acidic protein (GFAP, 313%) in the lean mice, these effects were exacerbated under the obese condition, 96, 86 and 602%, respectively. The neurotoxic outcome in *ob*/*ob* mice remained exacerbated even when lean and *ob*/*ob* mice were dosed with METH based only on a lean body mass. These findings demonstrate that the *ob*/*ob* condition exacerbates METH-mediated neurotoxicity and implicates obesity as a risk factor associated with toxicant-induced neurodegeneration.

69 SC ***Post-Doctoral Student***

ENVIRONMENTALLY RELEVANT MODELS OF α-SYNUCLEIN PATHOLOGY. A. Manning-Bog, A.L. McCormack, M. Lavasani, A. Parachikova, M. Isla, D.A. Di Monte. *The Parkinson's Institute, Sunnyvale, CA*

The protein α-synuclein is likely to play an important role in the neurodegenerative process underlying Parkinson's disease (PD). The mechanisms of α-synuclein-induced pathology have been suggested to involve its intraneuronal aggregation that could be initiated by a conformational shift into α-sheet structure and oligomerization. The purpose of this study was to assess whether exposure to environmental agents could change α-synuclein expression and enhance its tendency to aggregate. Mice were exposed either to a 3-week treatment with the herbicide paraquat or a 2-month combined administration of the fungicide diethyldithiocarbamate (DDC) plus aluminum (Al). Both experimental paradigms resulted in an up-regulation of α-synuclein within the *Substantia nigra*. Mid-brain sections from experimental animals were incubated with anti-α-synuclein antibody, revealing an increased nuclear and cytosolic immunoreactivity within nigral neurons in paraquat- and Al/DDC-challenged mice as compared to controls. The time course of paraquat-induced α-synuclein up-regulation was assessed by Western blot analysis of ventral mesencephalon homogenates. α-Synuclein expression was increased by 51, 25 and 17% compared to saline-treated mice at 2 days after each of three consecutive weekly administrations, and levels returned to control values by 7 days post-injections. Although no intraneuronal inclusions were observed, robust thioflavin-S staining was present in the *Substantia nigra* of paraquat- and Al/DDC-exposed animals, indicating α-sheet formation. Thioflavin-S staining was particularly evident in perinuclear regions. These findings indicate that α-synuclein up-regulation and increased intraneuronal α-sheet structures are consequences of exposure to environmental toxicants and may be crucial steps toward the formation of pathological aggregates and other neurodegenerative changes. *Supported by NIEHS grants ES10442 and ES10806.*

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GENETIC, HISTOCHEMICAL AND ANATOMIC CHARACTERIZATION OF AN EXCITING NEW MOUSE MODEL FOR PD. Marie E. Legare, William H. Hanneman. *Departments of Environmental Health and Pathology, Colorado State University, Ft. Collins, CO*

Parkinson's disease (PD) is a devastating clinical entity that encompasses both a wide range of clinical severity and age of onset. Although PD has been recognized for over a century, to date, there have been no genetic nor molecular pathways determined which could explain the phenotype of this disease. There is, however, indication that both a susceptibility to toxic compounds and an underlying genetic component together are responsible for the progression of the disease process. Toward the goal of understanding the interaction of toxicants with genetic background, we are poised to employ molecular and genetic tools to analyze the downstream cellular consequences, in cells of specific genetic background, to toxicants which are purported to be of critical importance toward development of PD. A new mouse neurologic mutant (NM3) exhibits several specific hallmarks of early onset PD, including severe movement disorders and decreased dopamine levels in the mid-brain of these mice, without evidence of cerebellar or hippocampal deficits. The initial screening of this mouse mutant will be presented, underscoring its potential use as a model for understanding the underlying genetic and molecular events of PD.

Parkinson's Disease, Environment and Genes

. . . to advance our goals of finding the cause, cure, and better treatment for Parkinson's disease.

Abstracts