GLAUCOMA AND NEUROPROTECTION:

THERAPEUTIC PERSPECTIVES

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ABSTRACT

Glaucoma is the main cause of irreversible blindness worldwide. It affects approximately 70 millions of people in the world. It is an optic neuropathy. It is characterized by a functional damage, caused by progressive retinal ganglion cells (RGC) and their axons progressive loss (1). It is caused by a high intraocular pressure (IOP) which is responsible of RGC death in open-angle glaucoma. There is also a low-tension glaucoma. The second risk factor of this disease is the age. It is higher every decade over 40 years old (2-4). Other risk factors are: Afro-american race, myopia, diabetes, positive family anamnesis. It is actually unknown why an increase of IOP may cause a thinning of retinal nervous fiber layer (RNFL), a cupping of optic disc and typical visual field damage. There are two aetiopathogenetic theories: mechanical and vascular ones (5,6). Modern research is exploring which molecular mechanisms upgrade or downgrade both mechanical and vascular damages even when IOP is in a normal range (7,8). We hope to stop the neural cell damage by using neuroprotective agents associated to conventional hypotonizing drugs.

KEY-WORDS: glaucoma, neuroprotection, optic disc, retinal nerve fiber layer.

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In glaucoma disease there is apoptosis either in animal model or in neuron cells (9,10) or in normal-tension glaucoma patients (11,12). It is not yet clear how the increase of IOP may trigger the apoptosis. Gregory M.S. et al. (13) proved the role of Fas Ligand (FasL). It is a transmembrane type 2 protein, belonging to TNF family. It is present in the ocular tissues and it contributes to the privileged immunological state. It prevents the angiogenesis and it triggers the apoptosis of the inflammatory cells (14). FasL is involved in the RGC T-cell mediated death (15,16). FasL activities depend if it binds to the cell membrane or if it is soluble. There are two FasL forms: the T-released microvescicles (mFasL) longer than a soluble form truncated by metalloproteinases in the cell membrane (17,18,19). In their experiment Gregory M.S. et al. (13) showed that when FasL is present, the RGC death is faster. Although, when FasL is not present, the RGC death stopped. Metalloproteinases (MP3 and MP7) truncate FasL (20). The IOP increase may increase the level of α-TNF, responsible for the anomaly of MP and their tissue inhibitors (TIMPs). In a previous study RGCs and glial cells were studied. The glial cells produce α-TNF and NO, responsible for the apoptosis of the ganglion cells. It happened after ischemia and increase of hydrostatic pressure. Apoptosis was reduced by 66% by a neutralizing α-TNF antibody and by 50% of an inducible nitric oxide synthetasis (iNOS) (21).

These results show that the glial cells are neurotoxic after ischemia or increased hydrostatic pressure. α-TNF is a neurotoxic agent on the ganglion cells. Their antagonist may be neuroprotective, considering that α-TNF may produce NO (22,23,24). In vivo an increase of NO is present in open-angle glaucoma, normal-tension glaucoma and pseudoexfoliative glaucoma patients (25,26). Cytokine is long-lasting and it is responsible of the neuronal loss even when the IOP is normal (27).

Another protein, beyond α-TNF, is produced by neural microglial cells when the IOP is high. It causes RGC death and it is called α2macroglobulin (α2M). Its gene is upregulated after 7 days of increased IOP and it lasts 20 days and it is responsible of RGC death (28,29,30). Bay et al. (31) proved the presence of α2M in the aqueous humor of either experimentally induced or in glaucoma patients. This protein is produced in the retina but it is present in the anterior chamber and it is a marker of ocular hypertension. α2M seems to neutralize the Nerve Growth Factor (NGF), protective neurotrophin of RGC upregulating TrkA receptors. This data explains why only high doses of NGF protect RGCs (32,33,34).

Guo et al. (35) supported the hypothesis that the increase of IOP induces the apoptosis of RGC, remodelling the extracellular matrix (ECM) and the optic nerve by lamina cribrosa axonal compression, axonal flux stop and then death. In vivo they showed a positive correlation between the increase of IOP and upregulation of MMP9 ($p<0.001$), TIMp-1 ($p<0.05$) and TGFβ-2 ($p<0.05$). MMP9 is positive correlated to the RGC apoptosis ($p<0.001$) and laminin loss ($p<0.01$). On the optic nerve head type 1 collagen increased ($p<0.01$).

These evidences are supported by an increase of MMP-9 associated to apoptosis in CNS (36) and a reduction of laminin (37,38).

The increase of MPP-9 may be the consequence of the mechanical effect of IOP on retinal ganglion axons and an increase of neurotransmitter glutammate after increased IOP, ischemia and damage (39,40,41,42).

The increase of TIMP-1 counteractes MMP9 (43). That's why it is important to stop the apoptotic cascade in the therapy of glaucoma. Autophagy is important in neuronal cell death in glaucoma.

In the eukariotes, autophagy is a physiological process of degradation of proteins, cytoplasmic organelles and in lysosomes. It may induce tissue remodelling after ischemia and retinal neurodegenerative diseases (44,45,46).

Piras et al. studied autophagy in ganglion cell neurons after ischemia/reperfusion in murine retinas. Autophagic markers, LC3 and LAMP1 increased after 12 and 24 hours. It was strongly stopped by 3-metiladenine, a strong inhibitor of autophagosomes (47).

Ischemia is an important clinical problem, shared by glaucoma and both diabetic and hypertensive retinopathy.

Fluctuation of retinal extracellular pH was associated to ASICs (Acid-sensing ion channels). ASIC1a is a Ca^{2+} and Na^{+} channel (48,49). In culture, ASIC1a upregulated after oxygen deprivation and an increase of intracellular Ca^{2+}. Amiloride and psalmotoxin 1 reduces RGCs death in vivo (50). This may be a target of neuroprotection in glaucomatous, diabetic and hypertensive patients.

Research focused on mithocondria, oxidative stress (51) and inflammation which cause the disease by neuronal death.

Liu Q. (2011, 52) evaluated 4-idrossi-2-nonenale (HNE) and heme-oxygenasis 1 (HO-1) in a retinal ganglion cell culture after 0, 30, 60 or 100 mmHg hydrostatic pressure for 2 hours and a murine model after increase of IOP at 30, 60 and 100 mmHg as long as 1 hour. Both experiments increased HNE and HO-1. HNE induced neuronal death .

Even photoreceptors may die during glaucoma but RGC are more sensitive (53).

An antioxidant, such as resveratrol, inhibits the oxidative stress and it may be useful in the neuroprotection of glaucoma.

Flavonoids showed a neuroprotective effect against oxidative stress, glutammate and hypoxia (54).

These drugs have a neuroprotective effect in cancer, cardiovascular and neurodegenerative diseases (55,56,57,58,59,60,61).

Nicotriflorin, rutin and quercitin have a neuroprotective effect. They are present in fruit and vegetables. Quercitin is present in tea. In a media, flavonoids were tested by inhibiting caspasis 3 and calpain (a cystein-proteinasis). Nicotriflorin and rutin were neuroprotective against hypoxia, glutammate and oxydative stress at a concentration of 1nM, while quercitin needed higher concentration (100 nM).

The flavonoid neuroprotection depends on their nucleus. They influence the glutathione metabolism, antioxidant facility and keep low Ca^{2+} concentration notwithstanding high free oxygen radicals (FOR) levels (62,63).

The flavonoids are useful as neuroprotectant in the oxydative stress by hypoxia and glutammate damage may depend on the influence of hypoxia and glutammate in the cell death.

Another factor involved in ganglion cell damage during glaucoma, diabetic retinopathy and ischemia is the light.

Li G. Y. et al. (64) proved that light may cause retinal ganglion cell damage destroying DNA and mitochondria.

RGC-5 cells were used (65). 2600 lux light may damage DNA and activate poly-ADP-ribose polymerase 1 (PARP-1). It acts to repair small DNA damage. Instead, PARP-1 inhibition is neuroprotective against cell damage. Benzamide and nicotinamide were used as PARP-1 inhibitor, increasing the cell survival from 25.4 to 38.1% at a concentration of 10 mM. NU1025, a new inhibitor, increased the cell survival by 77.1%. Also Nfenilmaleimide, an inhibitor of AIF (apoptosis inducing factor) increased the cells from 15.72 to 29.35%. It is a proapoptotic factor, anchored in the inner mithocondrial membrane. It binds to DNA and RNA and it causes a damage to caspasis-indipendent chromatine and DNA fragmentation.

Light increases ten times the Ca^{2+} intracellular concentration and cobaltus, an inhibitor of this ion, reduces the cell death, caused by inhibition of ATP production and NO production (66,67).

Mitochondria are involved in the ganglion cell death in glaucoma. The light may act on cycloxygenasis, P450 cytochrome and flavin, producing the perossinitrite anion (ONOO, 68).

Osborne N.N. (69), in order to neuroprotect against glaucoma, advices some drugs as creatine, α-lipoic acid, nicotinammide and epigallocatechingallate (ECGC).

Wang Y.S. et al. (70) recently studied the effect of Ginkgo biloba (EGb761) on the ganglion cell culture, associated to glutammate. In the control the survival was 61.94±7.75%, in glutammate culture 44.59±4.19%, in EGb761 75.05±3.90% and 63.19±9.44% in both glutammate and EGb761 culture.

Neuroglobin (NGB) is an endogenous neuroprotector. In an experimental murine glaucoma, it was induced by high IOP level to protect the RGCs. It reduced the superoxyde and ATP production. This globin may be a therapeutic target against glaucoma.

In 2011 more and more researches tried to identify new neuroprotective factors. Q.L. (71) found a new soluble antagonist NOGO-66 (sNgR-Fc), to stop the RGCs death at 5 days, 2 and 4 weeks (72).

Optineurin gene is expressed in RGC. Its mutation may be associated to open-angle glaucoma and amyotrophic lateral sclerosis. Neurotrophin 3 (NT-3) is a neuroprotective antagonist (73).

P53 and cycline-dependent kinase 5 (CDK-5), responsible of neurodegenerative diseases, increases p-N32A (S1232), one of N-methyl-D-aspartate (NMDA) receptors (74). In glaucoma, its activation causes RGC apoptosis (75).

IOP-independent neuroprotection was identified also in prostaglandin analogues such as latanoprost, tafluprost and bimatoprost, at a concentration of 100 nM (76,77).

Apart from neuroprotection, glaucoma is surely associated to ageing. Scanning electronic microscope (SEM) was very useful in identifying differences associated to ageing ($p<0.001$) in young and adult retinas about retinal thickness, ganglion cells, capillaries and synaptic junctions numbers (78).

Chierzi S. et al. (79) showed that the ability of cone regeneration depends on the ageing and inhibition of ERK (extracellular-signal regulated kinase 1,2) and Protein-kinase A (PKA).

These concepts may be useful in the neuroprotective therapy of glaucoma, optic neuropathy and other retinopathies. Further studies are needed to find oral pharmacological associations useful to neuroprotect the ganglion cells, bioavailable and without side-effects.

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