

Editorial

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

Cindy L Linn*

Department of Biological Sciences, Western Michigan University, USA

***Corresponding author:** Cindy L. Linn, Department of Biological Sciences, Western Michigan University, USA**Received:** April 18, 2017; **Accepted:** April 20, 2017;**Published:** April 28, 2017**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 $\alpha 7$ 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 $\alpha 7$ nAChRs play a role in the pathophysiology of schizophrenia [9-10].

In the retina, Retinal Ganglion Cells (RGCs) contain $\alpha 7$ 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 retina based 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 $\alpha 7$ 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 $\alpha 7$ 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 $\alpha 7$ 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 $\alpha 7$ 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 $\alpha 7$ nAChR antagonist, MLA, was introduced before application of the $\alpha 7$ 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 $\alpha 7$ 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 regimens along with agents to enhance ACh's neuroprotective effect in the retina.

References

- Casson RJ, Chidlow G, Ebner A, Wood JP, Crowston J, Goldberg I. Translational neuroprotection research in glaucoma: a review of definitions and principles. *Clin Exp Ophthalmol*. 2012; 40: 350-357.
- Marin P, Maus M, Desagher S, Glowinski J, Prémont J. Nicotine protects cultured striatal neurones against N-methyl-D-aspartate receptor-mediated neurotoxicity. *Neuroreport*. 1994; 5:1977-1980.
- Kaneko S, Maeda T, Kume T, Kochiyama H, Akaike A, Shimohama S, et al. Nicotine protects cultured cortical neurons against glutamate-induced cytotoxicity via alpha 7-neuronal receptors and neuronal CNS receptors. *Brain Res*. 1997; 765:135-140.
- Dajas-Bailador FA, Lima PA, Wonnacott S. The $\alpha 7$ nicotinic acetylcholine receptor subtype mediates nicotine protection against NMDA excitotoxicity in primary hippocampal cultures through a calcium ion dependent mechanism. *Neuropharm*. 2000; 39: 2799-2807.
- Gahring LC, Meyer EL, Rogers SW. Nicotine-induced neuroprotection against NMDA or beta-amyloid peptide occur through independent mechanisms distinguished by proinflammatory cytokines. *J Neurochem*. 2003; 87: 1125-1136.

6. Nakamizo T, Kawamata J, Yamashita H, Kanki R, Kihara T, Sawada H, et al. Stimulation of nicotinic acetylcholine receptor protects motor neurons. *Biochem Biophys Res Commun*. 2005; 330: 1285-1289.
7. Oz M, Lorke DE, Yang KH, Petroianu G. On the interaction of β -amyloid peptides and $\alpha 7$ -nicotinic acetylcholine receptors in Alzheimer's disease. *Curr Alzheimer Res*. 2013; 10: 618-630.
8. Kawamata J, Shimohama S. Stimulating nicotinic receptors trigger multiple pathways attenuating cytotoxicity in models of Alzheimer's and Parkinson's diseases. *J Alzheimer's Dis*. 2011; 24: 95-109.
9. Winterer G, Gallinat J, Brinkmeyer J, Musso F, Kornhuber J, Thuerauf N, et al. Allosteric $\alpha 7$ nicotinic receptor modulation and P50 sensory gating in schizophrenia: a proof-of-mechanism study. *Neuropharm*. 2013; 64: 197-204.
10. Young JW, Geyer MA. Evaluating the role of the $\alpha 7$ nicotinic acetylcholine receptor in the pathophysiology and treatment of schizophrenia. *Biochem Pharmacol*. 2013; 86: 1122-1132.
11. Whiting PJ, Schoepfer R, Conroy WG, Gore MJ, Keyser KT, Shimasaki S, et al. Expression of nicotinic acetylcholine receptor subtypes in brain and retina. *Mol Brain Res*. 1991; 10: 61-70.
12. Keyser KT, Britto LGR, Schoepfer R, Whiting P, Cooper J, Conroy W, et al. Three subtypes of α -Bgt-sensitive nicotinic ACh receptors are expressed in chick retina. *J Neurosci*. 1993; 13: 442-454.
13. Kaneda M, Hashimoto M, Kaneko A. Neuronal nicotinic acetylcholine receptors of ganglion cells in the cat retina. *Jpn J Physiol*. 1995; 45: 491-508.
14. Vaney DI, Sivyer B, Taylor WR. Direction selectivity in the retina: symmetry and asymmetry in structure and function. *Nat Rev Neurosci*. 2012; 13:194-208.
15. Kolb H, Fernandez E, Nelson R. Roles of Amacrine Cells. In: *The Organization of the Retina and Visual System*. Webvision Salt Lake City (UT): University of Utah Health Sciences Center. 2005; 343-388.
16. Famiglietti EV. On and off pathways through amacrine cells in mammalian retina: the synaptic connections of "starburst" amacrine cells. *Vision Res*. 1983; 23: 1265-1279.
17. Brandon C. Cholinergic neurons in the rabbit retina: dendritic branching and ultrastructural connectivity. *Brain Res*. 1987; 426: 119-130.
18. Masland RH. Amacrine cells. *Trends Neurosci*. 1988; 11: 405-410.
19. Zheng JJ, Lee S, Zhou ZJ. A developmental switch in the excitability and function of the starburst network in the mammalian retina. *Neuron*. 2004; 44: 851-864.
20. Masland RH. The many roles of starburst amacrine cells. *Trends Neurosci*. 2005; 28: 395-396.
21. Zhou ZJ, Fain GL. Starburst amacrine cells change from spiking to nonspiking neurons during retinal development. *Proc Natl Acad Sci USA*. 1996; 93: 8057-8062.
22. Hayden SA, Mills JW, Masland RM. Acetylcholine synthesis by displaced amacrine cells. *Science*. 1980; 210: 435-437.
23. Brecha N, Johnson D, Peichl L, Wassle H. Cholinergic amacrine cells of the rabbit retina contain glutamate decarboxylase and gamma-aminobutyrate immunoreactivity. *Proc Natl Acad Sci U S A*. 1988; 85: 6187-6191.
24. Grzywacz N, Amthor F, Merwine D. Necessity of acetylcholine for retinal directionally selective responses to drifting gratings in rabbit. *J Physiol*. 1998; 512: 575-581.
25. Vaney DI, Young HM. GABA-like immunoreactivity in cholinergic amacrine cells of the rabbit retina. *Brain Res*. 1988; 438: 369-373.
26. O'Malley DM, Masland RH. Co-release of acetylcholine and gamma-aminobutyric acid by a retinal neuron. *Proc Natl Acad Sci U S A*. 1989; 86: 3414-3418.
27. Wyatt HJ, Day NW. Specific effects of neurotransmitter antagonists on ganglion cells in rabbit retina. *Science*. 1976; 191: 204-205.
28. Caldwell JH, Daw, NW, Wyatt HJ. Effects of picrotoxin and strychnine on rabbit retina ganglion cells: lateral interactions for cells with more complex receptive fields. *J Physiol*. 1978; 276: 277-298.
29. Kittila CA, Massey SC. Pharmacology of directionally selective ganglion cells in the rabbit retina. *J Neurophysiol*. 1997; 77: 675-689.
30. He S, Masland RH. Retinal direction selectivity after targeted laser ablation of starburst amacrine cells. *Nature*. 1997; 389: 378-382.
31. Wehrwein E, Thompson SA, Coulibaly SF, Linn DM, Linn CL. Acetylcholine Protection of Adult Pig Retinal Ganglion Cells from Glutamate-Induced Excitotoxicity. *Invest Ophthalmol Vis Sci*. 2004; 45: 1531-1543.
32. Thompson SA, Smith O, Linn DM, Linn CL. Acetylcholine neuroprotection against glutamate-induced excitotoxicity in adult pig retinal ganglion cells is partially mediated through $\alpha 4$ nAChRs. *Exp Eye Res*. 2006; 83: 1135-1145.
33. Iwamoto K, Linn DM, Mata D, Linn CL. Neuroprotection of rat retinal ganglion cells mediated through $\alpha 7$ nicotinic acetylcholine receptors. *Neurosci*. 2013; 237:184-198.
34. Asomugha C, Linn DM, Linn CL. ACh receptors link two signaling pathways to neuroprotection against glutamate-induced excitotoxicity in isolated pig RGCs. *J Neurochem*. 2010; 112: 214-226.
35. Brandt S, Weatherly M, Ware L, Linn DM, Linn CL. Calcium preconditioning triggers neuroprotection in the retina. *Neurosci*. 2011; 172: 387-397.
36. Iwamoto K, Birkholz P, Schipper A, Mata D, Linn DM, Linn CL. A nicotinic acetylcholine receptor agonist prevents loss of retinal ganglion cells in a glaucoma model. *Invest Ophthalmol Vis Sci*. 2014; 55: 1078-1087.
37. Mata D, Linn DM, Linn CL. Retinal ganglion cell neuroprotection induced by activation of $\alpha 7$ nicotinic acetylcholine receptors. *Neuropharm*. 2015; 99: 337-346.
38. Linn DM, Blazynski C, Redburn DA, Massey SC. Acetylcholine release from the rabbit retina mediated by kainate receptors. *J Neurosci*. 1991; 11: 111-122.
39. Cooley-Themm CA, Ameer Q, Linn DM, Linn CL. Loss of Displaced Starburst Amacrine cells in a Rat Glaucoma Model. *Sci Pages of Ophthal*. 2017.