

The Neuroscience Graduate Program

presents:

STEPHANIE SYC

ADVISOR:

RICHARD LIBBY

IN A THESIS PROPOSAL

MONDAY, 14 SEPTEMBER 2015

1:30PM IN AUDITORIUM K-307 (3-6408)

Mechanisms of Endothelin-Induced Retinal Ganglion Cell Death

Visual impairment in glaucoma is caused by death of neurons in the retina, the retinal ganglion cells (RGCs). Increased intraocular pressure is the main risk factor for the development of glaucoma, yet pressure-lowering treatments do not prevent progression of visual impairment in many patients. Understanding the early signaling pathways necessary for disease progression is critical for the development of new treatment strategies for glaucoma.

The endothelin system is expressed in the central nervous system and has normal physiologic functions, however, this system has also been shown to play a role in neurodegeneration. Components of the endothelin system are upregulated during the early stages of glaucoma. Endothelin injection into the posterior chamber of the eye causes immediate vasoconstriction of the retinal vessels and eventual RGC death while nonselective pharmacologic antagonism of endothelin receptors significantly lessens glaucomatous damage in an ocular hypertensive mouse model of glaucoma. Determining the molecular mechanisms underlying endothelin-induced RGC death is complex because endothelin signaling occurs in both vascular and neural tissues. The endothelin system is comprised of three ligands and two receptors, endothelin receptor subtype A (EDNRA) and endothelin receptor subtype B (EDNRB). The receptors are preferentially expressed on different retinal tissue, one on the retinal vasculature (EDNRA) and the other on retinal neurons and glia (EDNRB). It is unknown, however, which endothelin receptor is contributing to RGC loss.

I propose to determine which receptor contributes to endothelin-induced neurodegeneration of RGCs by selectively inhibiting each receptor subtype pharmacologically prior to endothelin injection. In order to understand how endothelin signaling causes RGC death, it is important to determine the signaling pathway responsible for endothelin-mediated neurodegeneration. JNK-JUN signaling is known to be involved in endothelin-mediated neurodegeneration in the brain. JNK-JUN signaling also contributes to RGC death after glaucoma-relevant insults such as ocular hypertensive insult and axonal injury. Interestingly, an intravitreal injection of endothelin induces JNK activation and upregulation of its canonical target, JUN, in RGCs and Müller glia. I will determine if JUN activation is required for RGC death after endothelin injury by specifically deleting JUN in the neuronal retina. I propose to 1) determine the endothelin receptor subtype that contributes to endothelin-mediated neurodegeneration of RGCs and 2) determine if activation of JUN is required for endothelin-mediated RGC death. Together these experiments will provide insight into the early molecular signaling pathways that contribute to RGC death in glaucoma and may provide novel therapeutic targets for the treatment of the disease.