Self-destructive and Self-protective Processes in the Damaged Optic Nerve: Implications for Glaucoma

Michal Schwartz and Eti Yoles

Glaucoma has long been viewed as an optic nerve disease caused by factors external to the nerve. A risk factor commonly associated with glaucoma is high intraocular pressure (IOP), and a major research effort was therefore directed toward pressure reduction. It is now generally accepted, however, that normalization of pressure, although necessary, is often not sufficient as a remedial measure. This is because of the existence of additional risk factors, some of which emerge as a consequence of the initial damage. This situation is reminiscent of the response to a traumatic axonal insult, in which some of the damage is immediate and is caused by the insult itself, and some is secondary and is caused by a deficiency of growth-supportive factors as well as by toxic factors derived from the damaged tissue. Accordingly, we have suggested that glaucoma may be viewed as a neurodegenerative disease and therefore is amenable to any therapeutic intervention applicable to neurodegenerative diseases.

It is now well established that the primary causative factor in glaucoma, as in any neurodegenerative disease, initiates a series of biochemical events in the affected tissue. These events may arrest or impede the supply of essential neurotrophic factors. They also may lead to the appearance of compounds and processes that are toxic to the tissue and, by contributing to its progressive degeneration, act as tissue-derived risk factors (Fig. 1), even if the primary causative factor is no longer present. Such events are likely to lead to a self-perpetuating process of degeneration. Some of these events, on the contrary, may signify the onset of a self-repair mechanism (Fig. 1), which appears, however, to be insufficient to counteract effectively the destructive processes occurring in the nerve.

Self-destructive Processes

The primary insult in glaucoma triggers self-destructive processes that may be intracellular or extracellular and may in turn cause further nerve damage. An increase in IOP, for example, may interrupt normal axonal transport, resulting in deprivation of target-derived trophic factors, with consequent triggering of intracellular changes that may lead to apoptotic death of the affected retinal ganglion cells. The relative effects of the deprivation of target-derived neurotrophic factors and the reduction of locally produced neurotrophic factors on the progression of the disease is still an open question. Until recently, it was generally held that the loss of retinal ganglion cells in glaucoma could be explained by the trophic factor model. However, based on the relative kinetics of retinal ganglion cell death and neurotrophin loss, Johnson et al., in this issue of Investigative Ophthalmology and Visual Science, suggest that if neurotrophic deprivation plays a role in the death of retinal ganglion cells in glaucoma, it is only one of several mechanisms that do so.

Another potentially lethal risk factor triggered by the degenerating nerve itself is an uncontrollable increase in the levels of certain biochemical compounds, with harmful consequences for the tissue. One such compound is the excitatory amino acid glutamate, which normally acts as a major neurotransmitter but is neurotoxic when its physiological levels are exceeded. Glutamate levels were found to be increased in the vitreous of glaucomatous patients and in animal models of glaucoma or of crush-injured optic nerves. Similarly, the retinas of damaged optic nerves of both human eyes and animal models were found to contain increased concentrations of nitric oxide, a compound whose toxicity is evident from the fact that inhibition of the enzymes that mediate its increase arrests or at least slows down the degeneration. The presence of these biochemical compounds in abnormally high amounts may cause the death of neighboring neurons that were not destroyed or damaged by IOP or any other primary insult. As discussed in the next section, it should be noted that even if the level of environmental toxicity is not high enough to cause cell death directly, it may nevertheless lead to death because of enhanced susceptibility of any viable neurons within the damaged nerve to glutamate and other toxic mediators. At this stage, however, as emphasized by Johnson et al. regarding target-derived trophic factor deprivation, the chronology of action of these and other mediators, as well as their relative contribution to degeneration, is not clear.

Self-repair Mechanisms

As mentioned, the environmental deficiency or toxicity created by the degenerating nerve causes further neuronal damage. It seems, however, that the primary and secondary causative factors trigger not only destructive processes but also mechanisms of self-repair. The latter may partly account for the self-limiting nature of the progressive neurodegeneration seen in models of partially injured optic nerves. In the case of glaucoma, however, it seems that these self-repair mechanisms are either too weak or too transient to override the harmful effects.

In this connection, it is interesting to note that for glutamate, which exhibits essential physiological activity or lethal...
neurotoxicity depending on its concentration, there is an intermediate level at which it is not only not detrimental but is even beneficial in triggering an intracellular mechanism of self-protection. We found that in naive neurons exposed to above-normal—although subtoxic—levels of glutamate, increased resistance develops to further toxicity and not necessarily to glutamate toxicity only. That the resistance induced by such glutamate levels is not restricted to glutamate toxicity only. That the resistance induced by such glutamate levels is not restricted to glutamate toxicity only.

Another possible mechanism of intracellular self-repair is the induction of immediate early genes (such as c-jun), which are found to be triggered immediately after optic nerve injury, apparently as a result of trophic factor deprivation. The increase is transient and can be sustained by a peripheral nerve graft, known to increase the survival rate and to promote regrowth of injured optic nerve axons. A transient increase in BDNF was also found to occur soon after optic nerve mechanical insult or as an early response of the retina to low levels of N-methyl-d-aspartate. In the course of our studies we recently came across another mechanism, traditionally viewed as detrimental, that may be similar to the physiological self-repair mechanisms described—that is, normally too weak to be effective, yet amenable to exogenous boosting, and potentially lethal to the tissue if it gets out of control. The self-repair mechanism in this case is mediated by autoimmune T cells directed against myelin-associated proteins of the central nervous system (CNS). We suggested that the endogenous T cell immune response to optic nerve damage is beneficial, but limited. Our findings showed, against all expectations, that exogenous administration of T cells directed against the CNS self-antigen, myelin basic protein (MBP), significantly reduces the injury-induced spread of degeneration. Interestingly, the observed protection of neurons from secondary degeneration was not related to the intrinsic pathogenicity of the anti-MBP T cells. Thus, induction of clinical autoimmune disease was not a prerequisite for the protection against secondary degeneration mediated by the anti-MBP T cells. It is conceivable that the endogenous T cells that accumulate spontaneously at sites of CNS injury arise from an injury-triggered autoimmune response. Such a response may be beneficial but too weak to be effective and in need of boosting. It may therefore be worth seeking ways to augment therapeutically a beneficial autoimmune response without triggering a persisting autoimmune disease. Such boosting might be achieved, for example, by using T cells specific to the self-antigenic epitopes normally sequestered in the intact CNS. These autoimmune T cells would not accumulate in or interact with undamaged sites and thus would not induce disease, yet they might be able to assist in the repair of injured CNS tissue, if the covert epitope is exposed by the injury.

T cells can synthesize cytokines and neurotrophic factors. We have suggested that the accumulated autoimmune T cells may provide a source of neurotrophic factors. If so, these could compensate for the deprivation in supply or local production of trophic factors after injury to the optic nerve. Such an effect would illustrate the advantage of immune neuroprotection mediated by cells, rather than by pharmaceutical or physiological compounds. The immune neuroprotection may represent an extracellular mechanism of self-repair.

CONCLUSIONS

Progression of degeneration in glaucoma is similar to that in any neurodegenerative disease in which disruptive factors emerging from the nerve as a result of the primary insult contribute to the self-propagating processes of degeneration, and physiological mechanisms of self-repair are insufficient to counteract them effectively. Retinal ganglion cells depend on neurotrophic factors, mainly BDNF, for their survival. Early physiological attempts at compensation for the postinjury dearth of brain- or nerve-derived neurotrophins are transient, and the eventual outcome is long-lasting deficiency. The primary insult to the nerve apparently awakens extracellular and intracellular processes, as well as global immune mechanisms. Some of these processes are destructive and lead to degeneration; others are beneficial and are at least potentially capable of self-repair, although they appear to be transient and too weak to be effective unless boosted exogenously. Investigators in future research should attempt to determine what triggers these self-repair mechanisms and why they are transient and weak. Further understanding of the intracellular and extracellular mechanisms of retinal ganglion cell self-repair will con-
tribute to the design and development of therapies based either on pharmacologic remediation or on simulation of physiological pathways.

Acknowledgments

The authors thank Shirley Smith for editorial assistance.

References