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# Neuroprotection at a Retinal Synapse: A Novel Role for Starburst Amacrine Cells

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## Editorial

Neuroprotection refers to measures that prevent loss of neurons and/or function associated with age, trauma or disease [1]. The neurotransmitter, Acetylcholine (ACh), has been reported to be neuroprotective against excitotoxic cell death in the Central Nervous System (CNS) through activation of ionotropic nicotinic ACh receptors [2-6]. In particular, there is strong evidence that α7 nicotinic AChRs (nAChRs) are neuroprotective in Alzheimer's disease by reducing β-amyloid induced toxicity [7], by attenuating cytotoxicity in Parkinson's disease [8] and that α7 nAChRs play a role in the pathophysiology of schizophrenia [9-10].

In the retina, Retinal Ganglion Cells (RGCs) contain α7 nAChRs [11-13] and receive cholinergic input from a well-described population of Starburst Amacrine Cells (SAC) [14]. Amacrine Cells (ACs) are interneurons of the retina that make synapses with ganglion cells and bipolar cells in the Inner Plexiform Layer (IPL). There are an estimated 40 types of amacrine cells in the vertebrate retinabased on morphology, synapses and chemical messengers they contain [15]. Different types are classified by the width of their receptive fields, their stratification patterns, and by the type of neurotransmitter they release. Of these many types of amacrine cells, Starburst Amacrine Cells (SACs) receive synaptic input from cone bipolar cells [16-17] and are the only retinal neuron known to release acetylcholine [18]. Two known populations of starburst amacrine cells make synaptic connections in different layers of the Inner Plexiform Layer (IPL) onto RGCs [16].

During early retinal development, SACs release ACh to induce retinal waves of activity [19-20]. Studies have demonstrated that SACs induce action potentials transiently during developmental stages before photoreceptor differentiation but cease to produce the same activity upon maturation [21]. Besides ACh, SACs also release inhibitory Gamma-Aminobutyric Acid (GABA) in the vertebrate retina onto α7 nAChRs of directionally selective RGCs (DSGCs) [22-26]. Electrophysiology studies from DSGCs in rabbit retina have established that both GABA and ACh have important roles in generating the receptive-field properties of DSGCs in adult retina. GABA receptor antagonists abolish the directional selectivity of spiking responses, whereas cholinergic antagonists reduce the spiking activity by half, but leave directional selectivity intact [27-30].

Results from our lab have demonstrated another potential role of ACh in the adult mammalian retina. In isolated cultured adult pig and rat RGCs, acetylcholine provided neuroprotection against glutamate-induced excitotoxicity through activation of α7 nAChRs [31-33]. ELISA results provided evidence that neuroprotection against glutamate-induced excitotoxicity was mediated through the PI3-Akt-Bcl-2 cell survival pathway after calcium influx through α7 nACh channels, while simultaneously inhibiting p38 MAP kinase that initiated apoptosis under excitotoxic conditions [34-35]. In addition, intravitreal injection or topical application of the selective α7 nAChR agonist, PNU-282987, in an *in vivo* adult rat model of glaucoma, prevented the loss of RGCs normally associated with an induced ocular hypertension model [36-37]. Neuroprotection of RGC survival was blocked if the α7 nAChR antagonist, MLA, was introduced before application of the α7 nAChR agonist [36]. Previous studies have demonstrated basal efflux of ACh in adult mammalian retina, which significantly increases in response to flashing stimulus [38]. Perhaps ACh released from SACs provides endogenous neuroprotection that becomes compromised under glaucoma-like conditions.

To support this scenario, an induced glaucoma rat model was used to demonstrate a correlation between the typical losses of RGCs associated with glaucoma and displaced SAC populations [39], whose cell bodies lie exclusively in the ganglion cell layer. The results of this study provided evidence that displaced starburst amacrine cell numbers, ACh content, and α7 nAChR expression from the retina all significantly decreased before loss of RGCs associated with the rat glaucoma model [39]. These results support the hypothesis that SACs mediate endogenous cholinergic neuroprotection for RGCs that is compromised in glaucoma conditions. This indicates a potentially novel role of ACh in the mature mammalian retina and could lead to future glaucoma treatments that use current IOP lowering regiments along with agents to enhance ACh's neuroprotective effect in the retina.

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