



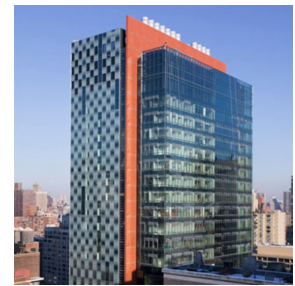
PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the
Brain & Mind Neuroscience Institute
Weill Cornell Medical College (WCMC)
&

The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 3/22/18, 3:45 PM

1300 York Ave, 9th Floor – A950



“Neurovascular and cognitive dysfunction in arterial hypertension”

Monica M. Santisteban, Ph.D., Lab of Costantino Iadecola, MD



Hypertension and high dietary salt intake are important risk factors for stroke and dementia. Almost 50% of US adults suffer from hypertension, and there is a strong relationship between mid-life HTN and late-life dementia, including Alzheimer's disease. The neurovascular unit works through complex regulatory mechanisms to assure adequate cerebral blood perfusion to the brain and maintenance of the homeostasis of the cerebral microenvironment. Hypertension is well-known to disrupt the function of the neurovascular unit, leading to neuronal dysfunction and cognitive impairment. However, the mechanisms mediating the deleterious effects of hypertension on the brain remain to be fully established despite extensive investigation. Deoxycorticosterone (DOCA)-salt hypertension is a well-established model of hypertension driven by sodium retention and brain renin-angiotensin system activation, which is highly relevant to human essential hypertension. Using this model, we established that hypertension leads to profound alterations in neurovascular coupling and endothelium-dependent relaxation, eventually leading to cognitive impairment. Using a combination of pharmacological and genetic approaches, we found that brain angiotensin II acts on the AT1 receptors on perivascular macrophages, innate immune cells closely associated with cerebral arterioles, to mediate the neurovascular and cognitive dysfunction through the production of reactive oxygen species. Since salt retention leads to activation of the adaptive immune system, we are currently investigating the involvement of adaptive immunity in contributing to the dysfunction in DOCA-salt hypertension. Our findings elucidate a novel mechanism by which hypertension affects neurovascular function leading to cognitive impairment.

“The BDNF Val66Met prodomain eliminates spines and synapses and alters maturing fear extinction circuitry”

Joanna Giza, Ph.D., Lab of Francis Lee, MD., Ph.D.



The common single nucleotide polymorphism (SNP) within the brain derived neurotrophic factor (BDNF) gene that changes Valine into Methionine (Val66Met) lies within the prodomain region that's cleaved off to produce mature BDNF. It is a susceptibility factor for a broad range of neuropsychiatric disorders including post-traumatic stress disorder (PTSD), which is characterized by the inability to extinguish the fear of impending danger associated with the cue that no longer signals a threat. The molecular mechanism causing this dysregulation in BDNF Met carriers has not been elucidated. We used super resolution imaging and found that the BDNF Met prodomain can eliminate synapses and spines in mature hippocampal neurons in vitro. By examining the receptor expression in vivo, we found that it affects specifically vCA1 neurons projecting into the PL. Testing real time activity of these neurons within a fear extinction circuit using fiber photometry revealed that vCA1 distal fibers in the PL are able to predict the tone that signals the threat with repeated trials and return to baseline shortly after the tone onset when the fear has been extinguished. However, the same neurons in BDNF^{Met/Met} mice are unable to adapt. Our findings provide a mechanism used by the BDNF Met prodomain to alter fear extinction circuitry maturation by acting during a peri-adolescent timeframe defined by the expression of p75^{NTR}/SorCS2 receptor complex, consequently modifying fear extinction behavior.