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BSc (Biology), University of Prince Edward Island, 2008

DEPARTMENT OF PHARMACOLOGY

TITLE OF THESIS:	STRATEGIES FOR NEUROPROTECTION AND IOP MODULATION IN EXPERIMENTAL MODELS OF GLAUCOMA
TIME/DATE:	10:00 am, Wednesday, December 6, 2017
PLACE:	Room 3107, The Mona Campbell Building, 1459 LeMarchant Street

EXAMINING COMMITTEE:

Dr. Claire Mitchell, Department of Anatomy and Cell Biology, University of Pennsylvania School of Dental Medicine (External Examiner)

Dr. Kerry Goralski, College of Pharmacy, Dalhousie University (Reader)

Dr. Ryan Pelis, Department of Pharmacology, Dalhousie University (Reader)

Dr. Melanie Kelly, Department of Pharmacology, Dalhousie University (Supervisor)

Dr. William Baldridge, Department of Medical Neuroscience, Dalhousie University (Co-Supervisor)

DEPARTMENTAL REPRESENTATIVE:	Dr. Christopher McMaster, Department of Pharmacology, Dalhousie University
CHAIR:	Dr. Nikhil Thomas, PhD Defence Panel, Faculty of Graduate Studies

ABSTRACT

Glaucoma is a blinding eye disease caused by death of retinal ganglion cells (RGCs). Intraocular pressure (IOP) is the only modifiable risk factor, and is the target of all current glaucoma therapeutics. However, IOP modification does not always successfully prevent further RGC loss. Therefore, therapies directly targeting RGC death may be additionally beneficial. The inflammatory cytokine tumor necrosis factor α (TNFα) is upregulated in glaucoma; however, how TNFα contributes to RGC death remains unclear. Recently, TNFα was suggested to promote calcium-permeable AMPA receptor (cpAMPAR) expression in experimental glaucoma, and was associated with excitotoxic RGC death. Furthermore, aside from IOP-lowering effects, cannabinoid receptor 1 (CB_1) modulation is suggested to be neuroprotective in experimental glaucoma, likely through multiple mechanisms of action. In other neurons, CB_1 modulation can inhibit TNFα-mediated increases in cpAMPAR expression; therefore, CB_1-mediated neuroprotection in experimental glaucoma could include manipulation of this pathway. However, there are several disadvantages of direct CB_1 orthosteric modulators, which may limit usefulness as clinically-relevant therapeutics. Recently, a new class of CB_1 modulators have been developed, CB_1 positive allosteric modulators (PAMs), which have the potential to modulate CB_1, while limiting some disadvantages. Therefore, the aims of my thesis were to investigate TNFα-induced changes in cpAMPAR expression, and modulation of this mechanism by CB_1, and to investigate the ability of CB_1 PAMs to decrease IOP and provide RGC neuroprotection in experimental glaucoma. IOP was assessed using rebound tonometry, and RGC density by Brn3a immunohistochemistry. Functional expression of cpAMPARs was evaluated through calcium imaging in *ex vivo* isolated retina. My data show that: (1) TNFα incubation increases AMPA-induced changes in calcium dynamics, consistent with an increase in cpAMPARs observed in at least one model of experimental glaucoma; (2) CB_1 PAMs can reduce IOP acutely; (3) chronic administration was not neuroprotective in two models of experimental glaucoma. Taken together, this work demonstrates that while TNFα-induced increases in cpAMPAR expression may contribute to RGC death, and CB_1 modulation may be a therapeutic target in modifying this pathway, the CB_1 PAMs explored here were insufficient in preventing RGC death when administered in experimental glaucoma.