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Neuroprotection in Glaucoma:

Drug-Based Approaches

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Abstract

In recent years the focus of glaucoma research has shifted toward neuroprotection, as the traditional strategies of lowering intraocular pressure have been shown to be unable to prevent progressive vision loss in some glaucoma patients. As a result various neuroprotective drug-based approaches have been shown capable of reducing the death of retinal ganglion cells, which is the hallmark of glaucomatous optic neuropathy. There has been increasing evidence that glaucomatous neurodegeneration is analogous to other neurodegenerative diseases in the central nervous system, with recent work from our group elucidating a strong link between basic cellular processes in glaucoma and Alzheimer's disease. Additionally, there is a growing trend for using existing neuroprotective strategies in central nervous system diseases for the treatment of glaucoma. In fact, a trial treating patients with primary open-angle glaucoma with memantine, a drug approved for the treatment of Alzheimer's disease, has recently been completed. Results of this trial are not yet available. In this review, we will examine currently advocated neuroprotective drug-based strategies in the potential management of glaucoma.

Keywords

glaucoma; neuroprotection; retinal ganglion cell apoptosis

Glaucoma is a multifactorial, neurodegenerative disease characterized by optic neuropathy, visual field loss, and retinal degeneration with retinal ganglion cells (RGC) apoptosis being a recognized early phenomenon.1 It is the second major leading cause of irreversible blindness worldwide affecting approximately 2% of the population over the age of 40.2

There are many factors associated with an increased risk of developing glaucoma.3-6 Currently lowering intraocular pressure (IOP) is the only clinical therapy available in the treatment of glaucoma7,8 with elevated IOP having previously been implicated as a possible primary insult in the disease resulting in mechanical or ischemic conditions leading to the development of RGC death and glaucoma. Unfortunately, patients can continue to lose vision despite successful IOP control.9 It is becoming clear that a methodology which only focuses on the reduction of IOP in patients is not the answer. As IOP is no longer regarded as the only therapy target in glaucoma, the focus of research is now shifting toward other strategies, such as neuroprotection of RGCs and the central visual pathway neurons.

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Neuroprotection may be defined as the use of therapeutic agents to prevent, hinder, and in some instances reverse neuronal cell death whatever the primary injury.10 Several neuroprotective treatments have been established in central nervous system (CNS) disease such as Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases.11-15

In recent years, there has been a growing trend for using existing neuroprotective drugs which have been found effective in other CNS disease for the treatment of glaucoma.16 Indeed our recent study has elucidated a strong link between mechanisms of cell death in glaucoma and AD.15 A good example of this trend is memantine, which is a drug that has Food and Drug Administration approval for the treatment of AD, and is currently in clinical trial phase IV in glaucoma patients.17-20 With the increasing association of glaucoma as a neurodegenerative disorder, it appears there may be a possibility of using and developing agents with applications to glaucoma and all neurodegenerative disease.

It should be noted that the notion of neuroprotective treatment for glaucoma has been around for a while, though there has been little significant breakthrough to date. Researchers have continued to focus on neuroprotection and as a result steady progress has been made giving rise to several different neuroprotective strategies. However, what is clearly lacking appears adequate clinical measures of neuroprotection, and this may account for the difficulty in assessing efficacy in patients. One of the obstacles for establishing neuroprotection in glaucoma is that glaucoma is a slow, progressive disease and the current method of measuring progression, a computerized visual field assessment, is highly variable. The advent of sophisticated optical instrumentation such as the Optical Coherence Tomography and new perimetric and electrophysiological techniques may lead to more meaningful assessment of disease. In particular, we believe that new methodologies for imaging cellular events, such as the in vivo detection of apoptosis such as detection of apoptosing retinal cells (DARC)15,21,22 should provide clinicians and researchers with new sensitive tools with which to assess neuroprotection.

In this review we will be focusing on neuroprotection strategies specifically aimed toward glaucoma, that are not gene or stem cell therapy-based, as these will be covered elsewhere in the journal. Fig. 1 briefly summaries current and potentially available approaches to neuroprotection in glaucoma. All these strategies have previously been advocated in CNS diseases.

Excitotoxicity

Glutamate is an essential amino acid that is abundant in all cells and known to play an important role as the main excitatory neurotransmitter in the CNS and retina. Glutamate release has been implicated as a mechanism of RGC death in glaucoma3,22-24 and inhibition or blockade of glutamate activity—in particular, modulation of the *N*-methyl-D-aspartate (NMDA)-type receptor has been advocated to be an important strategy for neuroprotection in glaucoma17,18,22,25,26 although its exact role is controversial. Dreyer et al. first reported an increase of glutamate in vitreous in glaucoma patients and experimental monkey glaucoma in 199627 and a similar result was reported by Brooks et al. using dogs.28 Although these results recently have been called into question,29-32 there is also an appreciation of the inherent difficulties in measuring in vivo glutamate levels.24

Glutamate is tightly regulated in the presynaptic cells as excessive expression of glutamate is potent and neurotoxic. Such is the importance of regulating glutamate; transporters are present in the membranes of neurons and glial cells to remove the excess glutamate from the synapses. Fig. 2A illustrates the induction of glutamate release from the presynaptic terminal by a nerve impulse and the binding of glutamate onto NMDA receptors located on the postsynaptic terminal. This leads to the influx of Ca^{2+} and Na^{+} ions. The term

excititotoxicity refers to the phenomenon where cells die via apoptosis (programmed cell death) because of the presence of excessive amounts of glutamate.33-35 When the cells undergo apoptosis, intracellular glutamate is released from the dying cell and dispersed among neighboring cells in the vicinity causing secondary degeneration and triggering a cascade of excititoxicity events leading to further cell death.36-39

The mechanism of excitotoxicity has been well researched. Several glutamate receptor systems have been identified, namely the ionotropic [NMDA, Kainate, and Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)] and metabotropic receptors, and disruption of their effects offer a promising strategy to preventing effects of neurodegeneration.22 Postsynaptic NMDA receptors are heteromeric ion channel complexes that are composed of several different subunits, two NR1 subunits and two NR2 subunits.40 Glutamate binds onto the target site on the NR1 subunit while glycine, which acts as a coagonist, binds onto the subunit NR2. Under normal physiological conditions, glutamate and glycine41 bind onto the receptors and the interaction causes transient conformational change in the channel and the depolarization of the cell resulting in the liberation of the Mg^{2+} ion which normally blocks the channel (Fig. 2B). The opening of the channel allows extracellular ionic molecules such as Ca^{2+} and Na^{+} to diffuse through the channel into the cell.42-45 Fig. 2C illustrates that in pathological conditions, the excess glutamate causes the channel to remain open for a long period of time thereby allowing a flood of extracellular Ca^{2+} into the cell triggering off the production of free radicals and the initiation of apoptosis.

NMDA receptors are expressed in many cell types of the retina. However, RGCs appear to be the most vulnerable in glutamate-mediated excitotoxicity.46 Selective loss of RGCs is a hallmark in glaucoma. Overexpression of NMDA receptors caused by increased glutamate release may at least partially explain selective RGC death in glaucoma. Glutamate induces a selective and dose-dependent loss of RGCs in cultured adult pig retina whereas amacrine cells and all other retinal neurons have been shown to be resistant.47 A similar result has been reported in the rabbit retina when NMDA was applied in vitro.48 The variable NMDA response by different retinal neurons may be attributed to discrepancy in NMDA receptor subunit nature, receptor density, and function properties.48 Furthermore, there is evidence that although RGCs express an abundant number of NMDA receptors,49 a large cohort of amacrine cells appear to have limited NMDA receptor function.49

In addition, reduced clearance of extracellular glutamate may also account for neuronal excitotoxicity.50 Muller cells in the retina play a major role in maintaining appropriate levels of glutamate and regulating synaptic transmission. Using high-affinity sodium-dependent transporters, Muller cells take up glutamate from the synaptic cleft and quickly convert it into glutamine which can be reused by neurons to synthesize glutamate for neurotransmission.50 Any disturbance in the pathway of glutamate uptake and recycling may cause increased extracellular levels of glutamate, as a result, not only prolonging synaptic transmission, but also triggering neuronal apoptosis and neuronal death. A significant reduction of the glutamate and aspartate transporters (GLAST) [Excitory amino acid transporter (EAAT1)] and Glutamate transporter (GLT-1) (EAAT2) has been observed in experimental rat glaucoma retina.51 Although other studies have failed to confirm the observation,52 a specific glutamate transporter GLT-1c, which is normally only expressed by photoreceptors, has recently been identified in RGCs in experimental glaucoma, and it may be indicative of an anomaly in glutamate homeostasis.53

MK801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5,10-imine], an uncompetitive NMDA antagonist is perhaps the best known glutamate modifier.25 We and others have demonstrated that MK801 is neuroprotective in experimental glaucoma.22,25

However, as MK801 is neurotoxic and induces acute neuronal vacuolization histologically, it has not reached advanced stages of clinical trials.54,55 The problem is believed to occur due to its high affinity for the NMDA receptor channel and its long dwell time,56 resulting in its accumulating in the channels and blocking critical normal functions.

Memantine is currently the only available clinical glutamate modifier. It was first synthesized in the 1960s by Eli Lilly & Company and was patented in 1968. Memantine is a derivative of amantadine which was used as an anti-influenza compound. Memantine has been demonstrated to be effective in the treatment of AD and PD.57-60 Up to the 1980s, it was believed that memantine was anticholinergic or dopaminergic and it was only relatively recently shown to be an NMDA-receptor antagonist.61 Like MK801, memantine is an uncompetitive open-channel blocker but with a dwell time in the channel to only inhibit NMDA-receptor activity when glutamate is elevated to pathological levels, sparing normal physiological levels required for homeostatic synaptic activity.62

Memantine has been shown to be a highly effective neuroprotective agent in both acute and chronic animal modes of RGC death.11,18,19,26,63-69 Daily administration of memantine (5 to 10 mg/kg) enhanced survival of RGCs in a laser-induced rat and primate model of chronic ocular hypertension.17,18,20 A similar effect was documented by Schuettauf et al. using a Dilute brown non-agouti (DBA)/2J transgenic mouse model of glaucoma.70 Memantine currently is in a phase IV clinical trial assessing its efficiency in glaucoma patients, the results of which should be known in 2008.

Mitochondrial Dysfunction

Mitochondrial dysfunction has been implicated in neuronal apoptosis, and shown to occur in experimental glaucoma.71,72 A recent in vitro study has provided additional evidence that the mitochondrial dysfunction accompanying RGC death may be induced by glaucoma-related stimuli such as tumor necrosis factor (TNF)-α and hypoxia.73 Furthermore, mitochondrial dysfunction-associated oxidative stress has also been implicated as a risk factor in glaucoma patients.74

A mitochondrion is a membrane bound organelle and can be found in most eukaryotic cells. Mitochondria is responsible for the production of chemical energy, via the electron transport chain, that is required for normal cellular function such as cell proliferation and cell differentiation to name a few. External stress can trigger mitochondrial dysfunction which in turn can lead to the production of reactive oxygen species (ROS) that cause cell death at neurotoxic levels. Mitochondrial dysfunction can be triggered by hypoxia, treatment with hydrogen peroxide, and oxidative stress.75,76

Nuclear factor (NF)-κB is a dimeric transcription factor, composed of the p50 and p65 subunits, responsible for inflammation, autoimmune disease, viral infection, and linked with cancer. The inactive form of NF-κB is bound to the inhibitory IκBα protein and is retained in the cytosol.77 NF-κB has been implicated in both the induction and prevention of apoptosis; the outcome depends on the cell type and the stimuli. Zamora et al.78 demonstrated that overexpression of adenine nucleotide translocase (ANT)-1 recruits the IκBα/NF-κB complex into the mitochondria resulting in the down-regulation of the expression of antiapoptotic genes, *Bcl-XL, MnSOD*2, and *c-IAP*2.

Coenzyme Q_{10} (CoQ_{10}) is a cofactor and plays a crucial role in energy production via the mitochondrial electron transport chain. CoQ_{10} is responsible for the transport of electrons from complex I and II to complex III.

There are three potential mechanisms suggested for CoQ_{10} to exert its neuroprotective effects: first, as shown in Fig. 3A, it causes the augmentation of complex I in the electron transport chain; second, it inhibits the action of NF-κB, a transcription factor responsible for inflammation, autoimmune disease, viral infection, and linked with cancer (Fig. 3B); and finally, it inhibits the opening of the mitochondrial permeability transition pore79,80 (Fig. 3C). Our group recently showed topical CoQ_{10} to be effective in experimental glaucoma,81 and clinical trials are currently planned.

Protein Misfolding

Protein aggregation is a prominent feature of many neurodegenerative diseases, such as AD, Huntington disease, and PD. These diseases are also called protein misfolding diseases as the proteins or peptides implicated are all self-assembled to form similar fibrillar structures. One such peptide is amyloid-β (Aβ), a 40 to 42 residue peptide and the primary component of the senile plaques found in AD brains.

Amyloid-β is derived from abnormal processing of amyloid precursor protein (APP) and is intricately involved in Alzheimer neuropathology.82 Aβ has recently been reported to be implicated in the development of RGC apoptosis in glaucoma, with evidence of caspase-3-mediated abnormal APP processing and increased expression of Aβ in RGCs in experimental glaucoma,83 and decreased vitreous Aβ levels (consistent with retinal Aβ deposition) in patients with glaucoma.84 Further evidence of a link between glaucoma and AD has emerged from studies showing that patients with AD have RGC loss associated with typical glaucomatous changes, such as optic neuropathy and visual functional impairment, 85-88 as is also the case in PD.89 In addition, both diseases are chronic neurodegenerative conditions with a strong age-related incidence.90,91 This is further supported by increasing evidence of similar pathological mechanisms involving Aβ leading to RGC loss as implicated in the brain.90,92-94

We have recently provided further strong evidence from experimental glaucoma supporting the involvement of Aβ in development of glaucomatous RGC apoptosis.15 Using our recently established novel imaging technique, DARC, we have further shown that exogenous Aβ peptide induces significant RGC apoptosis in vivo in a dose- and time-dependent manner.15 We next investigated the effects of targeting Aβ formation and aggregation in experimental glaucoma, using three different agents including a β-secretase inhibitor, an anti-Aβ antibody (Aβab), and Congo red.15 Fig. 4 illustrates the Aβ pathway, from the formation of Aβ from APP leading to Aβ aggregation and ultimately resulting in neuronal death. It also shows the target for each of the three inhibitors. All three treatments altered the profile of RGC apoptosis, but the anti-Aβ antibody appeared the most effective, with prolonged effects after a single application up to 16 weeks after IOP elevation. Perhaps the most exciting finding was the demonstration of combination therapy of all three strategies produced a maximal reduction of RGC apoptosis (>80%).

Another mechanism implicated in neurodegeneration is that involving molecular chaperones such as heat shock proteins (HSPs). HSPs are a family of highly conserved stress proteins which are constitutively expressed in most cells under normal and stress-induced conditions. The function of the HSPs and heat shock cognate proteins is to prevent the aggregation of denatured proteins and also acts as a molecular chaperone to facilitate nascent protein folding, protein unfolding, restoring the conformation of misfolded proteins, and translocation across membranes.

HSPs are classified according to their molecular weight expressed in kilodaltons (kDa). There are numerous families of HSPs including HSP-90, HSP-70, HSP-60, and HSP-25. Tezel et al.95 reported that the intensity of immunostaining for HSP-60 and HSP-27 was

significantly greater in glaucomatous eyes compared with age-matched controls. A study using cultured human optic nerve head astrocytes exposed to increased hydrostatic pressure revealed increased expression of HSP-27. This idea was supported by the finding that glaucoma patients have increased titers of HSPs autoantibodies in their blood. Ishii et al.96 has reported that the use of geranylgeraylacetone, an acyclic polyisoprenoid, induced the upregulation of HSP-72 expression in RGCs and protected them from glaucomatous damage in a rat glaucoma model. Although this drug has not yet been administered to glaucoma patients, it is promising as it is active orally with very low toxicity.97

Oxidative Stress

The term “oxidative stress” refers to when the production of ROS reaches a pathological level and the cell’s antioxidant capacity is insufficient in offering protection against oxidative damage. It is hypothesized that oxidative stress can cause RGC death by damaging the trabecular meshwork, the optic nerve head, and the retina.98 The main source of ROS is mitochondrial production as a byproduct of cellular aerobic metabolism and as second messengers in signal transduction pathways.

It is believed that oxidative stress plays a role in RGC death in glaucoma. Evidence comes from studies that have shown significant increase in the levels of ROS and lipid peroxides in experimental glaucoma eyes together with changes in the activities of antioxidant enzymes. 99-101 In addition, reduced levels of antioxidant glutathione and increased serum lipid peroxidation products have been identified in primary open-angle glaucoma patients. 102-104

Vitamin E (α-tocopherol) is the major source of lipid-soluble antioxidant in cells and acts as a scavenger of peroxyl radicals. Some studies have suggested that glaucoma patients receiving vitamin E have displayed improved visual fields,102,105-107 but long-term studies have been less convincing.

The compound Extract Ginkgo biloba (EGb) 761 is an extract from leaves of *Ginkgo biloba* and has demonstrated to increase the survival of RGCs in the episcleral vein cauterization model of experimental glaucoma.108,109 EGb 761 is a potent antioxidant and scavenger of free radicals. It has also shown to interfere with glutamatergic NMDA receptor. The precise mode of action of EGb 761 is still not fully understood.

Inflammation

Recently researchers have investigated the immune system as a means of providing neuroprotection against neuronal damage. Autoimmunity is traditionally regarded as an attack on the host cell by activated T cells resulting in pathological autoimmune-mediated disease. Studies have revealed that autoimmune responses increased the survival of RGCs after optic nerve injury,110,111 where the immune response was mediated by T cells directed against a CNS-associated self-antigen such as a myelin oligodendrocyte protein, myelin basic protein, and proteolipid protein.110,112 It was next demonstrated that the response could be achieved by either active immunization with the protein or by passive transfer of activated T cells.113 Interestingly, T cells which were derived from cryptic (non-encephalitogenic) myelin-associated peptides displayed the same effectiveness as T cells derived from encephalitogenic cryptic epitopes with the former inducing no autoimmune disease. Schwartz114-116 revealed that autoimmunity was not an artificial experimental phenomena but in fact a physiological endogenous response to stressful situations such as neuronal damage.116 In support, rats devoid of mature T cells had an increased number of RGCs dying following optic nerve crush, and by contrast, a prior unrelated CNS injury to the optic nerve crush protected RGCs from loss.117,118 Therefore, boosting autoimmunity

by vaccination appeared to be a promising therapy for glaucoma acting to enhance the protective effects of T cells.

Cop-1 (glatiramer acetate; copolymer-1; copax-1) is a synthetic, random oligopeptide comprising the amino acids, tyrosine, glutamate, lysine, and alanine residues. Cop-1 is Food and Drug Administration-approved drug for the treatment of multiple sclerosis patients. It is a low affinity antigen and can evoke both active and passive T-cell-mediated response at various sites of injury. It has been demonstrated that Cop-1 reduces the damage caused by mechanical injury to the optic nerve or by intravitreally administered glutamate.119-121 Another study has reported that vaccination with Cop-1 leads to a significant reduction in elevated IOP-induced RGC death in a rat model of ocular hypertension.117

TNF-α is a potent proinflammatory cytokine and its production is up-regulated during ischemic and excitotoxic brain injury.121,122 It has been implicated as a mediator of RGC death in glaucomatous retina because of its up-regulation.123,124 TNF-α binds onto the death receptor, TNF receptor-1 (TNF-R1) and can induce both the caspase-dependent and the caspase-independent components of the mitochondrial cell death pathway. A dopaminergic and antiglaucoma drug, GLC756 has been recently shown to Inhibit TNF-α release from activated rat mast cells and suggested a potential of the compound on neuroprotection in glaucoma management.125,126

TNF-α may also be neuroprotective, because of the up-regulation of NF-κB, a redox-sensitive transcription factor. NF-κB is involved in the expression of a wide range of genes that regulate cellular differentiation, proliferation, apoptosis, oxidative response, and inflammation. Activation of NF-κB mediates the expression of mitogen-activated protein kinases which is known to regulate the response to proinflammatory and other stress signals.

Neurotrophin Deprivation

The family of neurotrophins consists of four members: brainderived nerve factor, nerve growth factor, neurotrophin-3, and neurotrophin-4/5. Neurotrophins promote the development, survival, and differentiation of neurons by binding onto either the Trk receptor or the p75 receptor.127-129

Most of the work in this area has been associated with molecular-based therapies, and will be covered elsewhere in this journal.

CONCLUSIONS

Currently the only form of treatment for glaucoma patients is to reduce their IOP either surgically or therapeutically. However, it is known that reducing IOP is in some instances inadequate as patients with low IOP continue to suffer vision loss. In this review, we have addressed several potential neuroprotective strategies. Many of the approaches employ and manipulate the cell's endogenous mechanism to promote the survival of RCGs. Unfortunately except memantine, none of them have yet been adequately assessed in randomized clinical trials. One of the reasons for this is that currently recognized clinical end points in glaucoma, such as IOP and visual field, are not sufficient to adequately and swiftly assess the effects of neuroprotection. We believe that developments in perimetric, electrophysiological, and imaging techniques such as DARC technology and adaptive optics will provide a much needed objective measure in this field. As more and more understanding is gained into mechanisms of neuroprotection, it is likely that new neuroprotective agents will emerge, and be useful in the treatment of glaucoma.

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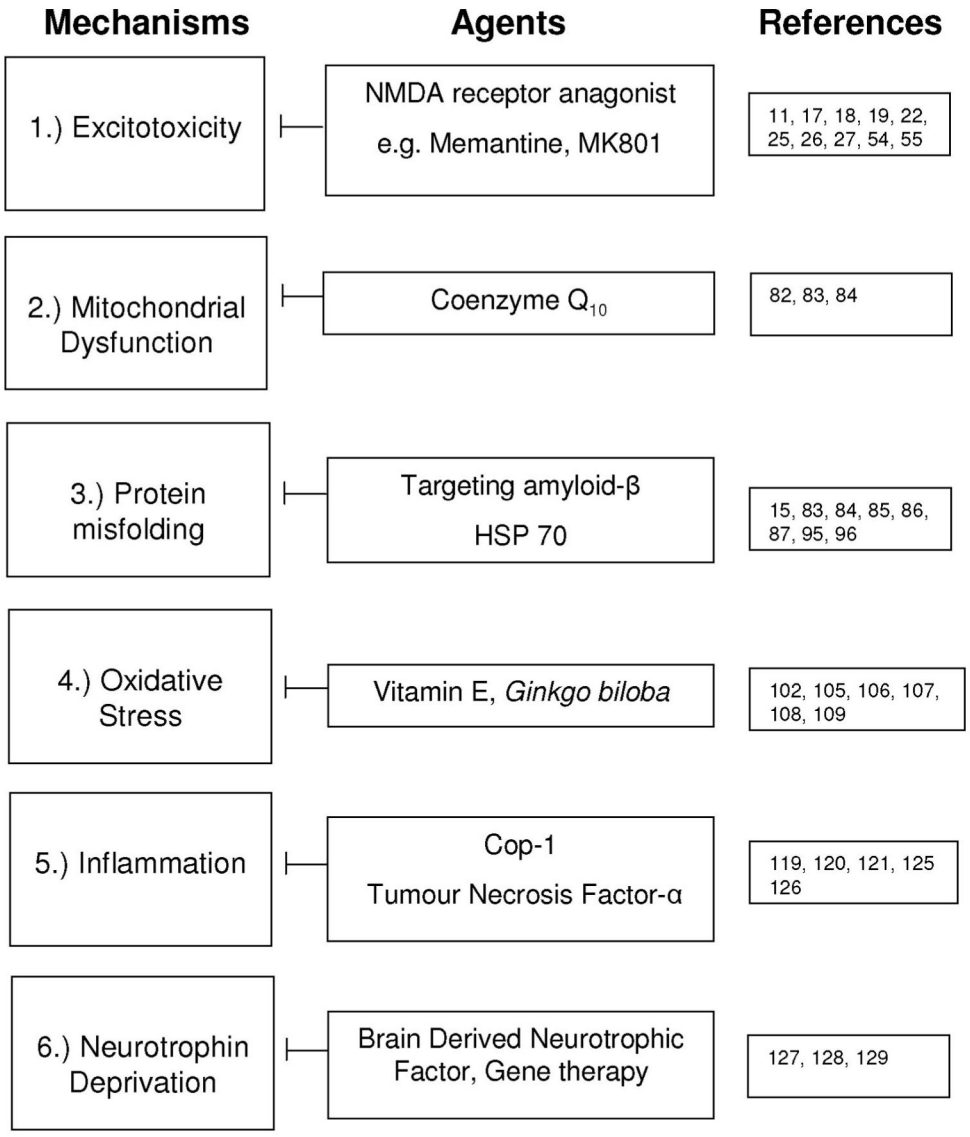

FIGURE 1.
Summary of current research strategies employed to study neuroprotection in glaucoma as previously applied in CNS disease.

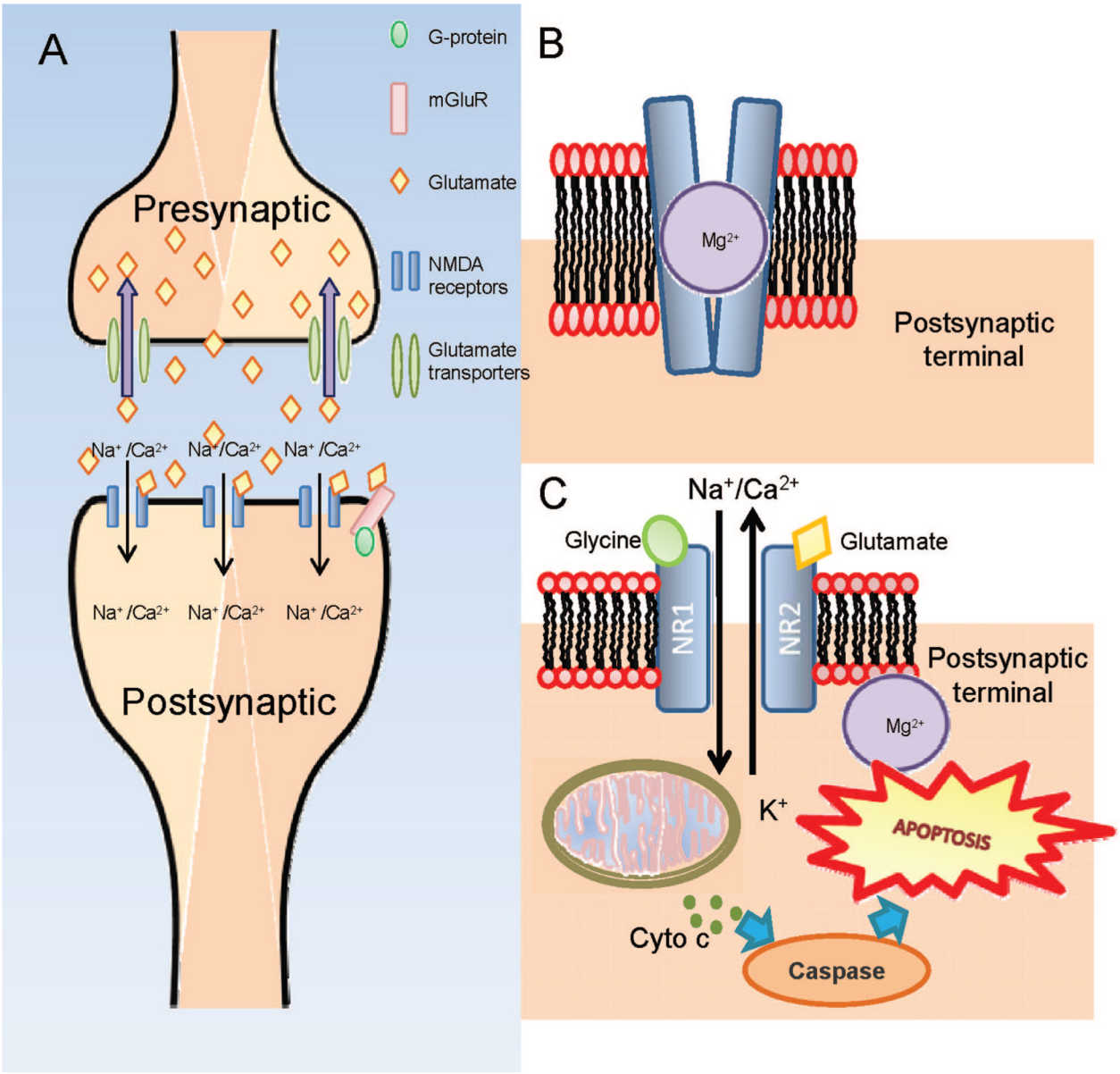

FIGURE 2.

A, Upon excitation by the nerve impulse, glutamate is released from the presynaptic terminal into the synaptic cleft where it binds onto the NMDA-receptors located on the postsynaptic terminal. Glutamate transporters located presynaptic terminal actively transport glutamate back into the terminal. B, Glutamate and glycine bind onto the receptors and the interaction causes transient conformational change in the channel and the depolarization of the cell resulting in the liberation of the Mg^{2+} which blocks the channel. The opening of the channel allows extracellular ionic molecules such as Ca^{2+} and Na^{+} to diffuse through the channel into the cell. Under normal physiological conditions, the NMDA channel is closed and is open transiently to enable the generation of a nerve impulse. C, When there is excessive glutamate present, the channel remains open causing a flood of Ca^{2+} and Na^{+} resulting in the depolarization of the mitochondrial membrane potential. Such events trigger off the release of cytochrome c which subsequently activates the caspase pathway leading toward apoptosis. A color version of this figure is available at www.optvissci.com.

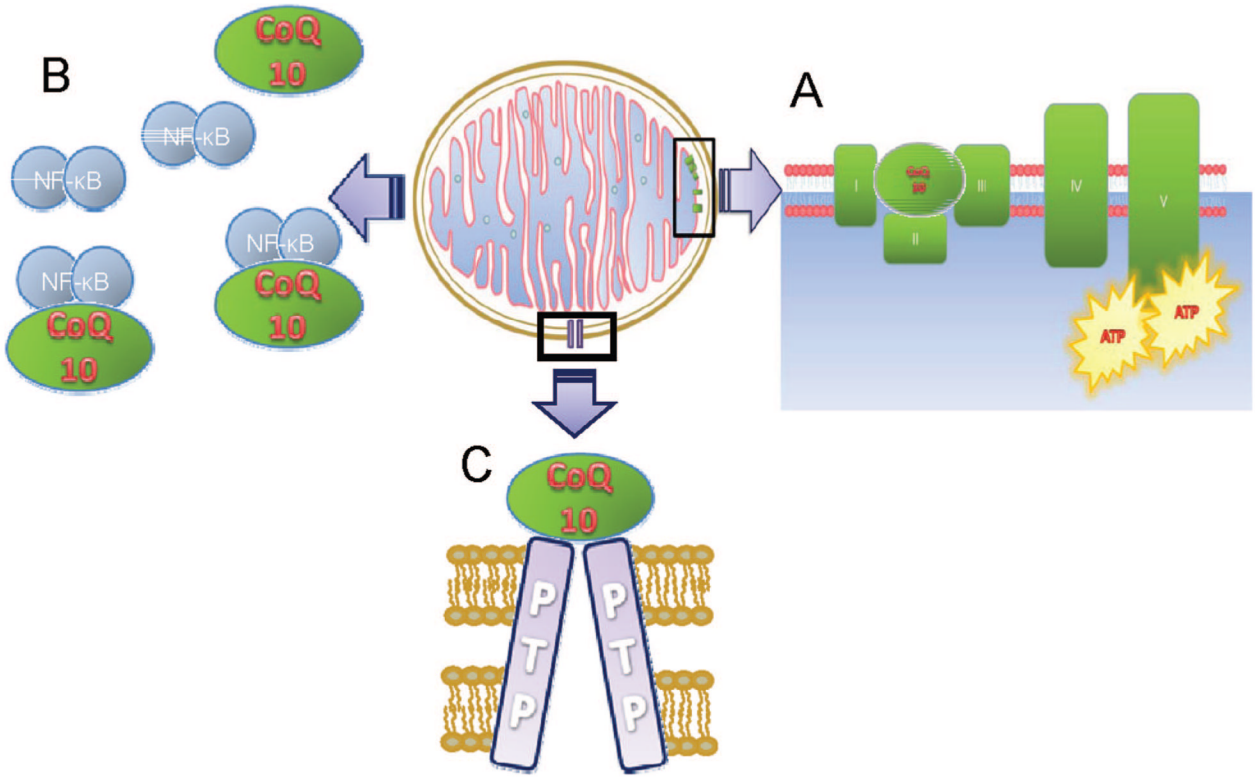

FIGURE 3.

Schematic diagram illustrating the role of CoQ10 in energy production in the mitochondria and its neuroprotective effects. CoQ10 transports electrons between complexes I, II, and III, and causes the augmentation of complex I in the electron transport chain (A). It is also believed to inhibit the action of NF-κB, a transcription factor responsible for inflammation, autoimmune disease, viral infection and linked with cancer (B); and finally, it inhibits the opening of the mitochondrial permeability transition pore (C). A color version of this figure is available at www.optvissci.com

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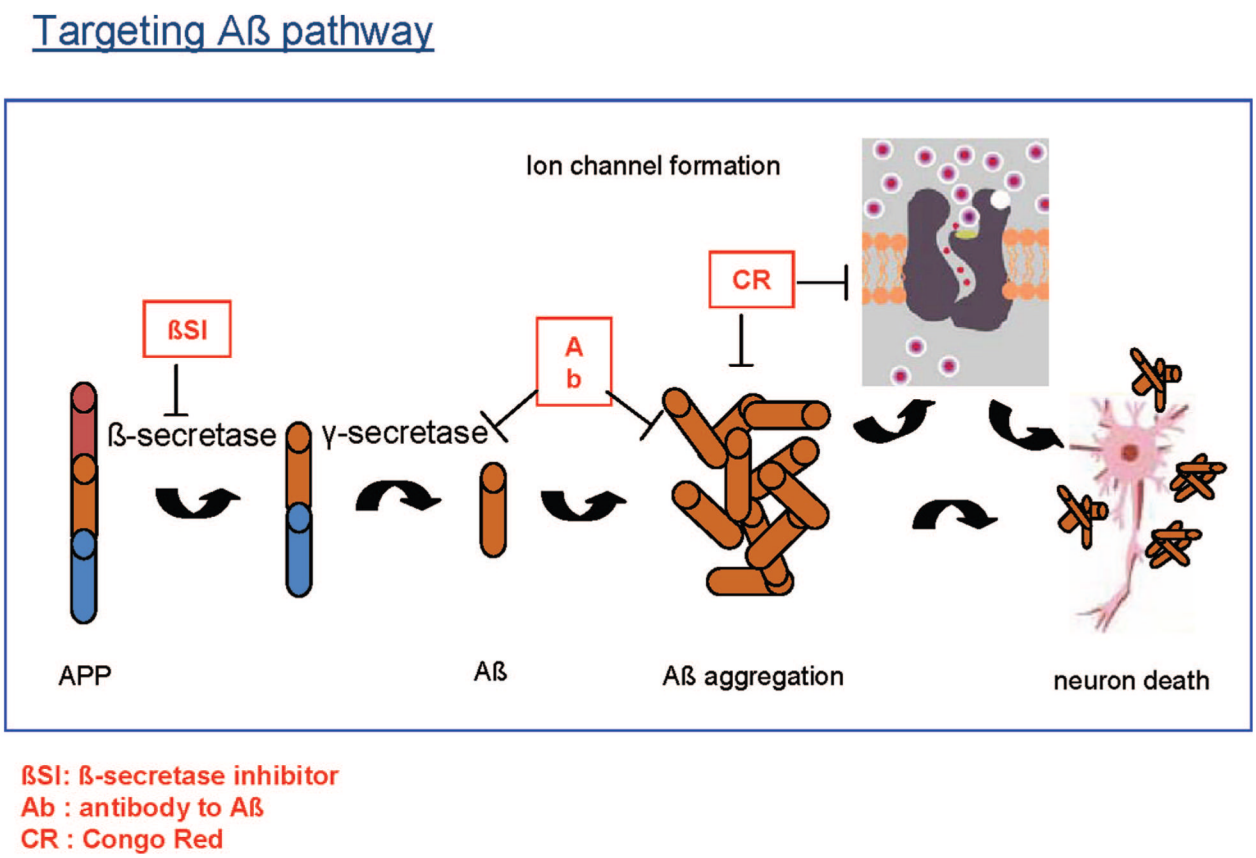

FIGURE 4.

Schematic diagram illustrating the formation of Aβ aggregates which ultimately leads to neuronal death. The red boxes represent three different agents which act on three different stages of Aβ pathway to block Aβ formation, deposition, and aggregation, respectively. A color version of this figure is available at www.optvissci.com.

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