



Neuroscience Graduate Program

***Presentation of Dissertation Proposal***

"The effect of PSCA, an endogenous proto-toxin, on alpha-7 nicotinic acetylcholine receptor containing neurons in the ciliary ganglia during embryonic development."

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## Abstract

Nicotinic acetylcholine receptors (nAChRs) are involved in signaling throughout the CNS and PNS. Of the many subtypes of nAChRs,  $\alpha 7$  containing nAChRs are particularly interesting because of their importance in diseases like Alzheimers and schizophrenia, their importance in modulating other cell signaling, and an unusually high calcium permeability, comparable to NMDA (N-methyl-D-aspartic acid) receptors. However, over-exposure to calcium can lead to excitotoxicity and neuronal death, necessitating mechanisms for altering the responsiveness of these receptors to ligand. It has been shown that glycosylphosphatidylinositol (GPI)-linked molecules related to  $\alpha$ -bungarotoxin, a component of snake venom, co-localize with  $\alpha 7$  nAChRs. The Nishi lab has identified one such molecule, Prostate Stem Cell Antigen (PSCA), in chickens. Over-expression of PSCA has been shown to rescue choroid neurons from apoptosis by selectively blocking  $\alpha 7$  nAChRs from being activated by nicotine. Studies have shown that  $\alpha$ -bungarotoxin-like molecules can alter calcium permeability in nAChRs and receptor kinetics in nAChRs. This suggests a neuromodulatory role for PSCA binding to  $\alpha 7$  nAChRs. However, the physiological role of PSCA in modulating nAChRs remains unclear. The purpose of this project is to investigate this role. **Overall, the hypothesis of this research is that PSCA is up-regulated in ciliary ganglion neurons by a target derived mechanism and functions to modulate the excitability of choroid neurons in the ciliary ganglion by binding to  $\alpha 7$  nAChRs during development in order to protect the cell from over-exposure to calcium and resultant cell death.** In order to investigate the possible modulatory function of PSCA, the chicken ciliary ganglion will be used as model system. Ciliary ganglia contain neurons expressing  $\alpha 7$  nAChRs, in fact 90% of signal passing through the ciliary ganglion is due to  $\alpha 7$  nAChR activation. Also, at E8 PSCA is not present in these neurons, but between E8 and E14 in development PSCA is highly upregulated in the ciliary ganglion. Studies of the target tissues for ciliary ganglia also indicate that a third of all  $\alpha 7$  nACh receptors are silenced, which is consistent with a mechanism for modulation of these receptors, perhaps through binding with PSCA. The overarching hypothesis of this research will be tested using immunofluorescence, immunoprecipitation, qRT-PCR and design-based stereology of ciliary ganglia from an RNAi-induced knockdown of PSCA, uninfected ganglia, or ganglia overexpressing PSCA; it will look at co-cultures of ciliary ganglion neurons with target derived tissue and it will use whole cell calcium imaging of acute cultures of ciliary ganglia to look at receptor function. The aims of the research are to (1) demonstrate binding of PSCA with  $\alpha 7$  nAChRs, (2) investigate whether loss of PSCA has a neurotoxic effect on developing neurons in contrast to the apparent neuroprotective effect of overexpression of this molecule, (3) establish whether the upregulation of PSCA during this period of synaptogenesis and naturally occurring cell death is caused by target derived signaling and (4) establish whether loss of PSCA alters whole cell calcium influx in neurons stimulated with nicotine. Understanding the role of this molecule and the mechanism by which it modulates  $\alpha 7$  nAChR function can lead to further understanding of the role of nicotine in brain development both in utero and during puberty; it might also lead to therapeutic targets for diseases whose pathology is influenced by  $\alpha 7$  nAChRs including schizophrenia, Alzheimers, addiction, ADHD and several others.