The Nerve of Glaucoma!

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Contemporary concepts of open angle glaucoma suggest that the current emphasis on reduction of elevated intraocular pressure could be augmented by other therapeutic approaches. In this article, we describe significant recent developments in the molecular and cellular biology and neuropharmacology of nerve damage that are likely, in coming years, to suggest new therapeutic approaches to the management of glaucoma. These developments may lead to the achievement of pharmacologic protection of the optic nerve from damage or possibly promotion of reversal of damage. We review selected studies of excitotoxins and *N*-methyl-D-aspartate receptor antagonists, Ca^{2+}-induced damage and calcium channel blockers, the intracellular messenger nitric oxide and its perturbation, free-radical damage and scavengers, nerve regeneration, and growth factors. Several basic research questions are posed, answers to which may transform our concepts of glaucoma therapy. *(Arch Ophthalmol. 1994;112:37-44)*

Clinical experience and epidemiologic research indicate that elevated intraocular pressure (IOP) is the single most common concomitant finding in primary open angle glaucoma.[1-3] This outcome explains the overwhelming emphasis on screening, treating, and investigating IOP.

However, evidence from the study of low-tension glaucoma and ocular hypertension suggests that elevation of IOP is neither necessary nor sufficient for the production of glaucomatous optic neuropathy. Thus, there are many patients with elevated IOP who, for unknown reasons, do not manifest glaucoma, while, conversely, there are many patients with low to normal IOP who do. In some survey studies, between one third and one half of patients with open angle glaucoma do not initially have ocular hypertension,[4-7] and as many as one sixth of patients with glaucomatous damage do not show elevated IOP, even on repeated testing.[7] Moreover, ocular hypertension may be as much as eight to 10 times as common a condition as glaucoma.[4,8] Furthermore, in some patients with glaucoma, progression of field loss is apparently not related to IOP.[9,10] Finally, although IOP elevation is certainly a primary risk factor for glaucoma, numerous risk factors other than elevated IOP have been reported.[11] Mounting recognition and recent expressions of these views are part of the *zeitgeist*, as reflected in the tide of recent expert opinion.[6,12-14]

One implication of these observations is that there may be other causal variables involved in glaucomatous damage, and, in concert with this idea, there should be other therapies. Indeed, if elevated IOP turns out not to be the direct cause of damage, then other modalities may even supersede reduction of IOP as the primary therapeutic modality.

There have been attempts to find means of pharmacologic protection of the optic nerve other than through reduction of IOP. Thus, phenytoin, a membrane stabilizer, has been reported to reverse partially the effects of an-

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oxia on neurons[15] and to retard glaucomatous damage in patients.[16] More recently, calcium channel blockers (CCBs), which may protect against vasospasm-induced hypoperfusion of the optic nerve head blood supply, have also been studied.[17-21] None of these has thus far proven to be clinically useful.

Where then to turn? As we look to other related fields, such as molecular and cellular biology, neurology, and neuropharmacology, we note dramatic progress in our knowledge of nerve cells, glial cells, vascular cells, and extracellular matrix-bound cells as well as the intracellular molecular events that follow transmembrane potential changes or receptor activation. Much is now known about the biochemical pathways involved in cell injury and death following ischemia or the application of endogenously occurring cellular toxins. Moreover, in certain clinical areas, such as stroke, degenerative neurological disease, and cardiovascular medicine, direct clinical and experimental applications of this knowledge have already been undertaken.

While there are not yet examples of successful clinical application of this knowledge within the field of glaucoma, these findings from other fields give hope that pharmacologic neuroprotection or even neurorepair may one day be viable approaches to glaucoma management.[22-25] Studies of Ca^{2+}-induced damage, excitotoxins and *N*-methyl-D-aspartate (NMDA) receptor antagonists, the messengers nitric oxide (NO) and carbon monoxide, free-radical scavengers, nerve regeneration, and growth factors, to name some of the more prominent areas, are opening entirely new investigational perspectives of neuro- protection that may radically transform how we think about glaucoma. A sampling of recent developments in these fields provides a glimpse of what may prove to be the next generation of therapies in glaucoma.

EXCITOTOXINS AND NMDA RECEPTORS

One area of intense recent study has been that of so-called excitotoxins, which are excitatory neurotransmitters that, if released in excessive amount, can induce a toxic effect on target cells.[26] With aspartate and glutamate as their likely endogenous neurotransmitters, receptors have been located throughout the brain and layers of the retina, which are excited by the nonendogenous experimental drug NMDA. Three different classes of ionotropic NMDA receptors (NMDARs) have been defined by the differential affinities of these receptors to the glutamate- and aspartate-analogues NMDA, kainic acid, and DL-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA).[27-29] These receptors have broad functions,[30,31] acting as neurotransmitter-gated ion channels and permitting voltage-dependent intracellular influx of calcium and sodium, the former activating "second messengers" that affect cell function. Importantly, when the excitatory transmitters are present in excess, their receptors also seem to play a major role in mediating ischemic neuronal damage.[32,33]

Excitatory neurotransmitters may be massively released following cellular ischemia or stress.[34,35] Sustained hypoxia leads to membrane depolarization, which, in turn, leads to increased synaptic glutamate release and reduced glutamate uptake, together resulting in a buildup of extracellular glutamate.[36-38] Excitotoxic effects result from the resulting enhanced action of the transmitter on its receptor, which leads to excess influx of Ca^{2+}, itself contributing to the postsynaptic cell's inability to regulate its own intracellular Ca^{2+} and hence to even more Ca^{2+} buildup, neuronal damage, and death.[39]

Activators of NMDARs, whether of endogenous origin or not, lead to neural damage within a wide range of neural structures and also lead to inner retinal degeneration.[40] Retinal ganglion cells possess receptors for excitatory amino acids,[41] and kainic acid, NMDA, and AMPA, in excess, are all toxic to ganglion cells. Each toxin, however, produces a specific pattern of cell death with larger or smaller retinal ganglion cells being more or less affected.[42,43] Of note, large retinal ganglion cells in culture are more susceptible to excitotoxic as well as hypoxic injury than are small ganglion cells,[44] a situation that may be analogous to glaucomatous damage.[45-47] Intriguingly, vitreous specimens from humans with open angle glaucoma have elevated concentrations of glutamate, but not other amino acids.[48]

Moreover, agents that inhibit the action of excitotoxins improve neuron viability following toxic exposure to excitotoxins.[49] Cell death in experimental conditions mimicking stroke is successfully and dramatically reduced by use of glutamate receptor blocking agents, such as MK-801, phencyclidine, NBQX, or D-CPP-ene.[50-53] For example, NBQX protects hippocampal neurons from death caused by bilateral carotid artery occlusion even when given 1 hour after the termination of ischemia.[50] Severe experimental cerebral ischemia produces large increases in intracellular calcium ion concentration. MK-801, along with the CCB nimodipine, reduces the influx of calcium in this model and also reduces histologic damage and improves the recovery of the electroencephalogram following reperfusion.[54] MK-801, which crosses the blood-brain barrier, seems to be most effective when NMDA channels are already open, ie, after excitotoxin buildup.

In the eye, the swelling and death of ganglion cells in chick embryo retinas in response to anoxic conditions is blocked by γ-D-glutamylglycine, an excitatory amino acid antagonist.[55] Retinal ganglion cells, grown in culture, or in the intact adult retina, are killed by NMDA and kainic acid, and these actions are blocked by NMDA receptor antagonists.[56-58] Pretreatment with the NMDA antagonist dextromethorphan, which protects against experi-

mental cerebral anoxic tissue damage,[59] enhances recovery of the electroretinographic (ERG) b-wave amplitude and reduces histologic alteration in an ischemic model of stroke in the rabbit retina produced by acutely elevated IOP.[60] MK-801 protects retinal ganglion cells in a similar model.[61] Can glaucomatous damage be similarly reduced?

Apart from the short-term toxic effects just mentioned, there is some evidence that in chronic, progressive conditions, such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, olivopontocerebellar atrophy, and Alzheimer's disease, NMDA receptor activation is involved in pathogenesis.[62-64] For example, NMDA receptor antagonists prevent glutamate-induced diphosphoralization of certain enzymes and thereby facilitate dopaminergic function in animal models of Parkinson's disease.[65] Might the damage of glaucoma fit into the category of these kinds of degeneration?

Preliminary, but highly encouraging, clinical applications of the new understanding concerning excitotoxic effects include successful clinical treatment of stroke, transitory ischemic attack, and multi-infarct dementia.[66,67] Useful drug development poses a challenge for the future. Many of the NMDA antagonists, such as phencyclidine and ketamine, have significant psychotomimetic properties in humans limiting their usefulness. However, certain anticholinergic or γ-aminobutyric acid–like agents have been reported to protect choroidal neurons against these adverse side effects,[68] and the recent cloning of many of the subunits of the glutamate receptor family[29,69,70] will doubtless facilitate novel and improved drug development.

CALCIUM CHANNEL BLOCKERS

By acting on vascular smooth muscle, CCBs can lead to vasodilation or relief from vasospasm. Indeed, after acute ischemic stroke, there seems to be a therapeutic window, perhaps hours in length, following the onset of ischemia during which damage may be reversible. Further, there is a penumbra of viable neural tissue surrounding a region of complete infarction, within which recovery is possible. In keeping with these concepts, efforts to improve blood flow after ischemic insults from stroke[71,72] have been made using CCBs. Following such leads, interest in CCBs within the field of glaucoma has arisen from a desire to improve optic nerve head blood supply.

However, CCBs may also act, in part, by reducing toxic intracellular Ca^{2+} levels, by altering the metabolism of target nerve cells, or by acting on receptors in the central nervous system (CNS) that are entirely different from those found in peripheral vascular tissue or even peripheral neurons. Elevation of intracellular calcium levels is likely to be neurotoxic for a number of reasons,[39] including activation of catabolic enzymes, phospholipases, superoxide or other free radicals, and protein kinases, and positive feedback stimulation of the release of additional glutamate.

There are two main types of calcium channels, ie, voltage-operated channels, requiring membrane depolarization for function, and receptor-operated channels, requiring a specific ligand, such as NMDA, to bind to a receptor molecule. Within the class of voltage-operated channels, there are four main types of channel:[73-75] T-type, L-type, N-type, and P-type. Calcium channel blockers currently available in the United States, mostly dihydropyridines, typically affect voltage-operated calcium channels and are targeted principally against L-type calcium channels, found mostly on cardiac and smooth muscle cells, such as vascular muscle cells. Neurons tend to possess T-, N-, and P-type channels. However, high conservation of binding regions on the known calcium channels has suggested that modifications of existing drug structures may yield selective antagonists of the other channel subtypes that are more specific for neuronal channels and which, therefore, may be valuable in the treatment of calcium-related neurodegenerative or neurotoxic conditions.[75]

Indeed, one CCB, flunarizine, available in Europe, has particularly high affinity for neuronal T-type channels and low affinity for peripheral or vascular sites.[76,77] Migraine, a condition previously identified as having an association with low-tension glaucoma,[78] has been successfully treated with flunarizine.[79] Flunarizine has been shown to protect neural tissue from the effects of ischemia in several animal models.[80,81] Interestingly, flunarizine also protects cultured cerebellar cells from glutamate-induced toxic effects,[82] raising the possibility that this CCB may also act at receptor-operated channels, either directly or perhaps through reduction of intracellular calcium-induced glutamate release.[74]

The clinical utility of CCBs in chronic forms of glaucoma has only begun to be explored.[17-21] Naftidrofuryl oxalate, another vasodilatory agent, which is an antagonist of serotonin (S2) receptors, has also been reported to be salutary in glaucoma.[83-85] Findings from the cardiac and neurologic literature[67] indicate the need for investigating further the role of these agents in glaucoma therapy.

NITRIC OXIDE

Nitric oxide is a short-lived compound that has been recently identified[86] in vascular endothelium, where it promotes vasodilation (and was previously known as endothelium-derived relaxing factor); in macrophages, where it seems to be bactericidal and tumoricidal; and in numerous different areas of

the brain,[87] where it may act as a neurotransmitter, although not of the conventional, synaptosomal variety.[88,89]

One action of glutamate on NMDA receptors is to cause Ca^{2+} to enter the postsynaptic cell and NO to be synthesized there.[35] Once inside the cell, Ca^{2+}, acting with calmodulin, activates the enzyme NO synthase, which generates NO from L-arginine.[90] Nitric oxide seems in turn to act by binding to the heme subunit of guanylyl cyclase, which transforms GTP into the intracellular second messenger cGMP.[91] This, in turn, activates a protein kinase that may phosphorylate other proteins leading to metabolic alteration of the cell through unknown mechanisms.

Further, NO may rapidly leave the cell through passive transport and may then exert toxic actions directly on adjacent cells.[92] The toxic effect itself may arise from the free radical (see below) nature of NO. The neurotoxic effect of NO has been demonstrated in numerous in vitro models.[49,93,94] A similar mechanism to that described for NO has been proposed for carbon monoxide, which is liberated by an enzyme similar to NO synthase, heme oxygenase, and which, like NO, acts on guanylyl cyclase to catalyze the formation of cGMP.[95]

Numerous inhibitors of the enzyme that synthesizes NO, NO synthase (NOS),[96] have been identified, and these substances have been shown to protect neurons from the toxic actions of NO.[97] For example, the competitive NOS inhibitor NG-monomethyl-L-arginine maintains action potential production during hypoxia in a hippocampal slice preparation.[93] Moreover, NMDA-induced cell damage is reduced in cultured neurons by various NOS inhibitors,[98] which, along with other evidence, suggests that NO may be the intracellular mediator of glutamate receptor–induced toxic effects. Also, the effects of experimental stroke in mice are attenuated not only by NMDAR antagonists[50-53] but by the NOS inhibitor nitroarginine,[99] which suggests that interruptions of the latter steps of the excitotoxic pathway can also protect cells from damage.

Nitric oxide synthase has now been identified in widespread structures of the CNS[87] and the eye, including retinal photoreceptors, choroidal nerve fibers, and some cells of the ganglion cell layer.[100,101] It has been found in just those neurons that were previously known to contain nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase (NDP),[100,102] which has intrinsic NOS activity.[103] This is of interest because NDP-positive neurons are reported to be resistant to degeneration in conditions such as Huntington's disease, Alzheimer's disease, ischemic stroke, and NMDA-induced toxic effects,[104-108] and there are groups of NDP-positive cells of the inner retina that also exhibit selective resistance to excitotoxic effects.[109] It may be that NOS activity, possibly owing to its vasodilatory activity, is somehow protective of these cells, a function that could be ascendent under different circumstances than those in which NO is toxic to neurons.

Investigations of the role of NO in our emerging concepts of ischemia, and in models of glaucoma, are continuing to be worked out, but this important new molecule in the sequence of cytotoxic mechanisms will almost certainly play an important role in future understanding of retinal ganglion cell damage.

FREE-RADICAL SCAVENGERS AND ANTIOXIDANTS

Cell death following stressful ischemic or excitotoxic conditions, as outlined above, requires certain molecular events that mediate long-term neural damage. Oxygen free radicals (OFRs), which are highly reactive molecules that contain one or more unpaired electrons, are one such particularly important class of mediator,[110] since they are formed by all cells, including neurons, since the high unsaturated lipid content of neuronal membranes may confer high vulnerability to OFR-induced damage, and since the NMDAR activation–induced increase in intracellular Ca^{2+} has been shown to generate oxygen radicals.[94] Oxygen free radicals (such as superoxide ion or hydroperoxyl radical) are formed massively during reoxygenation following the cessation of ischemia and appear to contribute to neural damage (reperfusion injury)[111-114] by increasing peroxidation of fatty or nucleic acids and breaking protein cross-linking.[115-119]

Evidence supporting the toxic role of OFRs comes from the demonstration, soon after reperfusion, of dramatic production of OFRs[120,121] and fatty acid oxidation products[122] as well as decreased endogenous antioxidant levels.[123] Further, agents that scavenge OFRs (eg, vitamin E, D-mannitol), catabolize them (eg, superoxide dismutase [SOD], catalase), or reduce their formation (eg, nonsteroidal anti-inflammatory drugs, steroids) can protect against excitotoxic or ischemic injury.[117,124-126]

For example, following the reoxygenation phase in a transient retinal artery occlusion model of retinal ischemia, both histologic damage and large transmembrane ion fluxes, including that of Ca^{2+}, are largely eliminated by the free radical scavengers SOD and EGB 761.[127-129] EGB 761, which has small molecular weight and is orally active, preserves the ERG b-wave from lipoperoxidation-induced extinction.[130] Further, catalase has been shown to protect both the ERG a-wave and b-wave following transient retinal ischemia produced by elevation of IOP in rabbits.[131] These results suggest that oxygen radicals are an important link in the pathways of damage.

Another pathway by which OFRs may cause damage is by interfering with the ability of naturally occurring NO to (adaptively)

regulate vascular tone. In a rabbit model of acute retinal ischemia induced by elevated IOP, exogenous NO, presumably acting as a vasodilator and not as a toxic free radical, prevented ERG extinction, and the free radical scavengers SOD and catalase also protected against acute extinction of the ERG. Suprisingly, the NOS inhibitor nitro-L-arginine eliminated the protective effect of the free radical scavengers,[132] implying that OFRs destroy or block the action of NO[133] and therefore that antioxidant protection promotes protective vasodilation. In addition, certain of the toxic effects of OFRs may be shared with excitotoxins,[134] and OFRs may even modulate NMDAR function.[135] Oxygen free radicals also can cause increased excitotoxin release, further contributing to a vicious cycle.[136]

The damaging role of OFRs may not be limited to brief periods of hypoxia, but could also be important in neural degenerations, such as chronic glaucoma. For example, in amyotrophic lateral sclerosis, motor neuron death may be secondary to increased levels of intracellular Ca^{2+}, leading to enzymatic production of superoxide radicals;[137,138] this in turn may be related to mutations in the copper/zinc superoxide dismutase gene[137] or, in part, to an excess of glutamate or its analogues.[139,140]

Possible therapeutic modalities to deter glaucomatous damage could involve the introduction of exogenous free radical scavengers[126,130,141] or the induction of endogenous tolerance to oxidative stress.[142] For example, brief pretreatment with the SOD inhibitor diethyldithiocarbamate promotes enhanced expression of SOD, which can result in reduced neuronal damage from subsequent ischemia.[142]

NERVE REGENERATION AND GROWTH FACTORS

A recent panel of experts on ganglion cell growth and connectivity concluded that "the goal of restoring vision through the regeneration of central visual pathways is a realistic one."[25] This optimism derives in part from the recent demonstration that axons within rat optic nerve show the surprising capability to regrow following transection.[143-145] Placement of a peripheral, axon-free nerve graft into the axotomy site induces the regrowth of retinal ganglion cells that may even produce functional inhibitory and excitatory synaptic contacts with CNS target sites.[146] It is believed that the peripheral nerve graft promotes ganglion cell growth through the action of certain growth factors.

For example, brain-derived neurotrophic factor, which is found in peripheral nerves[147] such as those used to promote transected optic nerve regrowth,[144,145] enhances cultured ganglion cell survival.[148,149] This protein is only one member of the family of neurotrophins, growth factors that stimulate differentiation, proliferation, and survival of many different CNS and peripheral nervous system target neurons through receptor binding.[150] Thus, following transection of hippocampally projecting axons of the medial septum, nerve growth factor, another neurotrophin, causes a dramatic increase in survival of the axotomized nerve cells[151] and also improves survival of axotomized ganglion cells within the eye.[152] Peripheral nerves that are inserted into lesioned CNS sites and that induce extensive axon regrowth express markedly increased levels of nerve growth factor.[153] Study of the factors that promote differentiation and growth in this paradigm may reveal an approach to preservation or reconstitution of degenerated axons in glaucoma.

COMMENT

It seems likely that significant parts of the rapidly unfolding excitotoxin, calcium, nitric oxide, and free radical story will be germane to our understanding of ganglion cell function and survival under stress. It may be that neural degenerative processes, such as those reviewed herein, are at work in some or all forms of glaucoma. Numerous new questions leading to novel kinds of research arise.

Could glaucomatous optic nerve atrophy be related to ischemic effects? Do studies of acute and reversible ischemic injury have application to our understanding of glaucoma, a chronic and progressive condition? Might transient and localized but recurrent ischemic episodes (related perhaps to waking IOP spikes[154] or to nocturnal systemic hypotension[155,156]) induce cytotoxic damage? Does elevated IOP lead to excess buildup of excitotoxins? Are excitotoxins responsible for neural atrophy in glaucoma? Are free radicals generated during transient ischemic/reoxygenation cycles caused by elevations in IOP? Would inhibitors of free radicals, NOS, NMDA receptor-type channels, or voltage-operated calcium channels retard glaucomatous damage? Can we replace or augment ocular hypotensive agents for the treatment of glaucoma? The answers to these questions just may favorably modulate the nerve of glaucoma!

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