NEW THERAPEUTIC SYSTEMS OF NEUROPROTECTORS AGENTS IN THE TREATMENT OF GLAUCOMA

NUEVOS SISTEMAS TERAPÉUTICOS DE AGENTES NEUROPROTECTORES EN EL TRATAMIENTO DEL GLAUCOMA

BRAO-OSUNA I¹, CHECA P¹, HERRERO-VANRELL R¹

Glaucoma is a degenerative neuropathy which constitutes one of the main causes of blindness in developed countries. Even though the pathogenesis of this disease is unknown, it is associated to a gradual death of retina ganglionary cells (RGC). Among the factors which increase cellular death, high intra-ocular pressure (IOP) has been traditionally considered as an essential cause. When IOP increases, the blood supply reaching the retina is compromised by the excessive pressure, thus affecting neuronal tissues. Apparently, an increased pressure on the connective tissue of the optic nerve head (lamina cribosa) interrupts the axoplasmatic flow, thus preventing endogenous neurotrophic factors from reaching the neuron body from the axons. Faced with these deficiencies, the cells can unleash a natural process of cellular degeneration (apoptosis). At present, it is considered that the intra-ocular pressure is the main risk factor for developing glaucoma, even though it can arise with IOP ranges within statistical normality. In fact, the drugs in the market for treating glaucoma are based on the reduction and control of IOP. However, it is important to emphasise that neither all patients with a high IOP will develop glaucoma nor the reduction of IOP will guarantee protection against it. About 10 years ago, researchers began studying other important factors in the genesis and process of retinal neuronal degeneration, such as the influence of the lack of sufficient to blood supply to the head of the optic nerve (in the absence of high IOP) and adjacent retinal cells (1).

Recent studies in cellular physiology have demonstrated that, in chronological terms, the neuronal degeneration process can be described in three steps: primary axon damage, death or damage of the neuron and damage and subsequent death of adjacent neurons in a process called «secondary degeneration». This secondary degeneration occurs in neurons which initially are not damaged, but end up dying due to exposure to cytotoxic agents released by the death of the neurons with primary axon damage (1). In what concerns said cytotoxic agents, it is known that high concentrations of glutamate hyperstimulate axon receptors, thus increasing the concentration of intracellular calcium and giving rise to the production of free radicals which are highly cytotoxic and produce the death of the neuron. Accordingly, the protection of the neuron is focused on protecting the neurons which may fall prey to said «secondary degeneration». This protection is useful even when the initial cause of the disease is not known, because it aims at limiting and preventing neuronal damage and death by blocking the mechanisms which give rise to this process (1).

The considerable interest in the use of neuroprotective therapy in the treatment of glaucoma in recent years has been substantiated in a growing number of researchers in the field. Neuronal protection is an alternative to therapies based on controlling IOP which, in many cases, is not sufficient for addressing a number of glaucoma pathologies. In addition, the development of treatments for other neuronal alterations and the good results obtained, for example, in treating Huntington’s disease, Parkinson, Alzheimer and others, give rise to hopes for the use of this new strategy in the treatment of glaucoma (1).
To date, it is known that the protection of RGC can be approached from different angles:

1. Prevention of the glutamate-induced excitotoxicity of RGC (antagonists of NMDA receptor (N-methyl-D-aspartate) such as memantine).

2. Blocking the apoptosis pathways (semaforine caspase inhibitors).

3. Administration of neurotrophic factors (GDNF, BDNF, CNTF, T-588).

4. Administration of free radical capturing elements (Carnitine, Carnosine, co-enzyme Q10, Omega-3 fatty acids, Vitamin B12, etc.).

5. Administration of calcium channel blockers.

Preliminary studies carried out with some of the above molecules in experimentation animals have yielded promising results for the protection of RGC. However, in contrast with the treatment for reducing IOP (which acts on the anterior segment of the eye and can be applied topically), the applicability of neuroprotective therapies involves the development of administration forms that are efficient directly at the level of the retina. In this regard, intravitreous administration appears to be the most direct pathway and one which allows for the best control of the amount of drug being administered as well as eliminating most of the systemic secondary effects. However, this pathway is not free of problems: in addition to be risks inherent to the utilisation of an invasive technique (such as infections), the drawback is that the administration is made in the form of a «bolus», which is not enough for an effective treatment of chronic problems like glaucoma that require active agent concentrations in the area of action for a sustained and prolonged period of time.

Since the repeated administration of intravitreous injections is discarded due to complications such as vitreous haemorrhage, retina detachments, cataracts, endophthalmitis, etc., it is clear that intravitreous administration forms are needed to provide therapeutic concentrations of the drugs in their place of action for long periods of time, while reducing as far as possible the number of applications.

Controlled release biodegradable microparticle systems are becoming a viable alternative for developing intravitreous formulations for this purpose. On the one hand, these systems can be injected in the vitreous in the form of a suspension without requiring surgery, and on the other, as they degrade with time to finally disappear, surgery is not required either for their removal. In addition, as these systems release the drug, progressively, high dosages can be administered, which considerably reduces the number of applications, allowing practitioners to administer successive applications several months apart. For example, some authors are working on the microencapsulation of neurotrophic factors (BDNF, GDNF) in microspheres of quitosane or poly(lactic-co-glycolic) acid (PLGA) with encouraging results.

Finally, an additional alternative which as yet has not been thoroughly explored for administering drugs for action in the posterior segment is the periocular pathway (subconjunctival or subTenon injections, etc.). The drug administered in this way must go through the sclera and may reach therapeutic concentrations in the vitreous and the retina, thus avoiding intravitreous injections. In this regard, microparticles and nanoparticles having surface characteristics capable of increasing the permeability of drugs through the sclera could be highly useful for treating ocular posterior segment diseases, specifically glaucoma.

In contrast with other neurodegenerative diseases, the use of neuroprotectives for the treatment of glaucoma is not highly developed. At present there are no formulations on the market based on neuroprotection. Therefore, basic research centres, hospitals, public administrations and pharmaceutical companies should make a joint effort to make available to patients and health professionals the considerable benefits which this new therapeutic strategy can bring as soon as possible.

REFERENCES


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