The Neuroscience Graduate Program

presents:

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IN A PHD THESIS DEFENSE

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1:00 PM IN AUDITORIUM K-307 (3-6409)

Developmental changes in astrocytic calcium signaling
and
microcirculatory failure in the setting of subarachnoid hemorrhage: a role for potassium

The purpose of following thesis was to better elucidate neuroglial signaling and its role in neurovascular coupling in the context of subarachnoid hemorrhage. After rigorous experimentation and study I have been able to show that metabotropic glutamate receptor 5 (mGluR5) is developmentally down regulated in adult vs. young murine and human astrocytes, implicated microcirculatory dysfunction in the course of subarachnoid hemorrhage, specifically delayed cerebral ischemia and discovered a role of potassium in modulating hypoxia mediated capillary hyperemia. mGluR5 expression in astrocytes has been a central tenet of the tripartite synapse, a model of neuroglial signaling, since the late 20th century. Using *in vivo* two-photon microscopy, ultrastructural microscopy and genomic analysis we showed that despite the prevalence of mGluR5 in young mouse astrocytes, adult mouse and adult human astrocytes do not express this receptor in measurable levels. This unexpected observation is by itself quite significant in the neuroglial field, because before our study it was commonly, but erroneously assumed that mGluR5 expression in astrocytes underlies the tripartite synapse in adults.

Subsequent work using *in vivo* two photon microscopy of a mouse model of subarachnoid hemorrhage allowed us to quantitatively measure changes in capillary perfusion. Additionally we were able to reverse the disturbance in capillary flow through the use of a novel hemorheological agent, hyaluronidase, which cleaves hyaluronan from the endothelial glycocalyx, decreasing microcirculatory resistance. This work is one the first *in vivo* reported studies demonstrating microcirculatory dysfunction in the context of subarachnoid hemorrhage and the first to use hemorheology primarily for the purpose of ameliorating delayed cerebral ischemia associated with subarachnoid hemorrhage. Finally, recent evidence has come to light demonstrating the ability of erythrocytes to sense local decreases in oxygen tension and increase their deformability accordingly in order to traverse capillary beds quicker, a new type of capillary hyperemia. My work primarily focused on the modulatory effects of extracellular potassium on erythrocytes as they pass through the cerebral microcirculation. I was able to show that increases in extracellular brain potassium cause an increase in erythrocyte velocity *in vivo* and is primarily due to increased erythrocytic deformability.

The results of these studies have brought the mechanisms of calcium signaling in astrocytes into clearer focus, helped to elucidate the pathophysiology involved in subarachnoid hemorrhage at the microcirculatory level and helped to better understand the role of potassium in erythrocyte mediated capillary hyperemia.