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Cholinergic nervous system and glaucoma: From basic science to clinical applications

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ABSTRACT

The cholinergic system has a crucial role to play in visual function. Although cholinergic drugs have been a focus of attention as glaucoma medications for reducing eye pressure, little is known about the potential modality for neuronal survival and/or enhancement in visual impairments. Citicoline, a naturally occurring compound and FDA approved dietary supplement, is a nootropic agent that is recently demonstrated to be effective in ameliorating ischemic stroke, traumatic brain injury, Parkinson's disease, Alzheimer's disease, cerebrovascular diseases, memory disorders and attention-deficit/hyperactivity disorder in both humans and animal models. The mechanisms of its action appear to be multifarious including (i) preservation of cardiolipin, sphingomyelin, and arachidonic acid contents of phosphatidylcholine and phosphatidylethanolamine, (ii) restoration of phosphatidylcholine, (iii) stimulation of glutathione synthesis, (iv) lowering glutamate concentrations and preventing glutamate excitotoxicity, (v) rescuing mitochondrial function thereby preventing oxidative damage and onset of neuronal apoptosis, (vi) synthesis of myelin leading to improvement in neuronal membrane integrity, (vii) improving acetylcholine synthesis and thereby reducing the effects of mental stress and (viii) preventing endothelial dysfunction. Such effects have vouched for citicoline as a neuroprotective, neurorestorative and neuroregenerative agent. Retinal ganglion cells are neurons with long myelinated axons which provide a strong rationale for citicoline use in visual pathway disorders. Since glaucoma is a form of neurodegeneration involving retinal ganglion cells, citicoline may help ameliorate glaucomatous damages in multiple facets. Additionally, trans-synaptic degeneration has been identified in humans and experimental models of glaucoma suggesting the cholinergic system as a new brain target for glaucoma management and therapy.

1. Introduction

Key hypotheses of glaucoma pathogenesis include chronically elevated intraocular pressure (Bonomi et al., 1998; Chan et al., 2017b; Choi and Kook, 2015; Coleman and Kodjebacheva, 2009; Hayreh et al., 1999; Leske et al., 1997), glutamate excitotoxicity (Dreyer, 1998; Lotery, 2005; Osborne et al., 2006), oxidative stress (Dada et al., 2018; Izzotti et al., 2006; Kimura et al., 2017), failure in axonal transport (Chidlow et al., 2011; Crish et al., 2013; Fahy et al., 2016), neurotrophic factor deprivation (Ghaffariyeh et al., 2011; Harvey et al., 2012; Johnson et al., 2011), mitochondrial dysfunction (Ito and Di Polo, 2017; Kong et al., 2009; Kumar et al., 2013b; Lee et al., 2011b), autoimmune dysregulation (Bell et al., 2013) and central insulin signaling deficit (Faiq et al., 2014b; Faiq and Dada, 2017), though other mechanisms have also been indicated (Burgoyne et al., 2005; Dai et al., 2012; Faiq, 2016, 2018; Faiq et al., 2014c, 2015, 2016b; Fry et al., 2018; Gruntzig and Hollmann, 2019; Hasnain, 2006; Janssen et al., 2013; Morrison et al., 2011; Rieck, 2013; Sun et al., 2017; Tamm et al., 2017; Wostyn et al., 2017, 2018). Citicoline, a precursor for the neurotransmitter acetylcholine and other neuronal membrane components including phosphatidylcholine and sphingomyelin, also mediates neurodegenerative events through reducing glutamate excitotoxicity (Mir et al., 2003), reducing oxidative stress (Qian et al., 2014), elevating neurotrophin level, ameliorating axonal transport deficits (Grieb et al., 2016), improving mitochondrial function including cardiolipin synthesis (Zazueta et al., 2018), restoring membrane integrity (Yildirim et al., 2015) and modulating insulin signaling (Krupinski et al., 2012). Since glaucoma is a neurodegenerative disease of the visual system, this puts forth an imperative justification that citicoline can be employed as a potential candidate for glaucoma prevention and treatment via

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Abbreviations

ACh	Acetylcholine
AChE	Acetylcholine esterase
AChR	Acetylcholine receptor
Akt	AKT Serine/Threonine Kinase
ATP	Adenosine triphosphate
BCL2	B cell lymphoma gene 2
CDP	Cytidine-5′-diphosphocholine
ChAT	Choline acetyltransferase
CMP	Cytidine monophosphate
CNS	Central nervous system
DNA	Deoxyribonucleic acid
GABA	Gamma aminobutyric acid
GFP	Green fluorescent protein
ICP	Intracranial pressure
IOP	Intraocular pressure
JAK2	Janus Kinase 2
Kir3	Inwardly Rectifier K + Channel 3
Kv7	Voltage-Gated Potassium Channel Subunit Kv7
mAChR	Muscarinic acetylcholine receptor
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRS	Magnetic resonance spectroscopy
nAChR	Nicotinic acetylcholine receptor
NMDA	N-methyl-D-aspartate
PCYTA	Choline-phosphate cytidylyltransferase A
PDHA	Pyruvate dehydrogenase
PEMT	Phosphatidylethanolamine n-methyltransferase
PERG	Pattern electroretinogram
PI3K	Phosphoinositide-3-Kinase
PKC	Protein kinase C
PLC	Phospholipase C
RGC	Retinal ganglion cell
RNA	Ribonucleic acid
ROS	Reactive oxygen species
VEP	Visual evoked potential
VGCC	Voltage gated calcium channel
YFP	Yellow fluorescent protein

protecting, rescuing/restoring or regenerating neurons (van der Merwe et al., 2016). Meticulous studies on the etiopathogenesis of glaucoma and citicoline actions are important to evaluate the mechanisms, efficacy and safety of neurotherapeutics as a treatment modality for neurodegenerative diseases of the visual system including glaucoma. Here we provide a conceptual outlook of the cholinergic system in the brain and retina followed by arguments and studies substantiating the rationale for using citicoline in glaucoma. Then we go on to discuss about the future of citicoline-based treatments as neuroprotective, neurorestorative and neuroregenerative regimens in degenerative diseases afflicting the central nervous system (CNS) and its extended parts including the retina. As a conceptual navigation, Fig. 1 guides through the key messages from each part of the paper.

1.1. Choline in the brain

Despite being the first neurotransmitter identified, our understanding of acetylcholine (ACh) and the cholinergic networks remains relatively poor. For example, a PubMed search of the term “acetylcholine” returned 92530 entries on 16th January 2019 whilst the term “glutamate” returned 155272 entries. A part of the reason is that the cholinergic system is complex and this intricacy increases as the level of inquiry deepens. For instance, distribution of the ACh receptors (AChRs) (Albuquerque et al., 2009; Dani, 2015) along with their tissue specific category differentiate and regulate their inter- and intra-neuron localization for multiscale (temporal and topological) neuromodulation with cumulative complexity at each level. This makes the cholinergic system capable of regulating both short-term and long-term circuit modulation in the CNS (Fagen et al., 2003; Mansvelder and McGehee, 2000; Picciotto et al., 2012). Differences in the expression of various cholinergic moieties by the CNS, the presence of several subtypes of cholinergic neurons [e.g. nicotinic/ionotropic AChRs (nAChRs) and muscarinic AChRs (mAChRs)] and their interactions with other neurons also provide a platform for neuromodulation at somatic, dendritic, and synaptic levels. A depiction of the *in situ* cholinergic system in and around a synapse during an action potential is given in Fig. 2.

Differential expression of various subtypes of the cholinergic receptors, their expression in multiple neuronal types within a region, and the varying locations within a neuron (i.e., somatic, dendritic, synaptic etc.) orchestrate a manifold symphony of neuromodulation. A representative example of this intricacy and the differential functional geography in the brain can be found when examining and comparing the olfactory system (Bohnen et al., 2010; D'Souza and Vijayaraghavan, 2014; Hellier et al., 2010), visual system (Bouskila et al., 2016; Groleau et al., 2015; Yi et al., 2015), and hippocampus (Alger et al., 2014; Frotscher et al., 2000; McQuiston, 2014; Yi et al., 2015) in light of cholinergic signaling (Vijayaraghavan and Sharma, 2015). In the olfactory system, nAChR activation has the capability to screen signals of odor in such a way that weak inputs stand rejected while the strong signals pass through the abstract threshold, giving rise to the gain of function in the olfactory circuit (D'Souza and Vijayaraghavan, 2014; Spindle et al., 2018) such as odor discrimination (D'Souza and Vijayaraghavan, 2014; Hellier et al., 2010; Spindle et al., 2018), whereas in the visual cortex, differential functional expression of mAChRs has a role to play in neuronal synchrony and gamma oscillations to modulate the network output during perceptual learning (Groleau et al., 2015). The hippocampus interestingly displays a different pattern where mAChRs control the release of endocannabinoids (Kano, 2014; Zhao and Tzounopoulos, 2011) thereby giving rise to intricate mechanisms involving higher-order primate function and behavioral regulation through cholinergic signaling (Alger et al., 2014; Zou and Kumar, 2018). Apart from the above, cholinergic receptors have been implicated in addictive mechanisms involving interactions of cocaine and nAChRs (Acevedo-Rodriguez et al., 2014). The behavioral changes underlying neurological and psychiatric ailments such as Alzheimer's disease, Parkinson's disease, schizophrenia, and autism are also thought to be the resultant phenotypes of cholinergic disturbances (Amodeo et al., 2014; Bohnen et al., 2010; Oddo and LaFerla, 2006; Wallace and Bertrand, 2013) apart from other non-cholinergic mechanisms (Kumar et al., 2017; McCoy et al., 2019; Saboory et al., 2019).

Although maps of brain ACh network have been recently constructed (Guo et al., 2015; Hoover et al., 1978; Li et al., 2018; Sugiura et al., 2012), the mechanisms of ACh-mediated signaling remain largely unclear. Anatomically speaking, the cholinergic system emerges in the CNS (Kasa, 1986; McCorry, 2007) from the basal forebrain and the pendunculo-pontine nucleus (Fig. 3). The basal forebrain is a collection of structures located to the front of and below the striatum including the nucleus accumbens, nucleus basalis, diagonal band of Broca, substantia innominata, and the medial septal nucleus. The pendunculo-pontine nucleus is a collection of cholinergic neurons located in the brainstem, caudal to the substantia nigra and adjacent to the superior cerebellar peduncle. The pendunculo-pontine nucleus comprises of two major divisions, one containing cholinergic neurons in the pars compacta (Gorbachevskaia and Chivileva, 2005), and the other containing mostly glutamatergic neurons in the pars dissipata (Fraigne et al., 2015). An important point to note is that a subset of neurons from these

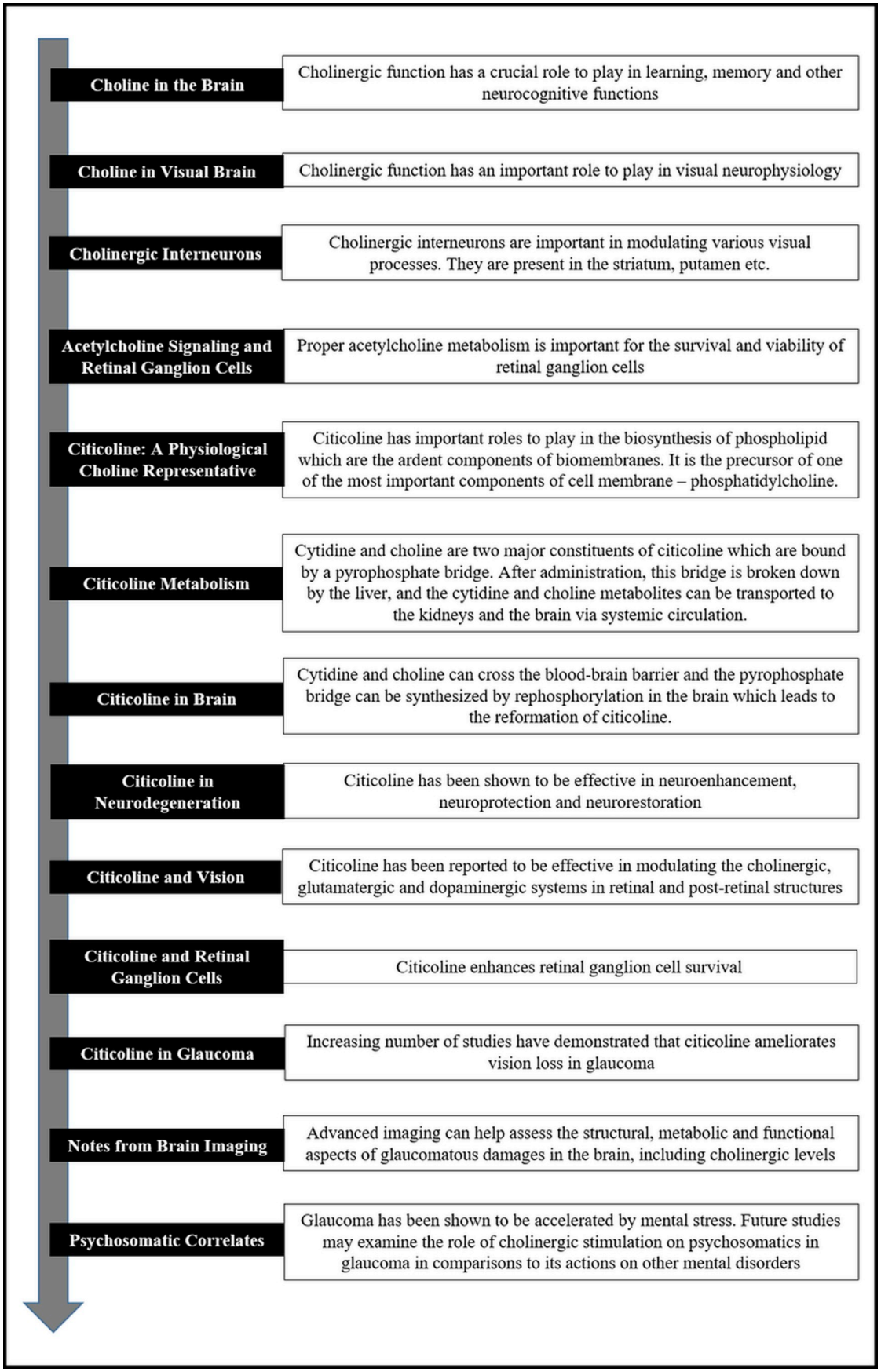


Fig. 1. Conceptual guide of the cholinergic system in vision. This figure highlights the key messages of this paper that are important to the understanding of the cholinergic system and the therapeutic effects of cholinergic drugs including citicoline on the visual system.

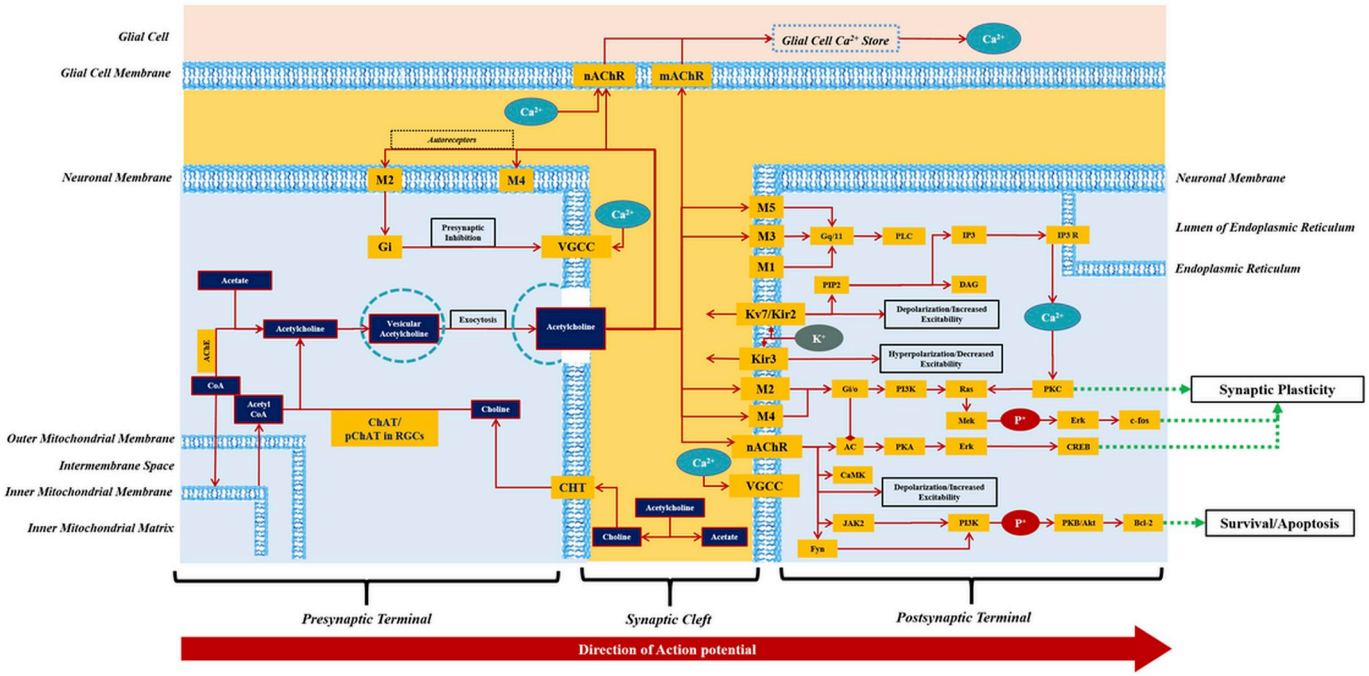


Fig. 2. Representative portrayal of the micro-anatomy and molecular biology of the cholinergic synapse. This illustration gives an overview of the molecular processes, proteins, receptors and pathways of the cholinergic synapses and their locale in and outside of the neurons. The timeline of the synaptic function runs from left to right. In the presynaptic neuron, ACh is synthesized from the building blocks in the mitochondria, and is transported by the vesicles and released in the synapse. ACh signaling occurs through binding with the muscarinic and nicotinic receptors on the postsynaptic membrane. Such signaling leads to important molecular processes including neuronal plasticity, regulation of apoptosis and other cellular functions. Visual plasticity and perception are relevant to cholinergic signaling in the visual cortex, whereas RGC survival/apoptosis is imperative in glaucoma. This figure also depicts the subtle differences between central cholinergic synapse and the cholinergic synapse in the RGCs. Specifically, the ChAT in RGCs is in an alternative spliced form called pChAT. In case of insufficient production of acetylcholine in the presynaptic neuron, choline is taken back from the synapse in an autoregulatory attempt to the presynaptic membrane thereby rescuing the cellular reservoir of choline for other functions like vesicle formation and membrane component synthesis. ACh also interacts between neurons (including RGCs) and glia, which helps maintain their proper functioning and calcium uptake for the prevention and mediation of hyperactivation.

structures send out a sparse network of cholinergic neurons to the target sites which become difficult to study in isolation. Hence the source analysis of traditional electrophysiological approaches has not been successful in identifying the exact mechanisms through which the brain cholinergic system works.

Donald Hebb in his 1949 book, *The Organization of Behavior*, had given an important idea to decipher the working of the complex wiring of the brain. He suggested an approach to activate or deactivate one type of neurons in the brain while keeping the other types unaltered. Optogenetics (Liu and Tonegawa, 2010; Miller, 2006; Sidor et al., 2015) and presumably chemogenetics (Vlasov et al., 2018), radiogenetics (Leibiger and Berggren, 2015) and magnetogenetics (Nimpf and Keays, 2017) have now enabled such facility and have advantages over other electrophysiological approaches (Gilbert et al., 2003). By employing selective manipulation of the excitability of ACh neurons, optogenetic approaches have explicated the role of ACh in modulation of various brain structures involved in visual processing (Luchicchi et al., 2014; Pinto et al., 2013). Some of the relevant areas that need to be further deliberated include the signaling mechanisms, the trans-synaptic and asynaptic modulation of neuronal activity, the synthesis, distribution, and modes of action of ACh metabolizing enzymes, and the interaction and competition arena with the co-release of other neurotransmitters around the cholinergic sites.

1.2. Choline in the visual brain

Visual stimulation can trigger the release of ACh in the primary visual cortex (Collier and Mitchell, 1966; Laplante et al., 2005) located in and around the calcarine fissure of the occipital lobe (Fig. 3). The primary visual cortex is the first stage of cortical visual processing receiving information from the lateral geniculate nucleus (LGN) in the thalamus and encompasses the whole map of the visual field covered by the eyes (Felleman and Van Essen, 1991; Maunsell and Newsome, 1987). Certain novel visual demands also lead to release of ACh in the primary visual cortex (Herrero et al., 2008). In light of these facts, the cholinergic innervation of the primary visual cortex and associated areas presents important candidature for biological and clinical investigations. The basal forebrain provides cholinergic innervations to the primary visual cortex via topographical projections (Carey and Rieck, 1987) and may play a role in visual perception, visual attention, and cortical plasticity (Kang et al., 2014a). It has also been shown in rodent studies that cholinergic corticopetal projections meet their termination at the visual cortex in a medio-lateral configuration (Carey and Rieck, 1987). The horizontal limb of the diagonal band of Broca, a structure derived from the ventral telencephalon during development, also supplies cholinergic innervations to the primary visual cortex (Gaykema et al., 1990; Laplante et al., 2005). Metabotropic muscarinic receptors (mAChRs) and the ionotropic nicotinic receptors (nAChRs) are the two major classes of receptors being acted upon by ACh to bring about modulation of the visual cortex (Disney et al., 2007; Prusky et al., 1987; Thiele, 2013; Volpicelli and Levey, 2004). They can be identified within every level of the primary visual cortex including the thalamic projections (layer IV), the lateral projections and the vertical intracortical connections that relay signals to the supragranular (layer I/II/III) and infragranular (layer V/VI) regions (Burkhalter, 1989; Van Hooser, 2007). Neurons arising from the thalamus, cortex, and basocortical structures, the pyramidal excitatory neurons and the inhibitory GABAergic interneurons branch out axons that display the expression of these receptors (Burkhalter, 1989; Hashimoto et al., 1994; Mrzljak et al., 1993; Thiele, 2013; Van Hooser, 2007; Zilles et al., 1989).

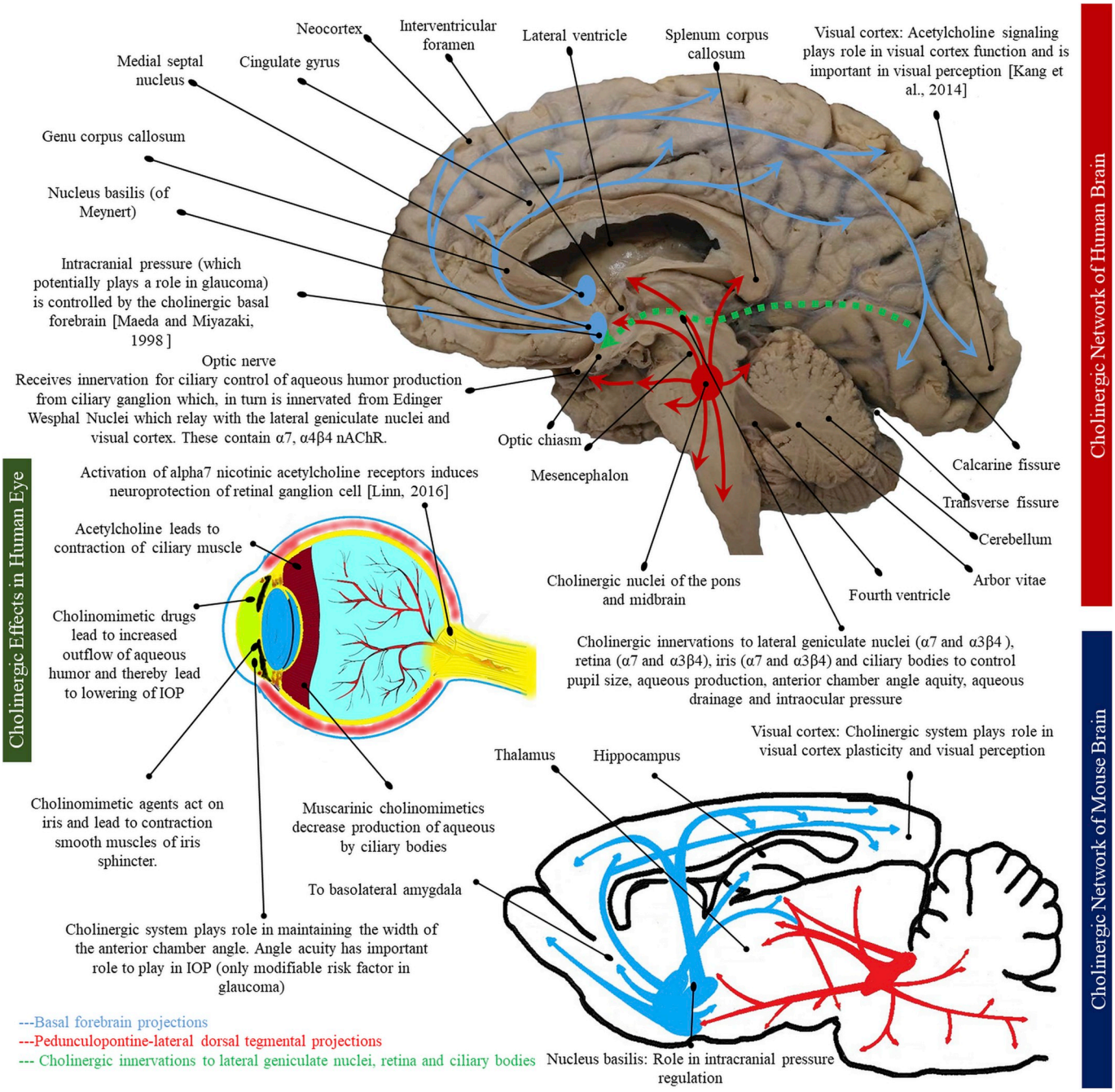


Fig. 3. The cholinergic system in the eyes and brains of humans and rodents. This figure illustrates the cholinergic mapping of the human and mouse brains. Note that the labels for the human brain also apply to the mouse brain. Humans and rodents share several similarities in the central cholinergic system. For example, the cholinergic neurons in the visual pathway mainly originate from the basal forebrain which may play a role in glaucoma in terms of visual plasticity, visual perception and regulation of intracranial pressure. The pedunculopontine-lateral dorsal tegmental projections have also been depicted in both human and rodent brains. Apart from the cholinergic innervations within the brain, the eye is sensitive to cholinergic function. Cholinergic modulation of ocular structures can help regulate intraocular pressure, which is currently the only modifiable risk factor in glaucoma. Cholinomimetics cause contraction of ciliary bodies and widening of anterior chamber angle leading to higher rate of aqueous clearance. The muscarinic cholinergic activation decreases the aqueous production thereby leading to intraocular pressure lowering. In addition to aqueous humor dynamics, activation of α-7 nicotinic ACh receptors in the eye induces neuroprotection of retinal ganglion cells (Linn, 2016).

The microcircuitry of the primary visual cortex is immensely complex and comprehensive but physiologically a few basic circuits can be identified. Previous cortical circuit models were based on rudimentary 'feedforward' circuits but now recurrent cortical circuits have been proposed - an enormous theoretical leap intended to explain actual circuits with realistic representation and computational precision (Martin, 2002). Being horizontally as well as vertically organized, the microcircuitry of the primary visual cortex presents as an essential organizational model to establish the anatomical structure to account for various aspects of the visual field including binocularity (Drager and Olsen, 1980; Grieve, 2005), ocular dominance (Cynader et al., 1987; LeVay et al., 1978), orientation (Grinvald et al., 1986), and contrast (Levitt and Lund, 1997). These properties of the neurons entangled in circuits work in different combinations and permutations to give rise to intricate microcircuitry. Development of these properties in a neuron may be thought to be a consequence of continuous adaptations to the

input signals that a neuron receives throughout the time course. The strength of the response of these neurons is a primary factor for the organizational characteristics of higher-order cognitive functions. In this way, the primary visual cortex is the first level of the organization of complex visual functions in terms of the integration of visual stimuli. In this context ACh becomes crucial as it determines the strength and temporality of the stimuli imminent from the retina through the LGN. ACh concentration and biochemistry are pivotal in determining and modulating the strength and specificity in response to stimuli in the visual field thereby giving rise to conscious visual perception (Kang et al., 2014b; Levitt and Lund, 1997). As the old adage goes, neurons that fire together, wire together; constant firing in synchrony leads to the formation of new circuits which makes the ACh-mediated visual cortex the center of neural circuit dynamics. This has important role to play in vision, perception, memory, learning and attention. Each stimulus augments its small share towards the fine tuning of the visual circuit. This is also the basis of the hypothesis evident in recent reports of vision restoration using electrical brain stimulation in glaucoma and other neurodegenerative diseases (Gall et al., 2016; Henrich-Noack et al., 2017b), whereby regular and synchronized electric pulses are applied to modify neuronal function by modulation of spontaneous activity and excitability (Antal et al., 2001, 2004b; Fedorov et al., 2011; Fritsch et al., 2017; Gall et al., 2016; Henrich-Noack et al., 2017a, 2017b; Sehic et al., 2016; Simonsmeier et al., 2018; Sun et al., 2018; Yavari et al., 2017). In the visual system, application of these electrical pulses induces changes in phosphene, contrast and motion perception as well as modification of the amplitude of visual evoked potential (Gall et al., 2011; Sabel et al., 2011a; Sun et al., 2018) indicating that these stimulations can alter excitability of the visual cortex and other vision related areas in the brain, optic nerve and the retina (Antal et al., 2003, 2004a, 2004b; Antal and Paulus, 2013; Fedorov et al., 2011; Khan et al., 1992; Vosskuhl et al., 2018; Zoefel and Davis, 2017). The efficacy of these interventions for vision restoration appears dependent on the individual's residual capacity (Sabel, 2008; Sabel et al., 2011b) and requires further studies.

1.3. Cholinergic interneurons

In addition to the above imperative sites of cholinergic signaling, certain areas of the cortex possess cholinergic interneurons (Eckenstein and Thoenen, 1983; Houser et al., 1985; Huppe-Gourgues et al., 2018; Jones, 2004; Scarr et al., 2018; von Engelhardt et al., 2007). The striatum harbors significant levels of ACh (Abudukeyoumu et al., 2018; Calabresi et al., 2000; Grady et al., 2007), nicotinic (Salminen et al., 2004; Wonnacott et al., 2000), and muscarinic receptors (Brann et al., 1988; Howe and Surmeier, 1995; Huff et al., 1994). Striatal ACh is primarily produced by cholinergic interneurons which are approximately 1–2% of all striatal cells (Lim et al., 2014). A subset of such interneurons are also suggested to be involved in Parkinson's disease.

Interneurons give rise to neural circuits (Dehorter et al., 2017; English et al., 2011) thereby making communications between various parts of CNS possible. Interneurons display important roles in reflexes (Burrows and Siegler, 1982; Cleary et al., 1995), neuronal oscillations (Bartos et al., 2007; Buzsaki and Draguhn, 2004; Wang and Buzsaki, 1996), and neurogenesis (Li et al., 2009; Masiulis et al., 2011; Rymar et al., 2004; Song et al., 2013) in the adult mammalian brain giving rise to optimism about the exploitation of the cholinergic system in neurodegenerative diseases including those affecting vision (e.g. glaucoma). Cholinergic interneurons are not restricted to the striatum, but also identified in the hippocampus (Frotscher and Leranth, 1985; Frotscher et al., 2000; Pitler and Alger, 1992). Lack of the availability of effective probes to the interneurons had given rise to wide gaps in our knowledge. As a result, no function was previously attributed to them. Nowadays, an increasing number of studies indicates that these interneurons are not just vestigial cellular moieties (Kepecs and Fishell, 2014) but have rather important roles to play. Studies by Yi and colleagues (Yi et al., 2015) are an important leap ahead in this direction. They examined hippocampal structures in the transgenic mice ChAT-tauGFP (choline acetyltransferase-tau green fluorescent protein) and ChAT-CRE/Rosa26YFP, and demonstrated that the hippocampus of ChAT-tauGFP was densely innervated with GFP-positive axons, whereas in ChAT-CRE/Rosa26YFP mice, ChAT-YFP (choline acetyltransferase-yellow fluorescent protein) positive cells were more densely present in the Cornu Ammonis 3 (CA3) and dentate gyrus than the CA1 with partial overlaps with calretinin and vasoactive intestinal polypeptide. Since GFP and YFP expression was driven by the ChAT promoter, it could be concluded that these areas were rich in cholinergic interneurons. Their studies investigated the anatomical distribution, membrane properties, neurochemical characteristics, and role in cholinergic modulation of these interneurons.

Approximately 2% of the neurons in the cerebral structures including caudate, putamen, striatum, neostriatum and nucleus accumbens are cholinergic. A composite structure of the caudate (a component of the visual corticostriatal loop) (Seger, 2013) and putamen makes the neostriatum. Distinct from the other parts of CNS where cholinergic neurons generate diffuse and sparse neuronal networks spreading over relatively larger areas, the striatal cholinergic interneurons are present as dense innervations. Cholinergic interneuron system gives rise to perpetual ACh signals mediated through action potentials tonically at approximately 5 Hz. Striatum contains high proportions of acetylcholinesterase thereby immediately ending the ACh signal. This phenomenon suppresses the desensitization of nicotinic AChRs (Zhou et al., 2002). Striatal nicotinic activity accelerates dopamine release which conjoins the local arbors of the cholinergic interneurons and afferent fibers of the dopaminergic system. This combination plays important roles in sensorimotor planning and learning processes (Zhou et al., 2002).

1.4. Acetylcholine signaling and retinal ganglion cells

The RGCs are one of the five neuronal cell types found in the vertebrate retina. They express NMDA as well as non-NMDA ionotropic glutamate receptors (GluRs) (Goebel et al., 1998; Hamassaki-Britto et al., 1993; Lin et al., 2002; Watanabe et al., 1994). These receptors play important roles in excitotoxic cell death thereby precipitating glaucoma. Hence there is a need to identify compounds that would break this continuum of NMDA/non-NMDA mediated excitotoxicity (Mosinger et al., 1991). Latest peer reviewed literature has identified that neuronal nAChRs modulate many processes of the CNS in addition to rapid cholinergic transmission. One key function is that alpha-7 nAChR is involved in neuroprotection precipitated by glutamate-induced excitotoxicity (Dajas-Bailador et al., 2000; Kaneko et al., 1997; Marin et al., 1994; Shimohama et al., 1996) (Fig. 3). Since the retina is the extension of the diencephalon, this function is likely to be valid in the retina also. Although the neuroprotective role of ACh in the retina has not been comprehensively studied, it is known that cholinergic neurons comprise amacrine cells (Famiglietti, 1983; Masland et al., 1984) that are evenly distributed in the retina. These cells, which are alternatively described as starbursts, are arranged as one distinct group in the inner nuclear layer and the other in the RGC layer (Mariani and Hersh, 1988; Masland et al., 1984). They are also found to be sensitive to ocular hypertension even before RGC or optic nerve degeneration (Gunn et al., 2011; Moon et al., 2005; Pang et al., 2015). It has been reported that activation of nicotinic AChRs in pig RGCs leads to neuroprotective effects against glutamate-induced excitotoxicity (Wehrwein et al., 2004). A comprehensive overview of these receptors, the associated molecular signaling pathways and cellular processes in the cholinergic synapse is depicted in Fig. 2. This, however, leaves an open question if the RGCs and their optic nerve axons possess the molecular machinery for synthesis and metabolism of ACh. Next section deals with this aspect in detail.

1.5. ChAT system in RGCs and optic nerve

The cholinergic essence of RGCs was suggested decades ago (Oswald and Freeman, 1980) but the notion of probing ACh functioning in RGCs was understudied as the concept of glutamate-mediated neurotoxicity came to forefront. Glutamate excitotoxicity initially seemed to explain most aspects of neurodegeneration but later research identified the need for additional mechanisms to explain the experimental observations. This gave rise to recent research revisiting cholinergic mechanisms. The neurotransmitter spectrum of RGCs is, in large part, unknown due to many reasons. RGCs have been verified to be immunoreactive to glutamate by many studies with its positive signals in the cell bodies (Crooks and Kolb, 1992; Davanger et al., 1991; Jojich and Pourcho, 1996; Kalloniatis and Fletcher, 1993; Sun and Crossland, 2000) as well as axon terminals (Beaudet et al., 1981; Ehinger, 1981; Mize and Butler, 1996; Montero, 1994; Ortega et al., 1995). These observations have strengthened the indication of glutamate excitotoxicity-mediated mechanism of glaucoma, despite the fact that the exact role of glutamate signaling in RGCs is still elusive. Positive labelling of (3H)-D-aspartate is indicative of the employment of glutamate as a neurotransmitter by a neuron (Beaudet et al., 1981; Ehinger, 1981). Since only 5–10% of all the cells in the ganglion cell layer are reported to be stained positively for [3H]-D-aspartate, it follows that the majority of RGCs may be utilizing other neurotransmitters for signal transmission, among which ACh is a good candidate. Also, glutamate is not released in a calcium-dependent manner from the optic nerve terminals (Sandberg and Corazzi, 1983; Tsai et al., 1990). Dipeptide-N-acetylaspartylglutamate is thought to play a role as a neurotransmitter in RGCs but there is no conclusive evidence (Anderson et al., 1987; Tieman and Tieman, 1996; Tsai et al., 1990). It is known that some ganglion cells are able to synthesize a variety of neuropeptides that are not fully elucidated (Cuenca and Kolb, 1989; Kuljis et al., 1984). Although speculations can be drawn, more definite molecular evidence is important to determine ACh as a candidate neurotransmitter in RGCs.

To view acetylcholine as a neurotransmitter in the retina, it is important to demonstrate that the retina contains not only ACh but also the enzymes required for its biosynthesis. The lack of identification and detection of ACh in the retina in past decades can partially be attributed to the lack of reliable histochemical approaches to detect ACh. Also, using immunohistochemistry, several studies have shown that ChAT antibodies stain amacrine cells specifically but not RGCs (Eckenstein and Thoenen, 1982; Pourcho and Osman, 1986; Schmidt et al., 1985; Tumosa et al., 1984; Tumosa and Stell, 1986; Voigt, 1986). Despite the negative affirmation, there is still a possibility that RGCs may utilize a different form of ChAT to synthesize ACh. Such form had been successfully cloned from the cDNA of the rat pterygopalatine ganglion as demonstrated by Tooyama and Kimura, indicating that the presence of enzyme machinery to synthesize ACh in the ganglion cells is confirmable (Nakajima et al., 2000; Nakanishi et al., 1999; Tooyama and Kimura, 2000). This alternative form of ChAT did not contain Exon-6, Exon-7, Exon 8 or Exon-9. Hence Exon-5 and Exon-10 are joined through the alternative splicing activity. This implies that an antibody against the Exon5:Exon10 junction should be used to identify this alternative form of ChAT (Nakajima et al., 2000; Nakanishi et al., 1999; Tooyama and Kimura, 2000). This novel ChAT was detected in the peripheral neurons but not the brain in these studies and thus was termed pChAT. Yashuhara et al. attempted to identify this alternative form of ChAT in the RGCs using pChAT antibodies for immunohistochemistry and Western blot analysis (Yasuhara et al., 2003). They also used real-time polymer chain reaction analysis to check the expression of pChAT at the mRNA level. With these techniques, the investigators were able to demonstrate the presence of pChAT in the rat retina and optic nerve. Additionally, they examined the effects of light exposure on pChAT expression and reported the presence of pChAT in the retina, optic nerve and optic tract. This indicates that the RGCs possess a viable ChAT system which may help modulate ACh synthesis and function. This is relevant because exposure to light induces the expression of *Fos* in retina (Koistinaho and Sagar, 1995; Sagar and Sharp, 1990). The *Fos* gene family comprises 4 members namely FOS, FOSB, FOSL1 and FOSL2 which code for leucine zipper proteins for dimerizing with proteins of the JUN family. The FOS group proteins can regulate cell proliferation, differentiation, and transformation as well as apoptotic cell demise. In the present context, *Fos* is a transcription factor for ACh synthesis (Koistinaho and Sagar, 1995). Taken together, these studies suggest that there is a *Fos* mediated regulation and expression of ChAT and ACh function in the RGCs. Whether this could be exploited as a mechanism to treat retinal disorders including glaucoma is a question that remains to be answered.

Apart from genetic studies in the retina, identification of genetics (Borras, 2017; Budde, 2000; Feng and Xu, 2019; Gobeil et al., 2006; Gong et al., 2004; Kanagavalli et al., 2004; Minegishi et al., 2016; Rozsa et al., 1998; Tamm, 2002; Wiggs and Pasquale, 2017) and gene/protein expression profiles (Feng and Xu, 2019; Funke et al., 2019; Gagrani et al., 2018; Hubens et al., 2019; Jakobs, 2014; Johnson et al., 2007; Oliver et al., 2019; Seet et al., 2016; Wang et al., 2017b) from the peripheral blood may serve as surrogate markers of pre-glaucoma as well as targets for therapeutic intervention. One study in this direction found 28 moieties that might have a potential in treatment for primary congenital glaucoma (Faiq et al., 2016a). In addition, the genome wide association studies (GWAS) have been looking into important loci that might play a role in glaucoma pathogenesis. Interestingly, one of the recently discovered loci for primary angle closure glaucoma on chromosome 10 is involved in synthesis of ACh via ChAT (Khor et al., 2016). Other genes such as CYP1B1 have also been implicated in a significant portion of glaucoma cases and may be involved in endothelial function (Faiq et al., 2013a, 2013b, 2014a, 2014c, 2015; Rosen et al., 2015; Smith et al., 2011). However, functional studies on CYP1B1 mutations and their effects on the ACh metabolism were lacking due to difficulties in heterologous expression of unmodified human CYP1B1. This problem was, however, solved recently with a novel protocol for enhanced expression of unmodified CYP1B1 in heterologous hosts (Faiq et al., 2014a). This line of research can likely help further understand the role of CYP1B1 in ACh-mediated endothelial function.

1.6. Cholinergic innervations in Rheology

The rheology of ocular structures and the CNS is gaining attention (Carreon et al., 2017; Flammer and Orgul, 1998; Harris et al., 1999; Yamamoto and Kitazawa, 1998) with new reports claiming that the eye is not only affected by the intraocular pressure (IOP) but also intracranial pressure (ICP) (Wang et al., 2017a). This has particular relevance to glaucoma as both pressure systems meet at the optic nerve head and interact with one another at the lamina cribrosa (Johannesson et al., 2018; McMonnies, 2016). It is becoming increasingly evident that translaminar pressure difference, or the difference in the pressure components of IOP and ICP at the lamina cribrosa, may be more important than IOP and ICP taken individually (McMonnies, 2016). Hence, interventions based on modulating translaminar pressure-mediated optic nerve deformation may be pivotal to glaucoma management (Siaudvytyte et al., 2014, 2015; Wostyn et al., 2016). Currently, IOP is the only clinically modifiable risk factor for glaucoma while ICP has been ignored at large. It is essential to identify factors that regulate ICP as well as their relations to IOP. Among these factors, the cholinergic basal forebrain has been shown to take part in controlling the ICP and the cerebrovascular volume via ACh-mediated decrease in vasoconstriction (Maeda and Miyazaki, 1998) (Fig. 3). Within the cortex, cerebrovasomotor reactions and ICP modulation can also be brought about by ACh release via activation of the cholinergic fibers in the nucleus basilis of Meynert (Sato et al., 2001). Although cerebrovascular factors have been implicated in rapid disease progression especially in normal tension glaucoma (Chen et al., 2016; Gungor et al., 2011; Lee et al., 2017), how these physiological factors are

regulated in normal conditions and altered in glaucoma remains unclear and requires further investigations. It is pertinent to mention that cholinergic medication as neurotherapeutics of choice has not been well recognized by researchers. The main reason for this seems to be the lack of carefully drafted studies and the limited number of randomized clinical trials conducted. The following section adds an anecdote on cholinergic medication in visual disorders with glaucoma as a representative disease.

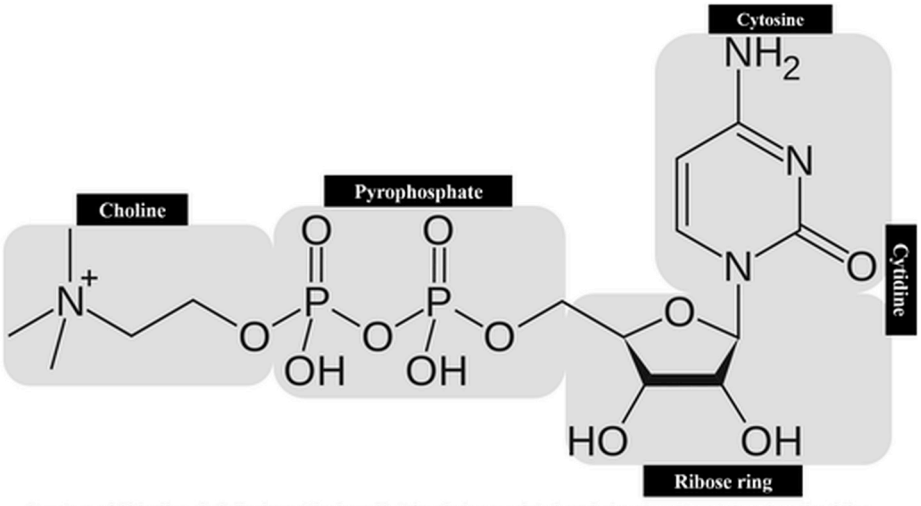
1.7. Cholinergic medication in glaucoma

The American Academy of Ophthalmology guidelines for diagnosis and treatment do not specify any preferred ophthalmic medication for primary open angle glaucoma. This may be due partly to the fact that the treatment of glaucoma is often tailored as per the individual's conditions, compliance, and response to therapy, which may change from time-to-time during the course of the disease. Nowadays, the most commonly used glaucoma medications include prostaglandins and β-adrenergic blockers due to their high tolerance index and availability of generic formulations. Cholinergic agonists can also lower IOP by pupil constriction, or miosis, which decreases resistance to the aqueous humor outflow. These miotic ophthalmic drugs can act on the iris sphincter and ciliary muscles directly (e.g. ACh, pilocarpine, and carbacol) or indirectly (e.g. echothiophate) via the parasympathetic nervous system (Cekic and Batman, 1999; Laranjeira and Buzard, 1996; Shaikh and Mars, 2001; Solomon et al., 1998; Wutthiphan et al., 2000) and may cause cytoskeletal changes in the trabecular meshwork (Yamagishi-Kimura et al., 2018). However, parasympathomimetic medications are presently considered as the third-line treatment for glaucoma (Lee and Higginbotham, 2005), partly because of the reported side effects from ophthalmic pilocarpine use including irritation and surgical difficulties from miosis and headaches. This inevitably slows down studies of the systemic effects of cholinergic drugs. In addition to acting through the aqueous-outflow pathway, pilocarpine has been shown to ensue protection against glutamate-induced apoptosis of the neurons via activation of muscarinic ACh receptor M1 (Tan et al., 2014; Zhou et al., 2008). Targeting NLRP3 inflammasome by activation of α7 nicotinic ACh receptor or by scutellarin that enhances ACh levels can also offer the antioxidant and antiapoptotic properties in experimental glaucoma and other neurodegenerative disorders (Hu et al., 2018; Zhu et al., 2018). Due to the limited randomized controlled trials on the systemic use of cholinergic agonists, it is premature to draw any conclusions about their efficacy when it comes to their use in glaucoma. Among the available cholinergic drugs, citicoline offers physiologically useful bioavailability through many routes of administration. Also, reports on the use of citicoline have shown improvement in visual evoked potential, pattern electroretinogram and visual field function. This indicates that citicoline might work through neuroprotective, neurorestorative and neuroregenerative paradigms, though its effect on IOP cannot be ignored as it also has cholinergic components in structure and activities akin to cholinergic function. In the following sections we discuss the biochemical, physiological and clinical effects of citicoline followed by its role in ameliorating vision loss in general and glaucoma in particular.

2. Citicoline: A physiological choline representative

Citicoline, also known by other names as CDP-choline, CDPCho and cytidine-5′-diphosphocholine, is a nootropic agent, a central stimulant and is a member of the drug class oral nutritional supplements (Colucci et al., 2012; Secades, 2011, 2016; Secades and Lorenzo, 2006). It has a molecular weight of 488 g/mol and is chemically recognized as cytidine 5'-(trihydrogen diphosphate), mono[2-(trimetylammonio)ethyl] ester hydroxide inner salt with chemical formula C_{14}–H_{26}–N_4–O_{11}–P_2. The use of citicoline arose in the early 1970s with a view that it might be a substance for treating drug abuse (Wignall and Brown, 2014). Then the first medical use of citicoline came from reports about its beneficial effects in Parkinson's disease (Obara, 1974).

Citicoline has important roles to play in the biosynthesis of phospholipids and their precursors such as phosphatidylcholine (Grieb, 2014; Zweifler, 2002). Owing to the high turnover rate, cell membranes require an uninterrupted supply of phospholipids for proper maintenance, and citicoline metabolism is a rate limiting step in this process (Jackowski, 1994). Also, citicoline is a nucleotide (Zweifler, 2002) with structural similarities with the building blocks of nucleic acids. For example, citicoline is a monomer with three distinct structures including ribose, cytosine, and choline (Fig. 4). Ribose is a pentose monosaccharide found in RNA while its 2-deoxy form is found in DNA also. Cytosine is one of the four main bases found in DNA and RNA. Choline is a water soluble vitamin-like essential nutrient which is a basic constituent of lecithin. Ribose and cytose combine to form the nucleoside cytidine, and choline is attached to the cytidine by means of a pyrophosphate bridge. When citicoline enters the body through oral or parenteral route, a quick metabolic process in the order of minutes follows (Grieb, 2014). The immediate catabolism of citicoline leads to the formation of pyramidine and choline derivatives, both of which are important bioactive substances and can be naturally present (Agut et al., 1983; Andersen et al., 1999; Grieb, 2014; Marti Masso and



Structure of Citicoline: 5'-O-[hydroxy({hydroxy[2-(trimethylammonio)ethoxy] phosphoryl}oxy)phosphoryl]cytidine

Fig. 4. Chemical structure of citicoline. The chemical name of citicoline is 5′-O-[hydroxy({hydroxy[2-(trimethylammonio)ethoxy]phosphoryl} Moxy)phosphoryl]cytidine. It contains two major structural components, choline and cytidine. Choline is bound to the ribose ring through a pyrophosphate bond. This chemical bridge between ribose and choline gives citicoline the chemical property to be easily broken down and readily resynthesized given the favorable conditions or the presence of relevant enzymes. This property is important to the delivery of citicoline to the CNS, as citicoline cannot cross the blood-brain barrier while choline and cytidine can, hence citicoline has to be hydrolyzed to cytidine and choline in the liver and resynthesized in the brain via the pyrophosphate bridge. Ribose and cytosine make citicoline a component important for RNA biology, though the exact role of which has not yet been deciphered. It is speculated that nucleic acid synthesis may be one of the roles of citicoline in the light of its chemical composition.

Urtasun, 1991). Thus citicoline is thought to be relatively benign and free of side effects, and is a safe moiety for potential clinical use, though few reports of mild digestive intolerance have been published. The therapeutic dosage of citicoline in humans is 500–2000 mg/day which amounts to 7–29 mg/kg body weight/day (Grieb, 2014).

2.1. Citicoline metabolism

A summary of the metabolism of citicoline is illustrated in Fig. 5. In brief, phosphatidylcholine is synthesized in a three-step enzymatic process from choline and cytidine (DeLong et al., 1999; Moessinger et al., 2014). In the first step, choline originates from the phosphatidylcholine metabolism and is phosphorylated by cytidine kinase utilizing one molecule of ATP into choline-phosphate. Choline phosphate is then converted to citicoline by combining with cytidine phosphate that is derived from cytidine. The enzyme that catalyzes this reaction is called choline phosphate cytidilyltransferase. Citicoline on the other hand leads to the formation of phosphaptidylcholine by an enzymatic process mediated through CDP-choline:1,2-diacylglicerol choline phosphotransferase. In the penultimate step of this metabolic pathway, citicoline is synthesized which then serves as the requisite element for phosphatidylcholine synthesis, thereby providing justification for the role of citicoline in membrane function and integrity. This pathway is vital to neuronal tissues to maintain the electrochemical gradient for proper action potential generation. The profound similarities in ACh synthesis and localization in and outside the cell in many species indicate that the ACh mechanism is relatively conserved in evolution, upholding the rationale that rodents and zebrafish are appropriate models to investigate this system and the diseases thereof.

A schematic outlook of the bioavailability and breakdown of citicoline through various routes of administration, different compartments of the body and different metabolic routes is given in Fig. 6. Citicoline can be administered by multiple routes but oral administration remains to be the most common because of several reasons. Citicoline is well tolerated orally and does not show adverse effects at the effective dosages. It also has remarkable bioavailability with negligible loss to metabolic processes. Oral or intramuscular administration of citicoline does not show apparent difference in the metabolism and bioavailability (Adhi and Duker, 2013; Clark and Clark, 2012; Fresta et al., 1994). After administration, citicoline is immediately metabolized by the liver into cytidine and choline in the circulation (Galletti et al., 1985, 1991), and after 30 min the resultant metabolites can be observed in liver, kidneys, and brain in rodents (Galletti et al., 1991; Martynov and Gusev, 2015). Cytidine is transformed into uridine which converts to uridine phosphate in the CNS. At the cellular level in the brain, this moiety is then converted into cytidine triphosphate. All the three major routes (urinary, fecal and respiratory) are used for excretion of citicoline (Dinsdale et al., 1983). Since the brain has been indicated a major target for vision loss (Faiq, 2016, 2018; Faiq et al., 2016b), in the following section we explore citicoline with respect to its availability and effects in the brain.

2.2. Citicoline in the brain

As explained in section 2.1 cytidine and choline are two major constituents of citicoline which are bound by a pyrophosphate bridge. This bridge is broken down during hepatic metabolism and the same bridge can be synthesized again by rephosphorylation leading to the reformation of citicoline. Such breakdown and reformation processes are particularly important to citicoline supply to the brain because citicoline does not cross the blood-brain barrier whereas the circulating cytidine and choline broken down from citicoline can (Grieb, 2014). Upon entering the brain, citicoline can give rise to phosphatidylcholine, ACh, sphingomyelin and cardiolipin (Adibhatla and Hatcher, 2002; Adibhatla et al., 2001, 2002), which play roles in neuronal membrane function, neurotransmission, axonal integrity, myelin homeostasis and inner mitochondrial membrane viability among others (Araki and Wurtman, 1997; Blusztajn et al., 1987; Galvan et al., 2005; Harel and Futerman, 1993; Kirkland et al., 2002; Posse de Chaves and Sipione, 2010; Schwarz et al., 1995). Phosphatidylcholine synthesis has an additional advantage to the formation of cytidine 5′–monophosphate which helps the synthesis of nucleic acids (DNA and RNA). The synthesis of cytidine 5′–monophosphate takes place when choline monophosphate binds with phosphatidylcholine. ACh is formed when choline from citicoline is acetylated.

Cholinergic neurons utilize choline in a dual manner namely the synthesis of the membrane structure phosphatidylcholine and biosynthesis of the neurotransmitter ACh. This signifies the usefulness of citicoline at both structural and functional levels. These two pathways simultaneously compete for choline for binding to cytidine monophosphate and for acetylation respectively (Farber et al., 1996; Ulus et al., 2006). Since brain function is an immediate requirement in most cases, acetylation is often the dominant pathway (Iulia et al., 2017). Thus, when choline supply is restricted or choline is depleted, phosphatidylcholine and other phospholipids are often broken down by hydrolyzation to salvage the shortage of choline levels. In other words, this

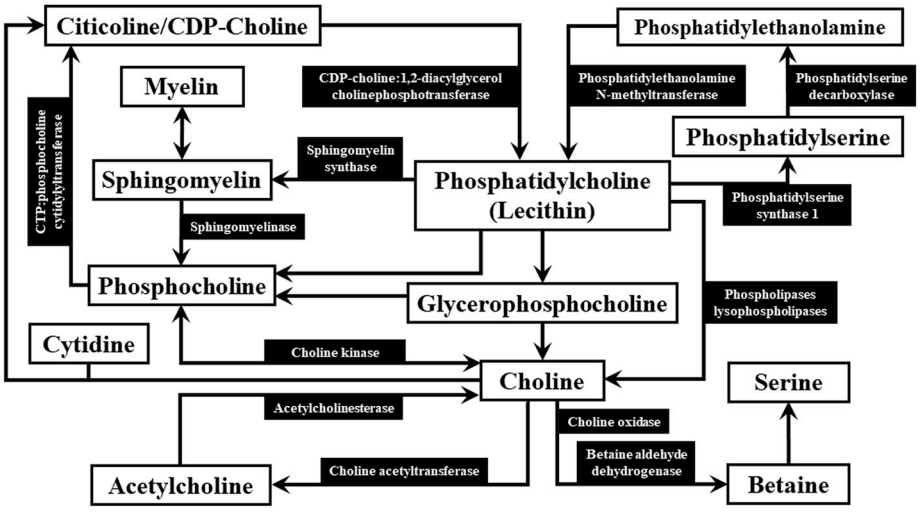


Fig. 5. Citicoline synthesis and metabolism. Citicoline and choline are closely related metabolically and are involved in the synthesis of a variety of active biochemical moieties that have widespread roles to play in membrane biology, neurotransmission, apoptosis and bioenergetics in the visual system. When being acted upon by the enzyme CDP-choline 1,2,-diacylglycerol cholinephosohotransferase, citicoline leads to the formation of phosphatidylcholine, which is an important component of neuronal membranes and is imperative to the membrane integrity of the retinal ganglion cells. Phosphatidylcholine can be converted to sphingomyelin and subsequently to myelin, a major white matter component in the brain. Phosphatidylcholine can also be converted to choline, which forms betaine upon catalytic reaction by choline oxidase, and subsequently to serine, which modulates the non-NMDA ionotropic glutamate receptors expressed by inner retinal neurons. By a variety of enzymes including choline acetyltransferase, choline is converted into ACh, which acts as a neurotransmitter and modulates aqueous humor production through parasympathetic activity. ACh can act as a substrate for the synthesis of choline, a process mediated by acetylcholinesterate.

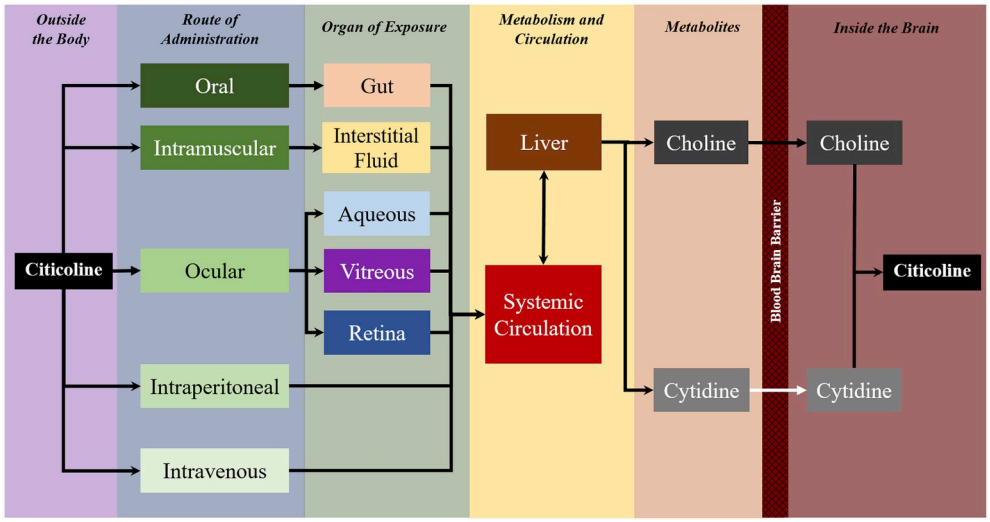


Fig. 6. Citicoline bioavailability and pharmacokinetics in different body compartments. This schematic diagram outlines how citicoline behaves as an exogenous agent (a drug or a supplement) in the mammalian biological system and how this external agent enters the brain. After being administered via oral, intramuscular, ocular, intraperitoneal or intravenous route, citicoline enters the organ of first pass, followed by the systemic circulation and the liver. Since citicoline cannot cross the blood-brain barrier, it needs to be hydrolyzed into choline and cytidine in the liver, which readily cross the blood-brain barrier. Once choline and cytidine enter the brain via the systemic circulation, they recombine to form citicoline which can be used up for various cholinergic functions including neurotransmission, myelin regulation, neuronal membrane rescue and regeneration.

network suggests that citicoline works via two vital mechanisms by first, serving as a source of choline to produce ACh and second, serving as a rescue recourse for breakdown of phosphatidylcholine and other membrane components. This way citicoline may avoid membrane breakdown in the neurons and may prevent apoptosis during neurodegenerative processes thus ensuring the functional viability of the neurons in question. Such mechanisms also identify the neuroprotective properties of citicoline.

2.3. Why citicoline in neurodegeneration?

The neurotherapeutic effects of citicoline appear to be multifarious. Regarding the structure, composition, and functional integrity, citicoline serves as a precursor for phosphatidylcholine, phosphatidylethanolamine and sphingomyelin, which are important structural and functional components of cell membranes (Marcucci et al., 2010; Skripuletz et al., 2015). They ensure proper enzymatic viability for the transport of substances across the membrane (Lagace, 2015; van Meer et al., 2008). In addition, they are indispensable in signal transduction (Exton, 1990, 1994) thereby governing numerous cellular processes and maintaining cellular communication with its environment. Most of the neurodegenerative diseases have their etiology mediated through neuronal membrane integrity (Chitnis and Weiner, 2017; de Groot and Burgas, 2015; Sonnino et al., 2014) which, in turn, is linked to these phospholipids. It is important to mention that membrane integrity is also a potential factor for axonal degeneration in glaucoma (Almasieh et al., 2017; Buys et al., 2014; Howell et al., 2013; Petty, 2018) be it the RGC membrane (Osborne et al., 1999; Risner et al., 2018) or the mitochondrial membrane (Munemasa et al., 2010; Osborne et al., 1999; Tatton et al., 2001). To this effect, cholinergic signaling in glaucoma becomes a potent candidate for therapeutic moieties addressing issues in membrane integrity.

On the other hand, the brain is generally devoid of resident endogenous antioxidant mechanisms in order to maintain proper electrophyisiological function (Deisseroth and Dounce, 1970; Kang et al., 1996; Shingu et al., 1985). Therefore, for neurodegenerative diseases involving oxidative stress, there is a need for antioxidants that penetrate the blood-brain barrier (Gilgun-Sherki et al., 2001). Glutathione is a metabolic product of choline that can bring down lipid peroxidation in the CNS. Since glutathione can also come from citicoline, it seems reasonable to view citicoline as a potent therapeutic substance to treat various oxidative stress-induced neurological diseases including, but not limited to, Alzheimer's disease (Gareri et al., 2017), Parkinson's disease (Kashkin et al., 2017), glaucoma (Iulia et al., 2017), and ischemic neuropathies (Parisi et al., 2008a, 2008b).

Citicoline has been reported to inhibit β-amyloid deposition, which makes it a therapeutic candidate for amyloidopathies like Alzheimer's disease and glaucoma (Cacabelos et al., 1996; Yan et al., 2017). Beta amyloid deposits elicit inflammation (Gorevic, 2013; Ruan et al., 2009) and lead to the disintegration of membrane phospholipids (Lau et al., 2006; McLaurin and Chakrabartty, 1996). In two classical studies, the electrical brain activity and cognitive profiles of Alzheimer's disease patients were reported to be improved after citicoline treatment as compared to controls (Alvarez et al., 1999; Franco-Maside et al., 1994). In particular, patients with mild dementia presented more profound improvements. This indicates that citicoline treatment may be more effective in early cases as compared to late presentation where a larger amount of damage has already occurred. Some initial studies on stroke models also reported the protective effects of citicoline as a single or combined therapy with some efficacy in reducing the infarct size and the consequent improvement in neurological deficits (Cacabelos et al., 1996). This effect was more profound in clinical trials particularly if citicoline was administered immediately after injury. Later studies, however, show conflicting results and the reproducibility remains to be confirmed (Cheng et al., 2004; Clark and Clark, 2012).

In addition to the above, ACh can be synthesized from citicoline and has an important role to play in the dopaminergic and GABAergic systems (Secades, 2011). Citicoline has been suggested to ameliorate neurobehavioral changes in humans and experimental models of Parkinson's disease via the dopaminergic pathway (Agnoli et al., 1982; Saligaut et al., 1987). Choline and ACh from citicoline can also mediate endothelial viability, nitric oxide production, tissue perfusion and mitochondrial integrity via upregulation of intracellular calcium concentrations and releases in the endothelial cells (Li and Wang, 2006; Zhang et al., 2017), and thereby preventing hypoxia-induced endothelial cell damage (Alkon and Rasmussen, 1988; Asaoka et al., 1992; Rasmussen et al., 1995; Tran et al., 2000; Zhang et al., 2017). Taken together, these results indicate a multipathway mechanism of citicoline action in ameliorating neurodegenerative conditions, which may include glaucoma and other vision-related diseases. Hence, we describe this aspect in the following section.

2.4. Citicoline and vision

Citicoline is effective in stimulating the dopaminergic system in the visual pathways including the retinal and post-retinal structures (Iulia et al., 2017; Rejdak et al., 2002). By doing so, citicoline improves the visual acuity, visual evoked responses, contrast sensitivity, and outcomes of patching treatment in amblyopia (Campos et al., 1996; Fresina et al., 2008; Pawar et al., 2014; Porciatti et al., 1998). In another

Table 1
Summary of the use of citicoline as a therapeutic agent in various experimental models of glaucoma and clinical trials. The details of this table bolster the working hypothesis that citicoline has neuroprotective, neurorestorative and neuroregenerative effects on the visual system.

Model/Organism/ Indication	Study design	Sample size	Route of administration	Dosage	Outcome measures	Techniques used	Reference	Results	Implications
RETINAL CELL CULTURES									
Tissue culture of mouse retinal explants	Case-control study	–	Media supplementation in retinal cultures	0.1–10 mmol/l citicoline	Regenerating neurite density	TUNEL assay and the assessment of regenerating neurites	Oshitari et al. (2002)	The number of regenerating neurites was higher in the citicoline treated cultures as compared to the control retinal cultures	Citicoline protects damaged RGCs in retinal tissue cultures
Cultures from embryonic rat retina	Case-control study	–	Media supplementation	10, 100 and 1000 μM citicoline for 96 h	Effects of citicoline on cell survival in primary retinal cultures and neuroprotective activity in conditions akin to retinal neurodegeneration	Apoptotic analysis, immunocytochemistry, morphometric analysis, electrophoresis, western blot	Matteucci et al. (2014)	At the concentration of 100 μM, citicoline blocked neuronal cell damage both in glutamate- and high glucose-treated retinal cultures	Citicoline has potent neuroprotective activity
EXPERIMENTAL ANIMAL MODELS									
Adult male Sprague–Dawley rats	Case-control study	n = 15 and 5 for experimental and control groups	Intraperitoneal	500 mg/kg/twice daily for 1, 3 and 7 days following intraocular kainic acid injection	Neuroprotective effect of citicoline on kainic acid -induced retinal damage	Retinal thickness and immunoreactivities of ChAT and tyrosine hydroxylase	Park et al. (2005)	Citicoline significantly attenuated the reduction in retinal thickness and immunoreactivities of ChAT and tyrosine hydroxylase.	Citicoline shows neuroprotective effects on retinal damage due to kainic acid-induced neurotoxicity.
Adult female Brown Norway rats	Case-control study	n = 24 and 15 for experimental and control groups	Intraperitoneal	1 g/kg daily for up to 7 days and 300 mg/kg daily afterwards	Effect of citicoline on glaucomatous degeneration of RGC as measure through RGC density and immunoreactivity to BCL2	Fluorescence microscopy to count the labelled RGCs and immunohistochemistry for BCL2 expression	Schuettauf et al. (2006)	Citicoline was associated with higher RGC density and expression of BCL2 in optic nerve crush.	Citicoline protects RGCs and their axons *in vivo* against optic nerve crush mediated degeneration and the effect may be mediated through BCL2 expression
CLINICAL TRIALS									
Open angle glaucoma	Cohort study	30 patients (47 eyes): 17 males and 13 females	Intramuscular	1 g/day for 10 consecutive days	Behavior of scotomatous area	Central perimetry, automated perimetry, applanation tonometry	Pecori Giraldi et al. (1989)	Significant improvement in perimetry in 75 percent of the eyes with stability of the effects for at least 3 months. Same results were obtained when the treatment was repeated after 4 months	Citicoline has the potential to complement the conventional ocular hypotensive therapy
Open angle glaucoma	Double-blinded placebo-controlled trial	40 patients (n = 25 and 15 for intervention and control groups)	Intramuscular	1000 mg/day for 60 days	VEP (P100 latency and N75–P100 amplitude), PERG (P50 latency and P50–N95 amplitude), and IOP	VEP, PERG and tonometry	Parisi et al. (1999)	Citicoline treatment was associated with significant improvements of VEP and PERG parameters	Citicoline induces improvement of the retinal and visual pathway function in glaucoma patients
Open angle glaucoma	Case-control study	23 participants (n = 11 and 12 for interventional and control groups)	Intramuscular	1000 mg/day for 15 days	Visual field parameters	Perimetry	Virno et al. (2000)	A stable visual field improvement was observed in glaucoma patients and this improvement persisted for 9 years	Citicoline leads to sustained improvement in visual fields in glaucoma patients
Open angle glaucoma	Cohort study	21 glaucomatous eyes	Oral	1000 mg/day for 15 days	VEP latency and VEP amplitude	Pattern-reversal visual evoked potentials	Rejdak et al. (2003)	VEP latency reduced and VEP amplitude increased significantly with citicoline treatment	Oral administration of citicoline improves visual evoked potentials in glaucoma patients
Open angle glaucoma	Double-blinded placebo-controlled trial	30 patients (n = 15 and 15 for citicoline and control groups)	Intramuscular	1000 mg/day for 60 days.	VEP and PERG parameters	VEP and PERG	Parisi (2005)	Citicoline significantly improves retinal and cortical bioelectrical responses in glaucoma patients	Citicoline can be used in glaucoma treatment as a complement to ocular hypotensive therapy

(*continued on next page*)

Table 1 (*continued*)

Model/Organism/ Indication	Study design	Sample size	Route of administration	Dosage	Outcome measures	Techniques used	Reference	Results	Implications
Open angle glaucoma	Case-control study	60 patients(70 eyes)	Oral/Intramuscular	1000–1600 mg/day for 60 days	VEP and PERG parameters	VEP and PERG	(Parisi et al., 2008a, 2008b)	Improvement of retinal function and neural conduction along visual pathways	Citicoline has neuroprotective effects in glaucoma
Open angle glaucoma	Cohort study in retrospect	41 patients	Oral	500 mg/day for 2 years	Visual field parameters	Perimetry	Ottobelli et al. (2013)	The rate of visual field progression significantly changed with citicoline treatment	Citicoline supplementation may be useful in slowing down glaucoma progression
Open angle glaucoma	Double-blinded placebo-controlled trial	34 patients (n = 16 and 18 for citicoline and control groups)	Intraocular (Topical eye drops)	3 drops/day for two months	VEP and PERG parameters	VEP and PERG	Roberti et al. (2014)	Improvement in RGC function shown by reduced P50 latency and increased P50–N95 amplitude of pattern electroretinogram	Topical citicoline has neuroprotective effect independent of hypotensive action of ocular hypotensive eye drops
Open angle glaucoma	Case-control study	56 patients (n = 28 and 28 for intervention and control groups)	Intraocular (Topical eye drops)	3 drops/day for four months	VEP and PERG parameters	VEP and PERG	Parisi et al. (2015)	Citicoline treatment was associated with shortening of VEP P100 implicit time, which was correlated significantly with the increase of PERG P50–N95 amplitude	Topical citicoline treatment in glaucoma induces enhancement of retinal bioelectrical responses with improvement in bioelectrical activity of the visual cortex

clinical trial involving patients with non-arteritic ischemic optic neuropathy, 60 days of oral citicoline treatment also showed beneficial effects on the visual acuity, visual evoked potential and pattern electroretinogram (Parisi et al., 2008a, 2008b). These investigators reported persistent improvements even after the washout period, suggestive of the neuroprotective or long-lasting neurorestorative effects of citicoline on visual function.

2.5. Citicoline and retinal ganglion cells

The molecular, cellular, and physiological interphases between citicoline and RGCs appear tightly linked. Citicoline is involved in the proper maintenance of sphingomyelin and cardiolipin levels (Adibhatla and Hatcher, 2002; Adibhatla et al., 2001, 2002; Gareri et al., 2015, 2017), whereas the RGCs are rich in myelin in their axons and are the primary site of glaucomatous injury (FitzGibbon and Nestorovski, 2013; Giacci et al., 2018; Yalcin et al., 2013). While sphingomyelin is a sphingolipid in the myelin sheath that surrounds the nerve cell axons, cardiolipin accounts for 20% of the total lipid composition in the inner mitochondrial membrane (Paradies et al., 2014) and is involved in maintaining optimal enzymatic activity in energy metabolism. Since neurons are energetically the most expensive cells of the body (Munzberg et al., 2016; Niven, 2016; Qadri et al., 2018), any hindrance in the maintenance of cardiolipin and sphingomyelin is likely to affect the neurons, especially those with long myelinated axons. RGCs are, for this reason, favorable candidates for such degenerative and proapoptotic insults. If sphingomyelin and cardiolipin damages are involved in glaucoma, citicoline administration may become one of the potential treatments for the prevention of cellular death in glaucoma. With this premise, we will describe the various aspects of possible citicoline use in glaucoma in the next section.

2.6. Citicoline and glaucoma

Citicoline appears to possess the potential for ameliorating glaucomatous damage or vision loss in a number of *in vitro* and *in vivo* studies involving retinal cell cultures, experimental animal models and clinical trials (Table 1). Using mouse retinal explants, the number of regenerating neurites was found to be higher in damaged RGCs that were treated with citicoline as compared to the control retina (Oshitari et al., 2002). On the other hand, glutamate excitotoxicity has been postulated to be a major factor of glaucoma onset and progression (Dreyer, 1998; Osborne et al., 1999; Salt and Cordeiro, 2006). Interestingly, citicoline was shown to counteract neuronal cell damage in glutamate-treated rat primary retinal cultures via decreasing proapoptotic effects and contrasting synapse loss (Matteucci et al., 2014). Kainic acid is a potent neuroexcitatory amino acid agonist that mediates its neurotoxic effects through activating glutamate receptors. In a rat model of kainic acid-induced retinal damage, animals receiving prolonged citicoline treatment appeared to show less profound retinal thinning and less attenuated immunoreactivities of ChAT as compared to the control (Park et al., 2005). Using experimental glaucoma models, adult rats with optic nerve crush presented higher RGC density after intraperitoneal citicoline treatment than vehicle treatment (Schuettauf et al., 2006). While citicoline did not appear to alter IOP in experimental glaucoma (van der Merwe et al., 2016), the above experimental studies provide direct evidence of the protective effects of citicoline on RGCs and an inference of the specific role of citicoline in alleviating glaucomatous damages. The biochemical mechanisms underlying such effects appear similar to citicoline actions on other neurodegenerative diseases (Faiq, 2016, 2018; Faiq et al., 2014b, 2016b; Faiq and Dada, 2017).

With regard to the metabolome across the spectrum of neurodegeneration, citicoline may crosstalk with glucose metabolism and may protect neurons from hyperglycemic conditions (Gao et al., 2017; Matteucci et al., 2014) thereby lowering the risk of neurodegeneration in hyperglycemia and diabetes. While initial evidence also suggests that

IOP elevation is associated with insulin resistance (Chun et al., 2015; Fujiwara et al., 2015; Oh et al., 2005), its implications in the development of glaucomatous neurodegeneration remain largely unexplored. Faiq et al. recently hypothesized the "brain diabetes theory of glaucoma" (Faiq et al., 2014b; Faiq and Dada, 2017) whereby insulin signaling dysfunction may be implicated in the glaucomatous visual system (Agostinone et al., 2018; Faiq et al., 2017; Hou et al., 2018) similar to other CNS disorders (Datusalia et al., 2018; Montgomery and Turner, 2015; Najem et al., 2014; Schubert et al., 2004; Stewart and Clearkin, 2008). Citicoline and its associated choline-containing components have been suggested to counter the effects of insulin resistance (Gao et al., 2017). Citicoline has also been shown to induce angiogenesis thereby improving the survival of human brain microvessel endothelial cells through insulin receptor substrate-1 mediation (Krupinski et al., 2012). Even though not all glaucoma patients have diabetes and not all diabetics have glaucoma, this line of research may point towards a new glaucoma phenotype involving insulin resistance and may implicate a potential role of citicoline action on this population (Faiq, 2018).

With regard to clinical evidence, it is important to note that the effectiveness of any treatment has to be proven by standard objective parameters and validated by well-accepted measuring techniques. Several gold standards that are important in the evaluation of neuroprotection and visual function in glaucoma include electrophysiology via pattern electroretinogram and visual evoked potential, and visual field perimetry via Humphrey Field Analyzer. These tools have been used in the investigations of citicoline as a therapeutic modality for glaucoma (Table 1). For example, one of the earliest clinical trials evaluating the efficacy of oral citicoline in glaucoma demonstrated improvement in visual evoked potentials after administrating 500 mg citicoline tablets twice a day (approximately 14 mg/kg body weight/day) to glaucoma patients (Rejdak et al., 2003). In another 2 randomized placebo-controlled studies involving intramuscular injection of citicoline, improvements in visual evoked potential and pattern electroretinogram were observed in the citicoline group as against the placebo group (Parisi, 2005; Parisi et al., 1999). Importantly, these effects maintained even after the washout period over the 8-year experimental period. These results indicate that citicoline sustainably improves retinal and cortical bioelectrical responses in glaucoma patients. When evaluating the efficacy of oral suspension citicoline against intramuscular injection (Parisi et al., 2008a), no apparent difference in visual evoked potential or pattern electroretinogram was observed in glaucoma patients with moderate visual field defects.

Since glaucoma involves selective loss of RGCs whose cell bodies are located in the inner layer of the retina, they are therapeutically easy to approach through the ocular route as compared to oral and intramuscular routes. It has also been observed that medication in the form of eye drops has better compliance and adherence than oral and intramuscular medications (Witticke et al., 2012). Thus, it becomes essential to evaluate if citicoline eye drops can cross the cornea and provide sufficient bioavailability at the site of action to the retina. With a dosage of 1% and 2% citicoline eye drop suspension at the frequency of twice daily, citicoline was detected in the vitreous of murine models (Roberti et al., 2014). 2% administration was also associated with systemic absorption of citicoline. The investigators then moved on to clinical studies and added citicoline eye drops to the regular ocular hypotensive medication in glaucoma patients for 2 months followed by a 1-month washout period. Although patients showed improvement in the electrophysiological function of the retina, such effect regressed after the washout period. Parisi et al., carried out a similar trial but with increased citicoline dosage and treatment duration to test if this shows any sustained effects (Parisi et al., 2015). They enrolled patients on β-blocker monotherapy with the intervention group taking an additional citicoline eye drop regimen at three times a day for 4 months followed by a washout period of 2 months. Results showed a significant improvement in visual evoked potential and pattern electroretinogram after 4 months of citicoline treatment. However, these observations also normalized to baseline levels after medication was stopped. These transient visual restoration effects suggest a constant loss or sub-optimal availability of choline upon topical citicoline treatment, indicating the need of further optimization for effective topical citicoline administration in glaucoma. We presume that early glaucoma treatment might show better and more long-lasting effects than treatment to more severe glaucoma, though practically most cases of glaucoma have already experienced severe RGC damage by the time they are diagnosed. In this regard, pilot studies aiming at detecting glaucoma early via advanced imaging and quality-of-life assessments may be helpful.

3. Brain imaging in glaucoma

Since glaucoma is considered an irreversible disease, it is important to identify early glaucomatous changes and slow down the disease progression effectively. Recent advancements in imaging modalities have begun to shed light on this. For example, within the eye, substantial structural loss in terms of retinal nerve fiber layer thinning appears to be necessary before functional visual field defects become detectable in open-angle glaucoma (Alasil et al., 2014; Wollstein et al., 2012). On the other hand, increasing evidence suggests the involvements of trans-synaptic deteriorations of post-retinal structures along the central visual pathway in glaucoma (Gupta et al., 2006), yet the majority of neuroimaging studies focus on subjects with glaucoma approaching advanced stages (Lawlor et al., 2018). Longitudinal evaluation of brain changes along the entire spectrum of the disease severity is essential to determine the temporal characteristics and causal relationships between biomarkers in the eye and the brain. Such studies and the testing of targeted neurotherapeutics have been performed preclinically using rodent glaucoma models (Chan et al., 2019; van der Merwe et al., 2016; Yang et al., 2018) while clinical neuroimaging studies have also been initiated in patients at different stages of glaucoma. Specifically, initial evidence from Murphy et al. showed that glaucoma deterioration is already present in the brain before vision loss can be detected clinically by conventional visual field tests (Murphy et al., 2016). This observation has been reproduced independently in another laboratory along the optic radiation (Wang et al., 2018), whilst demyelination appears to precede axonal loss in the trans-synaptic spread of human glaucoma, suggesting that the mechanism of trans-synaptic damage may be at least partially mediated by glial components at the cellular level (You et al., 2019). Within the visual cortex, it is also reported that cortical cholinergic and glutamatergic abnormalities are associated with other conventional glaucoma biomarkers in subjects with varying glaucoma severity (Aksoy et al., 2018; Chan et al., 2009; Guo et al., 2018; Murphy et al., 2016) (Fig. 7). In this context, citicoline can be evaluated as a therapeutic option apart from ocular hypertensives who are at high risk of glaucoma but have not developed glaucoma as yet. Positive family history can also be considered as the initial stage of glaucoma continuum.

As mentioned in the preceding section, glaucoma damage can be identified by optical coherence tomography (Adhi and Duker, 2013; Mwanza and Budenz, 2018; Schuman, 2008; Schuman et al., 1995) and magnetic resonance imaging prior to detectable clinical vision loss (Murphy et al., 2016; Wang et al., 2018). Though such a statement does not endorse the absence of early functional deterioration, the underlying premise is that vision loss cannot be detected by clinical perimetry as early as the changes in the central visual pathway are picked up by imaging modalities. Latest studies support the inference that glaucoma is a neurodegenerative disease with signs of early deterioration in brain as well as CNS control of visual field loss (Chan et al., 2008, 2009; Crish et al., 2010; Faiq et al., 2016b; Gupta and Yucel, 2007; Reilly et al., 2015; Risner et al., 2018; Sponsel et al., 2014). Such a notion has numerous implications with respect to the brain as an investigative, diagnostic, therapeutic, and prognostic target for glaucoma from genetic, biochemical, molecular, physiological, pharmacological, and imaging

points of view (Faiq et al., 2013a, 2013b, 2014c, 2015, 2016b; Faiq, 2018; Kasi et al., 2019). This is where neuroimaging comes into picture with the prospect of different MRI techniques including the standard anatomical MRI, diffusion tensor imaging of structural integrity of brain connectivity (Ho et al., 2015; V et al., 2018; Yang et al., 2018), manganese-enhanced MRI of physiological anterograde axonal transport and neuronal activity (Calkins et al., 2008; Chan et al., 2008, 2017a; Ho et al., 2015; Yang et al., 2018), functional MRI of hemodynamic brain activity (Murphy et al., 2016; Zhou et al., 2017), and magnetic resonance spectroscopy (MRS) of biochemicals and metabolic processes in the brain (Chan et al., 2009; Chow et al., 2011; Murphy et al., 2016). In particular, choline concentrations in cerebral white matter and grey matter can be identified with proton magnetic resonance spectroscopy (^{1}H MRS) *in vivo* (Ross and Bluml, 2001). Also, radiolabeled choline (e.g. 11C and 18F) can be effectively employed (Calabria et al., 2018). Citicoline is known to be involved in myelin and acetylcholine synthesis through choline as a metabolite. Since a variety of neurodegenerative diseases and their cardinal features like inflammation are associated with change in choline concentration, an integrative metabolic map of the status of neural tissues may be useful in identifying brain abnormalities early in both glaucoma patients and experimental glaucoma models (Fig. 7). By this approach, the effects of drug interventions can be monitored in both clinical trials and preclinical models (Babb et al., 2004). Fig. 8 depicts a classical triad of neuroprotection, neurorestoration, and neuroregeneration that may represent the possible neurotherapeutic strategies for future glaucoma management. Fig. 9 illustrates a schematic diagram of normal, early, and advanced stages of glaucoma and the potential neurotherapeutic approaches in correspondence to visual field loss, retinal nerve fiber layer thinning, and brain damages in humans via perimetry, optical coherence tomography, and MRI. Such structural and functional imaging paradigms can also be used to explore the neurobehavioral effects of citicoline as demonstrated initially in novel rodent glaucoma models (Chan et al., 2018, 2019; Harwerth et al., 2010; van der Merwe et al., 2016; Yang et al., 2018).

4. Psychosomatic correlates

A major comorbidity of glaucoma is the patients' fear of blindness over time, which is thought to be far beyond the actual risk (Janz et al., 2007). At the same time, cholinergic neurons are known to be involved in regulating cognitive functions including fear (Boskovic et al., 2018; Wilson and Fadel, 2017). To date, whether such cholinergic neuromodulatory drive can directly affect visual function remains unclear (Chen et al., 2015). In a study assessing the psychological impact of glaucoma, it was found that 80% of the 589 enrolled patients suffered from negative emotional reactions after knowing that they had glaucoma, among which nearly one third had apprehension of developing blindness (Odberg et al., 2001). This is in line with later cross-sectional studies that observed higher anxiety levels (Bechetoille et al., 2008; Hamelin et al., 2002) and depression prevalence in patients with increasing glaucoma severity (Bramley et al., 2008; Skalicky and Goldberg, 2008). Longitudinally, visual field loss in glaucoma (Artes and Chauhan, 2005) appears to progress at a faster rate if the patient is presented with depression-like symptoms (Diniz-Filho et al., 2016). Whilst mental stress can modify cholinergic neurotransmission in the brain (Caspi et al., 2003; Meerson et al., 2010), malfunction of the ACh system can also lead to stress and anxiety (Kumar et al., 2013a; Mark et al., 1996; Mineur et al., 2013; Picciotto et al., 2012, 2015) as well as elevation of cortisol (Walker et al., 1990), which in turn is associated

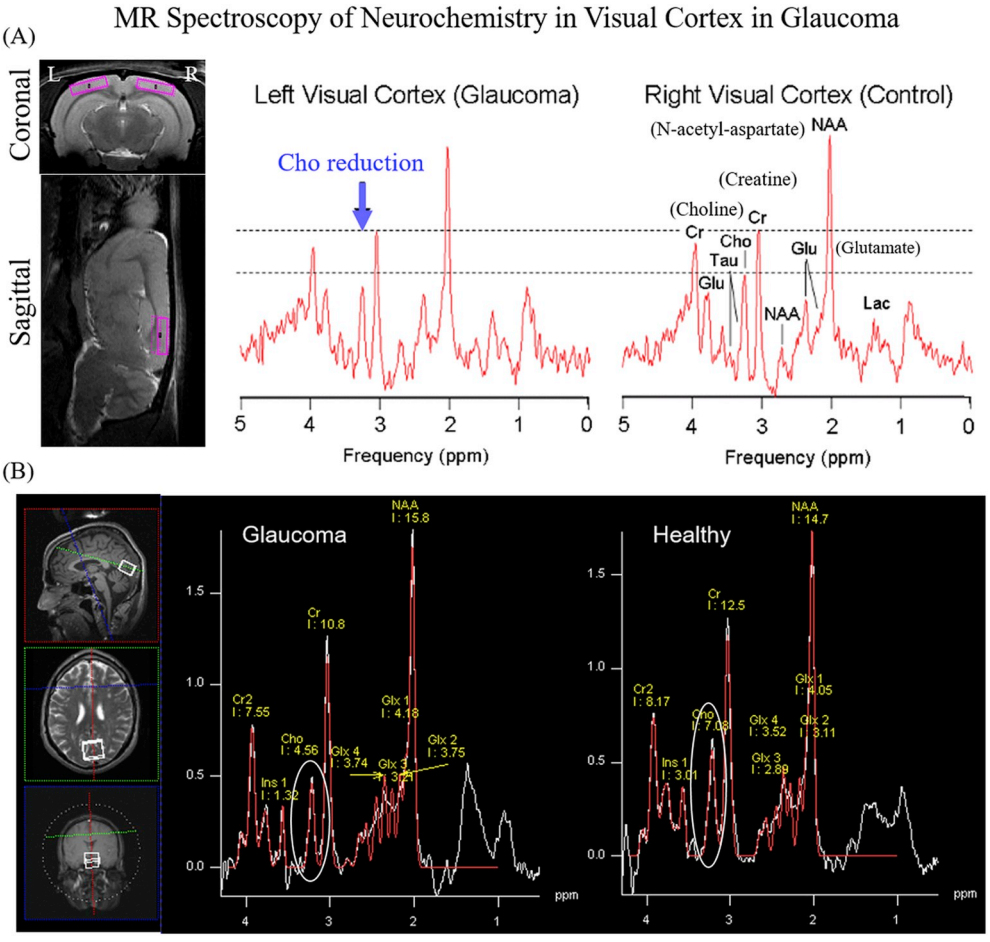


Fig. 7. In vivo metabolic assessments of the brain in glaucoma. Using magnetic resonance spectroscopy, the neurochemistry of the visual cortex in glaucoma can be evaluated non-invasively and can be compared across species spanning from the conventional experimental rat model of unilateral chronic ocular hypertension **(A)** to glaucoma patients **(B)**. It is important to note that both humans and rodents show a lower choline (Cho) level in the glaucomatous visual cortex relative to the control visual cortex, whereas the creatine (Cr) level appears relatively comparable between glaucoma and control visual cortices. This suggests the reduction of choline-containing compounds in the glaucomatous visual cortex during trans-synaptic degeneration. The volumes of interests sampled are shown in the purple **(A)** and white boxes **(B)** in the multiplanar magnetic resonance brain images on the left for references. (Reproduced with permission from (Chan et al., 2009) and (Murphy et al., 2016)).

with IOP elevation (Schwartz and Seddon, 1981) and vascular dysregulation with relevance to Flammer syndrome or endothelial dysfunction-mediated glaucoma (Buckley et al., 2002; Bukhari et al., 2016; Flammer and Konieczka, 2017; Konieczka et al., 2014, 2017; Liu et al., 2016; Resch et al., 2009). Collectively, this overview presents a potential vicious circle whereby vision loss in glaucoma elicits psychological stress and anxiety, which then exert influence on the brain cholinergic system to cause further vision loss. From another viewpoint, this information also provides opportunities to address the pathogenic features of glaucoma at multiple levels, as ameliorating ACh metabolism dysfunction or severity of depression and psychological stress may help to pacify the risks for glaucoma (Chamoun et al., 2017; Dada et al., 2018; Faiq, 2016, 2018; Gagrani et al., 2018; Sabel et al., 2018b). Even though the primary outcome measure of most clinical trials was IOP which is currently the only modifiable risk factor for glaucoma, these studies lend support to the notion that interventions based on eliciting relaxation response may be helpful in ameliorating glaucoma-related symptoms as well as positive changes in gene expression and other markers of stress and well-being (Sankalp et al., 2018).

Additionally, glaucoma patients often present visual attention deficits (Rosen et al., 2015; Smith et al., 2011). Visually impaired individuals typically possess a reduced visual span as compared to the normally sighted counterparts. This necessitates the glaucomatous individuals to distribute attention between functioning and deficient visual fields, which in turn elevates the burden on attention reserves for cognitive tasks (Swenor et al., 2017). Damage to the retinal nerve fiber layer or post-retinal visual pathway in glaucoma may also reduce the efficiency of the visual system to execute immediate target detection in the visual field (Loughman et al., 2007). Using advanced neuroimaging, widespread structural and functional brain changes within and beyond the central visual pathway have been found in glaucoma, and these brain regions are often involved in high-order cognitive functions (Murphy et al., 2016; Nuzzi et al., 2018; Song et al., 2014; Wang et al., 2016). It is known that the cholinergic systems may be altered in attention–deficit/hyperactivity disorder (Demeter and Sarter, 2013; Luchicchi et al., 2014; Sarter and Paolone, 2011), whereas nicotine alleviates symptoms due to attention deficit (Conners et al., 1996; Sahakian et al., 1989; Wignall and de Wit, 2011). This brings about two questions of whether the central nicotinic cholinergic function may augment the attention deficits in glaucoma, and if it can be a target similar to attention-deficit/hyperactivity disorder (Potter et al., 2006). Citicoline supplementation has been shown to improve attention, working memory and performance speed (Bruce et al., 2014; McGlade et al., 2019) which suggests that citicoline may work as a therapeutic measure to improve glaucoma outcomes through similar pathways. Since citicoline is a precursor of choline-related compounds, it seems apparent that citicoline may aid in addressing the cholinergic glaucoma-stress relationship in addition to other neuroprotective and neurorestorative realms. More studies are necessary to confirm how specifically cholinergic dysfunctions are involved in glaucoma and whether the multifarious factors aforementioned are indeed effective targets for citicoline therapy. With this note, the final section deals with the status quo and the future prospectus of ACh modulation and citicoline therapy in glaucomatous vision loss.

5. Future directions and conclusions

In this paper, we put forth the hypothesis of the cholinergic nervous system as a mechanistic and therapeutic modality in vision and behavior, and exploit the evidence of its role in the etiopathogenesis of glaucoma. Fig. 10 elucidates the above with cross references to citicoline biology. These preclinical and clinical studies justify citicoline supplementation by various routes including oral administration, intramuscular injection, intraperitoneal injection and eye drops across different neurodegenerative diseases and species. Various concentrations of citicoline have been used from 50 mg/kg body weight to 1g per day. Outcome measures like retinal catecholamine levels, thickness of retinal layers, expression of choline acetyl transferase and tyrosine hydroxylase, RGC density, expression of anti-apoptotic BCL-2, apoptosis evaluation by TUNEL assays, caspase 3 and caspase 9 activity, structural and functional brain imaging, pattern electroretinography, visual evoked potential measurements, and optokinetic behavioral assessments have been investigated with study designs ranging from animal model studies to case control and randomized placebo-controlled trials. In light of the above overview, it seems that citicoline holds a strong promise to be a future treatment modality for glaucoma and other neurodegenerative diseases. It is not clear whether citicoline affects IOP or ICP, but citicoline may act through the neurodegenerative, neuropathic and psychosomatic paradigms in glaucoma.

Two obvious approaches towards citicoline use emerge from the studies reported to date. One is aimed at exploring the therapeutic mechanism by employing animal and clinical studies, and the other is focused on the safety and efficacy by animal studies and randomized controlled trials. While citicoline has been found safe at the therapeutic doses being currently administered, an ideal clinical study to evaluate the neurotherapeutic effects of citicoline in glaucoma may be difficult to perform owing to the inherent issues in the natural history of glaucoma such as a long term and rather variable progression curve, the difficulty to predict disease severity and glaucoma risks in terms of elevated IOP, variable and unclear age of onset, involvements of the brain apart from the eye, the lack of consensus in cupping paradigm, the potential role of endothelial dysfunction, the systemic effects on disease onset and progression, role of stress and anxiety, and other psychosomatic involvements (Weinreb, 2007). To circumvent this difficulty, a pre-glaucomatous state identification protocol and long-term follow up would be advantageous but that would require meticulous study design and long periods of monitoring. We explicate on this issue in the following paragraphs on the potential clinical trial settings and their feasibility in both early and advanced glaucoma (Guymer et al., 2019; Levin et al., 2017; Quigley, 2012).

The mechanistic assembly of cholinergic system-glaucoma relation

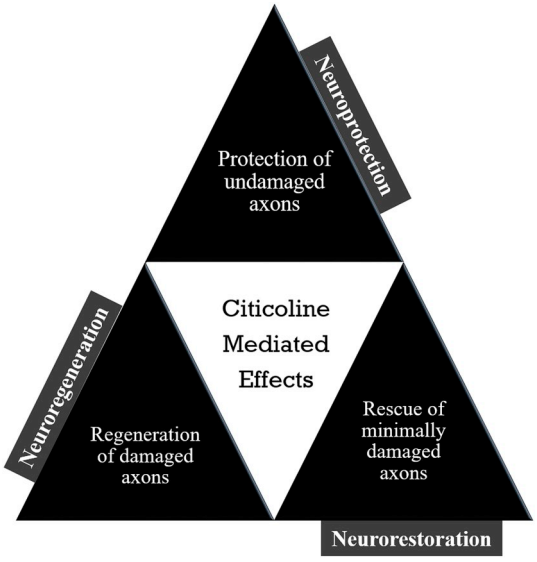


Fig. 8. The classical triad of citicoline actions on neurodegeneration. This figure summarizes the biochemical and biological activities of citicoline into the triad of pharmacodynamics for treating neurodegeneration. Citicoline protects undamaged axons and hence is neuroprotective (Adibhatla et al., 2002; Bogdanov et al., 2018; Grieb, 2014; Hurtado et al., 2005; Parisi et al., 2018). It rescues the partially damaged neurons presumably through membrane re-integration and therefore is neurorestorative (Saver, 2008). The regenerative function of citicoline arises from the initial *in vitro* evidence for the drug to regenerate neuronal cells (Ozay et al., 2007; Skripuletz et al., 2015).

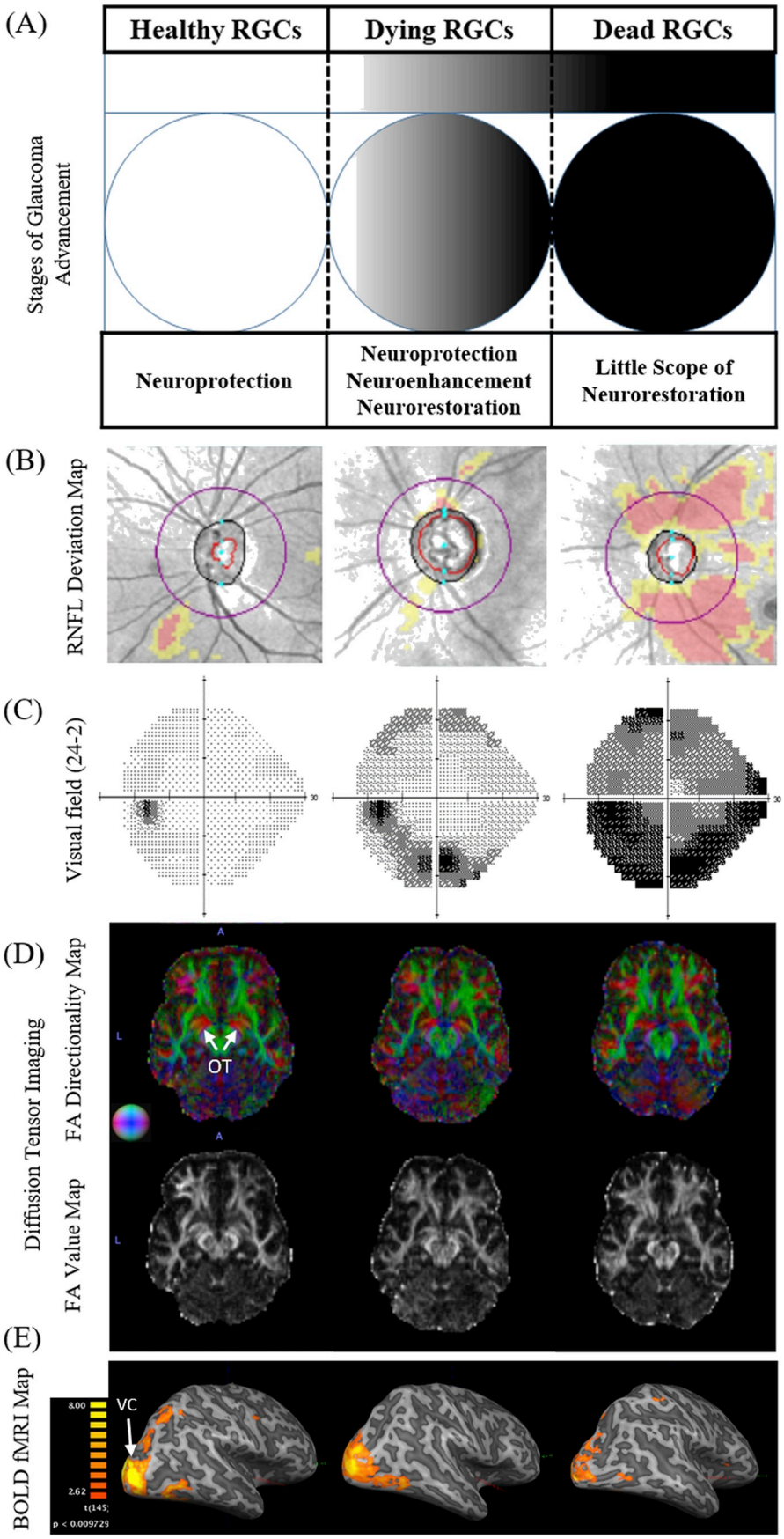


Fig. 9. Representation of various severity of ocular and central vision loss in glaucoma and the candidate plan for neurotherapeutic intervention. This figure explicates the idea of glaucoma being a neurodegenerative disorder with definite ocular and brain manifestations. **(A)** portrays a schematic representation of healthy **(1**st **column)**, partially lost **(2**nd **column)** and completely lost visual function **(3**rd **column)**. The corresponding clinical manifestations are illustrated in terms of peripapillary retinal nerve fiber layer (RNFL) thickness by optical coherence tomography **(B)** and visual field perimetry **(C)**. The concomitant structural and functional brain changes in diffusion tensor MRI **(D)** and functional MRI **(E)** across increasing extents of vision loss bolsters the notion of glaucoma being a neurodegenerative disease of the visual system. This figure also considers the candidature of each condition for neurotherapeutic intervention. Since citicoline is neuroprotective, a healthy visual field (in high risk individuals) is a candidate for neuroprotection. The neurorestorative and neuroregenerative properties of citicoline make it a candidate for partially damaged and completely damaged visual fields **(A)**. Color representations for the principal diffusion directions in (D): blue, caudal-rostral; red, left-right; green, dorsal-ventral. (FA: fractional anisotropy; OT: optic tract; VC: visual cortex; BOLD fMRI: blood-oxygenation-level-dependent functional MRI).

can be broadly classified into 3 domains: protection of undamaged RGCs and axons, rescue of minimally damaged RGCs and axons, and regeneration of damaged RGCs and axons (Fig. 8). In terms of conceptual neurobiology, there is no clear boundary between these three processes and the therapeutic effects of citicoline are presumably mediated through the combination and permutation of all three contributions. It is assumed that citicoline may mainly act through the first and second mechanisms (i.e. neuroprotection and neurorestoration) if glaucoma can be diagnosed early. These RGCs and axons often appear in the transition zones of the visual field and are often undetected or ignored clinically. Fig. 9 demonstrates this scenario both schematically and from actual data obtained under clinical and experimental neuroimaging settings. Ophthalmologists generally examine visual field results in terms of "black-and-white" where black means lost vision and white means intact vision. The often ignored grey areas may be from a mix of healthy and damaged RGCs or axons given the limited resolution of perimetry. Alternatively, there is initial evidence that corresponds these regions to the minimally damaged cells or axons in early apoptosis stage, whereby the most reservoir for vision rescue and regeneration can be potentiated (Fedorov et al., 2011; Gall et al., 2016;

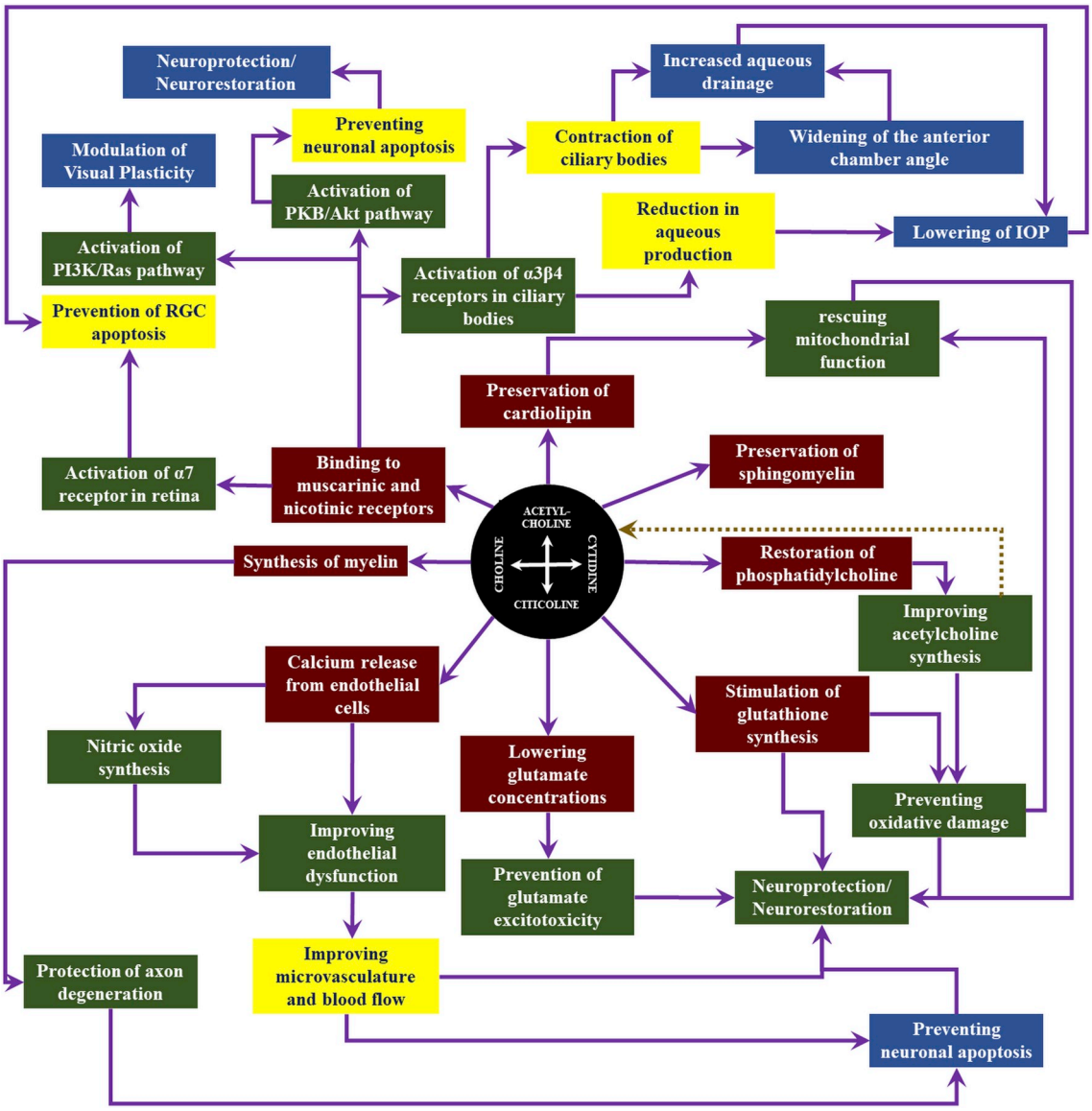


Fig. 10. Overview of the involvements of cholinergic metabolism in neuroprotection, neurorestoration, and vision rehabilitation in both basic and clinical domains. ACh and citicoline are reciprocal precursors and are interconvertible through various enzymatic systems. Choline and cytidine are also metabolites within this network. The reported effects of this pool of moieties (citicoline, ACh, choline and cytidine) include: (1) Preservation of cardiolipin for rescuing mitochondrial function and consequently aiding in neuroprotection and neurorestoration; (2) Preservation of sphingomyelin for myelin formation and thereby protection of neurons and assurance of proper membrane function; (3) Restoration of phosphatidylcholine for improved ACh synthesis. This may help prevent oxidative stress and is important in neuroprotective and neurorestorative processes by maintaining mitochondrial function and viability and preventing mitochondrial genome instability; (4) Stimulation of glutathione synthesis works through two main mechanisms including prevention of oxidative stress and direct neuroprotection. Prevention of oxidative stress, in particular, ensures better bioenergetics and prevents neuronal apoptosis; (5) Lowering of glutamate concentration. This primarily prevents glutamate excitotoxicity thereby promotes neuroprotection and neurorestoration; (6) Releasing calcium from endothelial cells for modulating nitric oxide and improving endothelial function. Proper functioning of the microvasculature and proper tissue perfusion is important for neuronal viability. Ameliorating endothelial dysfunction leads to improved microvasculature and better blood flow, which, in turn, prevents neuronal apoptosis; (7) Myelin synthesis for axon protection and prevention of the axonal degeneration; and (8) Binding to muscarinic and nicotinic receptors for activating molecular pathways that are involved in the prevention of RGC death and neuronal apoptosis, neurorestoration, modulation of neuroplasticity, contraction of ciliary bodies, and widening of the anterior chamber angle with increased aqueous outflow and consequent drop in IOP.

Henrich-Noack et al., 2017b; Kasten et al., 1998; Sabel et al., 2011b, 2018a). Citicoline might act in the window between cellular/axonal dysfunction and death which offers a pragmatic approach from the end-user point of view. Preclinically, optic nerve crush models may be useful in investigating the neurorestorative/neuroregenerative potentials of citicoline while ocular hypertension models are likely helpful to further our understanding of the neuroprotective/neurorestorative mechanisms thereof. Also, animal models that represent the normotensive subset of glaucoma such as impaired glutamate transporters and transgenic optineurin E50K or TANK-binding kinase 1 (TBK1) mice may help in understanding neuroprotective and neurorestorative processes upon IOP-independent mechanisms of RGC apoptosis (Harada et al., 2019). In animal models, the outcome measures can be pattern electroretinogram, visual evoked potential, IOP, ocular and cerebral integrity, protein expression profiling, and gene expression profiling. Visual behavioral assessments are often ignored in preclinical studies but are important to evaluate any overall improvement in functional vision after neurotherapeutics to the eye and the brain's visual system. Designing rigorous experiments in this direction may provide answers to the roles of the cholinergic system in glaucoma, and at the same time give rise to novel and relevant questions. Furthermore, detecting the disease early and tracing disease progression in the same subjects are important to research fields to minimize biovariability and develop better understanding of causality, whereas direct detection of the cholinergic signaling *in vivo* could help improve specificity of our investigative experiments and for personalized medicine.

With regards to clinical studies, various study designs like case control and prospective or retrospective cohort have been investigated (Ottobelli et al., 2013; Parisi, 2005; Parisi et al., 1999, 2008a, 2008b, 2015; Pecori Giraldi et al., 1989; Rejdak et al., 2003; Roberti et al., 2014; Virno et al., 2000) (Table 1). Given the safety of citicoline and the absence of serious adverse events reported, this compound has entered clinical trials for a variety of neurodegenerative diseases including glaucoma. There is, however, a caveat on the sustainability of the therapeutics as the additional beneficial effects supplemented by citicoline eye drops appear to fall back to baseline after the washout period. This indicates the need for further optimization of the pharmacokinetics of different administrative routes and treatment paradigm for improved long-lasting effects. On the other hand, there have been no clinical trials in the use of citicoline treatment on congenital glaucoma, juvenile onset glaucoma, developmental glaucoma, or angle closure glaucoma. It is either unclear whether citicoline acts on secondary glaucoma including steroid-induced glaucoma or neovascular glaucoma. Since outcomes measures such as changes in scotomatous area, visual evoked potential, pattern electroretinogram, and visual field have been initially evaluated in citicoline supplementation, a more well-structured clinical trial makes the next coherent rationale. This may include a randomized controlled trial with four arms instead of two: (i) ocular hypertension with no glaucoma, (ii) high-tension glaucoma, (iii) normotensive glaucoma and (iv) healthy controls. Furthermore, the 'visual quality of life' assessment has been ignored by the majority of clinical trials. The European Glaucoma Society guidelines emphasize on 'incorporation of quality of life measure in the outcome of treatment' (*Terminology and Guidelines for Glaucoma,* 4th Edition, Clause B3). A general quality-of-life (e.g. WHO-BREF) or glaucoma-specific quality-of-life (e.g. GQL-15 or NEIVFQ25) assessment should be one of the outcome measures in the clinical trials to be carried out in future. Combining the clinical outcomes with exploratory studies like gene expression pattern, reactive oxygen species markers, aging markers, inflammatory markers, apoptosis markers, psychological personality evaluation, and stress level evaluation will reveal a wealth of information to determine the clinical, biological, genetic, and psychosocial elements in glaucoma and citicoline treatment.

As citicoline addresses many aspects of neurodegeneration (Adibhatla et al., 2002; Bogdanov et al., 2018; Grieb, 2014; Hurtado et al., 2005; Matteucci et al., 2014; Parisi et al., 2018), clinical trials of citicoline-based intervention in glaucoma may be guided by trials already reported on other neurodegenerative diseases (Cesareo et al., 2015; Ghiso et al., 2013; Mancino et al., 2018; Nucci et al., 2015; Ou et al., 2012). However, since glaucoma is a slowly progressing disease, clinical trials with long-term monitoring are often preferred yet remain challenging (Leske et al., 2003; Parisi et al., 1999, 2008a; Virno et al., 2000; Weinreb et al., 2018) considering the large sample size needed for deriving statistically and clinically meaningful results from the small effect size within short time frames, the high cost of the studies, the potential patient dropout or loss of adherence, and the compromise in drawing robust conclusions from incomplete data (McGhee et al., 2016; Stanzione and Tropepi, 2011). For example, if visual field tests are performed every 3 months for 2 years, a sample size of 495 patients per group would be necessary to detect 30 percent reduction in the mean deviation rate of change (De Moraes et al., 2017). There is, however, some hope regarding the design of smaller scale trials that may still provide useful and reliable results (Quigley, 2012). For instance, the United Kingdom Treatment Study employed a novel method of clustered testing paradigm combined with point-wise event based approach to investigate visual field progression upon IOP lowering treatment in a trial spanning less than 2 years with 258 participants per arm (Garway-Heath et al., 2015; Wu et al., 2019). In most clinical trials for glaucoma, IOP is the primary outcome. Recently, a growing number of trials begin to use other outcome measures such as visual field, retinal nerve fiber layer thickness, and electroretinogram (De Moraes et al., 2017; Quigley, 2012, 2019; Weinreb, 2007; Weinreb et al., 2018; Wu et al., 2019). Since citicoline is expected to act on glaucomatous neurodegenerative events rather than IOP (Adibhatla et al., 2002; Grieb, 2014; Hurtado et al., 2005; Matteucci et al., 2014; Ou et al., 2012; Parisi et al., 2018), visual field, pattern electroretinography, structural/functional imaging or quality of life may be considered as the primary/secondary outcomes for citicoline-based glaucoma trials (Quigley, 2012, 2019; Wu et al., 2019). Citicoline trials should also take IOP lowering into consideration since halting the regular anti-glaucoma medication may pose risks to the patients in addition to other ethical concerns. In such case, the milestone of effective citicoline intervention should be set above the effects from IOP lowering medication alone. Inter-observer variability and time of IOP measurements should be properly accounted for as spontaneous IOP fluctuations and other systematic errors could potentially mask the IOP-independent neurotherapeutic effects and render the data inconclusive or underpowered (Quigley, 2012, 2019). In terms of dosage, citicoline does not pose major side effects up to 1600 mg/day (Grieb et al., 2016; Grieb and Rejdak, 2002; Parisi et al., 1999, 2008a, 2018; Rejdak et al., 2003; Virno et al., 2000). However, its short- and long-term dose-dependency remains to be systematically evaluated such as using futility trials (Levin, 2015; Schwid and Cutter, 2006; Tilley et al., 2006). To improve adherence, electronic reminders can be used (Boland et al., 2014) whereby different user-friendly and customizable mobile apps have been recently developed for this purpose. Caregivers can also be trained to ensure adherence. Last but not least, future studies can take into consideration more sensitive methods to monitor disease progression and detect therapeutic effects using smaller sample sizes as technology advances (Quigley, 2012, 2019; Wu et al., 2019).

A growing body of molecular, *in vitro,* and *in vivo* studies has revealed that cholinergic signaling is closely related to various neurocognitive functions including visual information processing and RGC viability. In light of the above overview, glaucoma may also be understood in terms of cholinergic dysfunction. Such a conceptual outlook provides the premise to subject cholinergic drugs to experimentation. To further bolster this, cholinergic drugs are one of the earliest therapeutic modalities for glaucoma. A search for novel cholinergic moieties is imperative in this connection. A naturally occurring, inexpensive, and relatively harmless compound with good bioavailability and no adverse side effects would be an ideal candidate for glaucoma therapy. Citicoline is a natural product approved as a food supplement.

It is safe at the currently approved dosage in clinical trials, and can be metabolized in the body into cytidine and choline which then re-assemble in the brain to form citicoline. Citicoline is the source of phosphatidylcholine, ACh, sphingomyelin, and cardiolipin and hence is important in maintaining the structural and functional viability of various neurons including RGCs. Citicoline also prevents glutamate excitotoxicity and improves dopamine signaling. This indicates that citicoline may be a potential drug to treat neurodegenerative diseases including glaucoma. It is also pertinent to examine if citicoline can be combined with other substances [e.g. scutellarin (Hu et al., 2018; Zhu et al., 2018) and quercetin (Lee et al., 2010, 2011a, 2016)] and treatments that in part regulate ACh or ACh receptor levels for further improving the antioxidant and antiapoptotic properties in glaucoma and other neurodegenerative disorders. Taken together, intensified research efforts targeting the cholinergic system as glaucoma neurotherapeutic sites are warranted to help reduce the global prevalence and burden of the disease. Next decade is likely to shed light on this issue.

Conflicts of interest

The author(s) have made the following disclosure(s): J.S.S.: Royalties e Zeiss, Dublin, CA (for intellectual property licensed by the Massachusetts Institute of Technology and Massachusetts Eye and Ear Infirmary)

Author statement

Percentage of work contributed by each author in the production of the manuscript:

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