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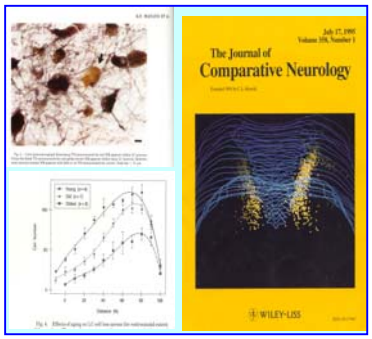
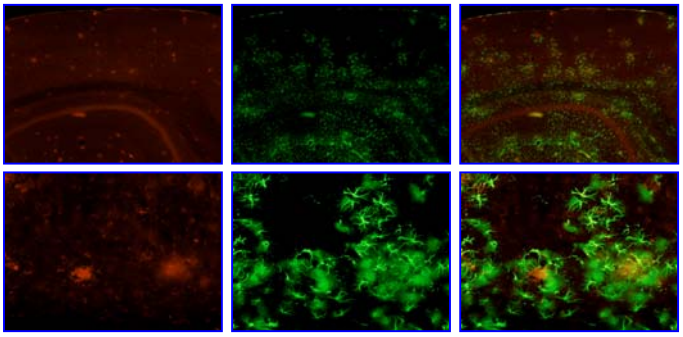
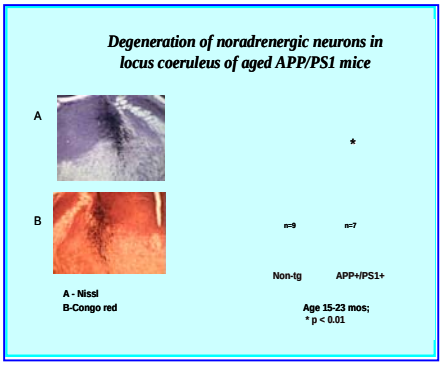
My laboratory focuses on the cellular and molecular mechanisms responsible for aging and age related neurodegenerative disorders. Human post-mortem tissue and animal models of both Alzheimer's disease and depression are studied to understand the mechanisms responsible for selective vulnerability of specific populations of neurons. We use post-mortem tissues from individuals with affective disorder to identify cellular and molecular alterations and to provide insight into the etiology of the disorders. Our interests include the use of animal models to develop strategies for the therapeutic management of patients with these disorders.



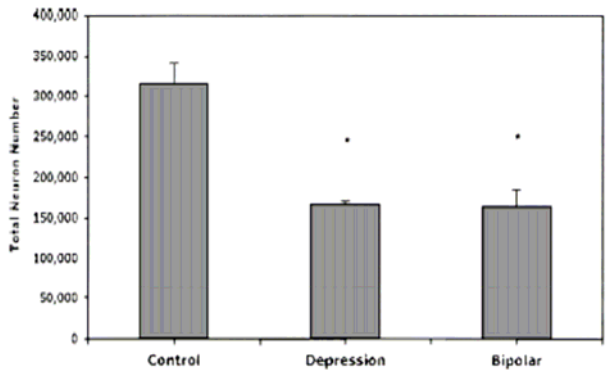
Our current studies in the NIH-funded Specialized Neuroscience Research Program (SNRP) involve understanding the role noradrenergic system in aging and Alzheimer disease. Loss of Locus coeruleus (LC) noradrenergic (NA) neurons occurs in several neurodegenerative conditions including Alzheimer's disease (AD). In vitro and in vivo studies have shown that NA influences several features of AD disease including inflammation, neurodegeneration, and cognitive function.



We have previously investigated the role of noradrenergic neurons in brainstem from postmortem tissue obtained from normal aged and age-related disorders, including Alzheimer's disease, Parkinson's disease and Down syndrome. Design-based stereological techniques allow for testing whether aging and brain diseases are associated with loss of locus coeruleus (LC) neurons, as identified by immunohistochemical staining for the tyrosine hydroxylase in human brains and animal models.



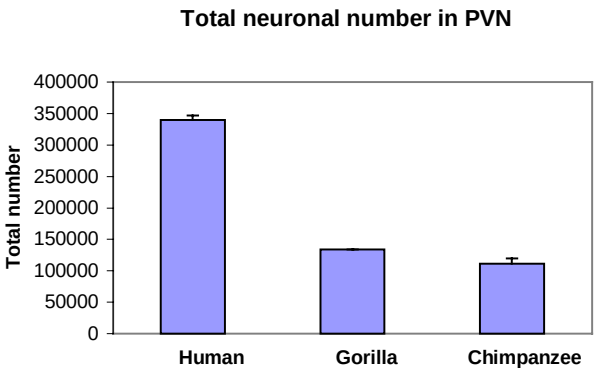
Using a double transgenic APP/PS1 mouse model of Alzheimer's disease (AD) we have found some of the pathological features of the human disease, including gliosis; a loss of noradrenergic - containing neurons in locus coeruleus; reduction of noradrenergic nerve terminals; the formation of amyloid-beta plaques in the cortex, amygdaloid complex, and hippocampus. Hormone replacement therapy with the gonadal steroid estradiol may affect cellular function in brains of postmenopausal women. In vitro studies suggest that 17-beta estradiol and raloxifene can alter the microglial and astrocyte expression of immuno-neuronal modulators, such as cytokines, complement factors, chemokines, and other molecules involved in neuroinflammation and neurodegeneration. We are currently investigating whether therapeutic interventions (estradiol) alter the course of neurodegeneration and



plaque pathology in these models. Our preliminary results show that long-term 17-beta estradiol treatment in normal aged female C57Bl/6 mice and aged female dtg APP/PS1 female mice significantly lowered the numbers of astrocytes and microglial cells in dentate gyrus and CA1 regions compared with placebo.

Our studies of depression in humans indicate that the number of neurons in paraventricular (PVN) of the hypothalamus is significantly reduced in post-mortem brains from patients with major depressive disorder (MDD), and bi-polar disorders (BD); and, that the reduction is correlated with the severity of depressive symptoms. We found no neuronal loss in supraoptic nucleus of the hypothalamus. Thus, we find a selective loss of PVN neurons in depression.

The paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus are involved in the regulation of autonomic functions, including fluid and electrolyte homeostasis. Among the cells in the SON and PVN are populations of arginine vasopressin (AVP) - and oxytocin (OT)-synthesizing neurons that send projections to the neurohypophysis; and, in the case of the PVN, project to other brain areas including cortex. Recent research indicates that these nuclei may also play a role in CNS functions, including social affiliation and emotional cognition, which are frequently disturbed in aging and in neuropsychiatric disease. This cross-species investigation using chimpanzee, gorilla, and human brains seeks to contrast and compare differences in the total number of neurons in SON and PVN regions of hypothalamus. We have previously reported that there was a 50% reduction in the number of PVN neurons in patients of major depression and bipolar disorders Manaye et al., 2005). The greatly expanded population of PVN neurons in humans is the product of recent evolution and may be particularly vulnerable to pathology. Understanding the neuronal circuitry related to social bonding, emotions, and cognition in human and closely related primate species, which share about 98% DNA homology, may provide insight into the neurobiological basis for human's neuropsychiatric disorders.



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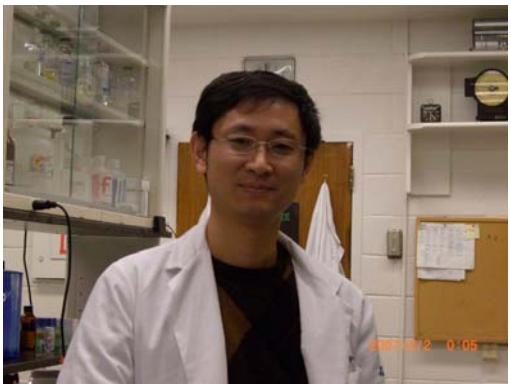
Previous Graduate Students

Joanne S. Allard, Ph.D.
Post-doctoral fellow at NIA/NIH

Jahn O'Neil, Ph.D.
Post-doctoral fellow at John Hopkins University

Post-Doctoral Fellows

Yukti Sharma, Ph.D.



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