NEUROPROTECTION IN GLAUCOMA – DELUSION, REALITY OR HOPE?

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Abstract: The global definition of glaucoma considers it as an optic neuropathy with multifactor etiology, which affects the optic nerve head (ONH), provoking visual field loss and permanent impairment of visual function.

Bearing in mind the fact that the exact pathogenic mechanism is still not completely established, glaucoma treatment strategies so far are based upon the identification of glaucoma risk factors. Among them, only elevated intraocular pressure (IOP) could undergo therapeutic treatment.

However, in spite of the adequate therapy and IOP lowering, very often the disease is still progressing, leading to definite visual loss and permanent blindness. This especially refers to "normal tension glaucoma".

Over the last decade, there has been significant scientific research on new strategies for the delay or prevention of retinal ganglion cell loss (RGC), which is the basic pathophysiological event that initiates the cascade of processes leading to optic atrophy.

Therefore, a great deal of expectation has been put on the concept of what is known as "neuroprotection". This includes the development of treatment strategies (pharmacological, immunological, genetic) that would be capable of preventing apoptotic death of retinal ganglion cells.

The concept of neuroprotection is based upon increasing evidence that glaucoma degeneration is analogous with other neurodegenerative diseases of the central nervous system suggesting a strong relation between the basic cellular processes in glaucoma and Alzheimer’s disease, for example.

It is considered that retinal ganglion cell death goes through two phases – primary injury responsible for initiation of damage that is followed by slower secondary degeneration related to a harmful environment surrounding the degenerated cells.
Neuroprotection in glaucoma refers to any intervention that is aimed at prevention of the optic nerve head injury and ganglion cells death.

Pharmacological intervention is aimed at neutralizing some of the effects of the nerve-derived toxic factors by increasing the ability of the remaining neurons to cope with stressful conditions.

On the other hand, immunological reaction stimulates the body’s repair mechanisms so as to hinder the toxic effects of various chemical agents generated during pathological events.

Key words: neuroprotection, glaucoma, intraocular pressure, neuroprotective agents, retinal ganglion cells.

Introduction

The modern concept of glaucoma does not include only diseases with elevated intraocular pressure, but considers it as "a multifactorial, degenerative disease characterized by optic neuropathy, visual field loss and retinal degeneration as a result of apoptosis of retinal ganglion cells as an early phenomenon".

Glaucoma affects approximately 2.0% of the total population over the age of 40. The elevated IOP has been implicated for a long time as a possible primary insult in the disease resulting in mechanical and ischaemic conditions leading to the death of retinal ganglion cells via the so-called process of apoptosis that initiates the onset and development of glaucoma.

However, therapeutic strategies in which the unique target is the elevated IOP have shown to be insufficient and hence there is intensive work under way on new concepts of therapeutic approaches for the management of glaucoma.

One such concept with many ongoing contradictory attitudes and expectations is the concept of neuroprotection.

Selective death of retinal ganglion cells (RGC) is the hallmark of glaucoma and is associated with structural changes in the optic nerve head. The process of retinal ganglion cell death is considered to be biphasic: the onset of a primary injury responsible for the initiation of damage that is followed by slower secondary degeneration related to the harmful environment surrounding the degenerated cells.

Neuroprotection within the nervous system is a therapeutic paradigm directed at delay or prevention of death of the affected neuronal tissue in order to preserve and maintain its physiological function.

Globally, neuroprotection is a process that attempts to preserve, that is, protect the cells spared during the primary insult, but still to a large extent vulnerable to injury.
Today there is a large body of evidence showing that glaucomatous neurodegeneration is analogous to other neurodegenerative diseases of the central nervous system suggesting a strong relation between basic cellular processes in glaucoma and Alzheimer’s disease, for example.

Neuroprotection in glaucoma refers to any intervention that is aimed at the prevention of optic nerve head injury and ganglion cells death. The treatment can be directed to extracellular factors, such as a decrease of the intraocular pressure (IOP), or can affect cellular factors derived from the optic nerve, such as blocking of the signals for intracellular death.

Today it is considered that neuroprotection can be achieved through two global approaches:

– Pharmacological approach
– Immunological approach

Pharmacological intervention is aimed at neutralising some of the effects of the nerve-derived toxic factors by increasing the ability of the remaining neurons to cope with stressful conditions.

On the other hand, immunological reaction stimulates the body’s repair mechanisms to hinder the toxic effects of various chemical agents generated during an apoptotic cascade of events.

Randomized clinical studies are the golden standard for assessment of neuroprotection in glaucoma. However, to date, there has been no randomized clinical study to demonstrate the evident benefit from neuroprotection, although in vitro cell models as well as in vivo models of optic nerve injury have suggested positive effects. Potential reasons for these discrepancies include the following:

– An animal model cannot adequately simulate human disease;
– The pathophysiology of human diseases is significantly different from that in animal models;
– There is more variability in human diseases than in laboratory models.

Moreover, an RGC culture cannot reflect the complex pathophysiology of the human disease [1].

Neuroprotection

In order to understand the concept of neuroprotection, it is necessary to recognize the most important risk factors for glaucoma, including:

– Values of IOP
– Age
– Positive family history of glaucoma
– C/D ratio (cup/disc)
– CCT < 555 microns
– High myopia
– Migraine headaches.

The only proven risk factor which currently undergoes therapeutic treatment is the value of \( IOP \).

Bearing this in mind, the concept of neuroprotection has been designed to substitute the therapeutic approach based merely on IOP control, which does not exclude the possibility of further progression of glaucoma even if IOP has been normalized [2].

Neuroprotective properties have been assigned to a larger number of agents, drugs, different substances and processes. However, the major neuroprotective attributes were defined back in the year 2001 [3].

Criteria for defining the neuroprotective properties
Cioffi GA: Glaucoma in the 21st Century Meeting, 2001

1. Evidence for the mechanism of realization of neuroprotective action
– Mechanism of cell death and models of glaucoma

2. Route of drug administration/delivery – localization of the site of action and pharmacological doses

3. Human clinical studies
– Criteria for conducting the study, progression rate, population studies

Is there an agent/drug/therapeutic treatment with proven neuroprotective properties?

Let us find out, after presenting a review of neuroprotection in glaucoma.

Potential models of neuroprotection in glaucoma

Three basic types of potential models are defined. These are supposed to accomplish neuroprotection in glaucoma [4].
– Reduction of intraocular pressure
– Improvement of intraocular circulation
– Direct neuroprotective action

Contemporary studies suggest glaucoma to be correlated with multiple factors that cause apoptotic death of RGC and subsequent optic nerve atrophy. Clinical signs of glaucoma include defects of retinal nerve fibre layers (RNFL),
neuroretinal rim thinning with "cupping" of the optic nerve head, and irreversible visual field loss.

Neural degeneration in glaucoma is not limited to the retina alone, but it also affects neurons in the corpus geniculatum laterale and the visual cortex [5].

Kaushik [6] in 2003 defined the potential mechanism of retinal ganglion cell death, as follows:

*Mechanisms of retinal ganglion cell death*

- Loss of neurotrophin due to retrograde axoplasmatic transport block
- Glutamate-induced excitotoxicity
- Free radical release
- Neurotoxicity due to NO
- Phenomenon of apoptosis

Over the last decade there has been a large body of evidence confirming that glaucomatous neurodegeneration is analogous to neurodegenerative diseases of the central nervous system, suggesting a strong relation between the basic cellular processes in these two groups of diseases.

In this context, the following diseases have been examined: Alzheimer's disease, Parkinson's disease, insults, spinal cord injuries and amyotrophic lateral sclerosis.

The processes of neuronal damage and death in these diseases overlap with those factors that are considered to participate in the initiation of glaucoma: hypoxia, nutritive insufficiency, oxidative stress, excitotoxicity, immune-related attack and apoptotic death [5].

Multiple factors involved in the pathogenesis of glaucoma cause apoptotic death of RGC and consequent optic nerve atrophy with definite loss of the visual function.

The process of apoptotic cell death occurs in the absence of inflammation and is characterized by DNA fragmentation, chromosome clumping, cell shrinkage and membrane impairments [5].

The study of the Research Group Neuroprotection [7] has determined the most important aspects of neuroprotection, including:
- Defining the glutamate excitotoxicity and its prevention;
- Role of endogenous neuroprotective substances (KYNA-Kynurenic acid);
- Finding a long-term model for in vivo [route of drug administration/delivery];
- Ocular gene therapy.
The term **excitotoxicity** refers to the phenomenon where cells die via the process of apoptosis ("programmed cell death") due to an excessive glutamate concentration.

**Glutamate** is an essential amino acid that plays an important role as the main excitatory neurotransmitter in the central nervous system and retina.

During the process of apoptosis and RGC death glutamate is released from the damaged cells and dispersed among neighbouring cells causing secondary degeneration and triggering a cascade of excitotoxicity events leading to further cell death. Moreover, reduced clearance of extracellular glutamate might also cause neuronal toxicity [8].

Bearing in mind the role of glutamate in the mechanism of RGC death, inhibition or blockade of glutamate activity, especially modulation of the NMDA receptors (N-Methyl-D-Aspartate) has been indicated to be an important strategy for neuroprotection in glaucoma, although the exact mode of this inhibition has not yet been completely elucidated [8].

Algorithm No. 1

Algorithm of glutamate excitotoxicity

- **Cell death**
  - Liberation of intracellular glutamate
  - Dispersion in surrounding cells
  - Secondary degeneration of ganglion cells
  - Initiation of excitotoxic chain of events with profound cells death

**Kyneurenic acid (KYNAs)** is an endogenous neuroprotective substance which is present in numerous tissues under physiological conditions, having a potentially important role in the treatment of neurodegenerative diseases [7].

**Role of the ocular gene therapy**

The understanding of the genetic pathways of apoptosis can help in designing new treatments that could prevent activation of apoptosis or arrest the process when started.

Generally, in gene therapy, genes for potentially neuroprotective substances "are delivered" directly to the retinal ganglion cells [9]. This delivery

can be done via several various mechanisms – viral vectors, artificial liposomes, or direct gene transfer [6]. Selective inhibition of certain genes responsible for the increased loss of ganglion cells has also been indicated [7].

Besides the above-mentioned factors, there are a large number of phenomena and processes implied to be involved in the pathogenesis of cell death.

The most significant are:

– **Mitochondrial dysfunction** is assumed to be involved in neuronal apoptosis and is registered in experimental forms of glaucoma. It may be induced by certain stimuli, such as hypoxia and TNF-α.

– **Oxidative stress** as a risk factor for glaucoma can act genuinely, or in association with mitochondrial dysfunction it can cause damage of the trabecular meshwork, the optic nerve head, and the retina [8].

– **Inflammation** might induce the process of apoptosis and RGC death.

The mechanism of RGC damage and structural damage to the optic nerve head are presented in the following algorithm.

Algorithm No. 2

Research group Neuroprotection, UEH Tuebingen
Potential neuroprotective agents and substances

Different studies suggest a large number of agents and substances with registered neuroprotective properties.

1. **Antagonists (inhibitors) of excitotoxicity**

   The most prominent representative of this group is **Memantine**. At the moment, Memantine is the unique available clinical glutamate modifier. Memantine is a derivative of amantadine and it has shown positive effects in the treatment of Alzheimer’s and Parkinson’s diseases. However, no positive neuroprotective properties have been registered in phase III of clinical studies.

2. **α-2-adrenergic agonists**

   **Brimondine** has been shown to have certain local neuroprotective attributes.

3. **Ca-channel blockers**

4. **"Delivers" brain neurotrophic factor (BDNF) to the retinal ganglion cells**

5. **Antioxidants and "hunters" of free radicals**

6. **Inhibitors of NO synthesis**

7. **Exogenous neurotrophines** – delay, but do not prevent ganglion death

8. **Caspase inhibitors**

9. **Radiation treatment** – demonstrated in animal models

10. **Transplantation of stem cells**

11. **Vaccination** – in animal models

12. **Modulation of immunological system and inflammation.**

   All these agents and types of treatment in preclinical studies have shown encouraging, but still unsatisfactory, effects in the prevention or delay of RGC death in the pathogenesis of glaucoma [10].

   However, if we bring to mind the criteria of Cioffi, which define neuroprotective properties, it has to be stated that none of the offered neuroprotective agents and approaches satisfy the three indispensable criteria for confirmation of neuroprotective capacity.

   Therefore, it remains that reduction of IOP is the only quantitative parameter which helps in assessment of neuroprotective effects.

**Conclusion**

At present there is no scientifically conclusive evidence that any of the presented therapeutic approaches and agents has confirmed neuroprotective
attributes, which would enable delay or prevention of apoptotic RGC death. Induction of apoptosis escalates with the development of glaucomatous optic neuropathy, irreversible vision loss and significant impairment of quality of life in individuals with glaucoma. Although neuroprotective drugs are still not available for serial use, they might be exceptionally useful, especially in arresting the progression of glaucoma.

On the other hand, there are certain objective limiting factors for assessment of the effects of neuroprotection, such as:

- Insufficient sensitivity of available functional diagnostic methods for quantitative evaluation of glaucoma progression and effects of neuroprotection;
- Great hopes and expectations lie in the so-called DARC-technology (Detection of Apoptosing Retinal Cells), which enables inspection in a real-time in vivo imaging, that is, a technique for visualization of an in vivo apoptotic event that will give real quantitative assessment of the neuroprotective properties of certain drugs and agents.

The concept of neuroprotection and synthesis of neuroprotective drugs is a successful substitution and supplement to the currently unique therapeutic strategy for glaucoma based on reduction of IOP.

Finally, intensive research in the last decade has confirmed that neuroprotection in glaucoma is not a delusion. At this moment, individuals/patients with glaucoma have to rely on hope. How long we will wait for it to become reality, remains to be seen.

REFERENCES


Резиме

НЕВРОПРОТЕКЦИЈА НА ГЛАУКОМОТ – ЗАБЉУДА, РЕАЛИНОСТ ИЛИ НАДЕЖ?

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Глобалната дефиниција на глукомот денес се дефинира како оптичка невропатија со мултифакторска етиологија, која ја афектира главата на видниот нерв (papilla n. optici), предизвикувајќи оштетување на видното поле и трајно намалување на видната функција.

Со оглед на факту дека точниот патогенетски механизам сè уште не е наполно утврден, досегашните стратегии за справување со глукомот се базираат на идентификација на ризичните фактори за развој на глуком, при што единствено зголемениот интраокуларен притисок (ИОП) е единственот ризичен фактор на кој може да се влијае со тераписки средства.

Меѓутоа, и покрај важниот тераписки принос, многу често напредува прогресијата на заболевувањето, која води до дефинитивен губиток на видот и трајно слепило, а ова особено се однесува на т.н. „глукумо сè нормален очен притисок“.

Заради ова, во последната децении интензивно се работи на развој на нови стратегии за одлажување или превенција на смртта на ретиналните ганглиски клетки, како основен патофизиолошки настан и супстрат од кој потекнува каскадата на настани кои завршуваат со атрофија на виднот нерв.

Во тој контекст, особено големи надежи се полагаат во концептот на т.н. „невропротекција“, односно развој на тераписки пристапи (фармаколошки, имуноцелуларни, генетски), кои сè овозможат превенција на апоптотичната смрт на ретиналните ганглиски клетки.

Концептот на невропротекција се базира на зголемениот број на докази дека глукомната невродегенерација е аналогна со другите невродегенеративни заболувања на централниот нервен систем, со сугвестија за цврста врска помеѓу базичните целуларни процеси кај глукомот и Alzheimer-овата болест, на пр. Се
смета дека процесот на умирање на ганглиските клетки е бифазен – се работи за примарна повреда одговорна за иницијација на оштетувањето, која е следена со побавна секундарна дегенерација поврзана со токсичното опкружување во околината на дегенерираните клетки.

Невропротекцијата кај глаукомот се однесува на било каква интервенција со цел да се спречи оштетувањето на напилата на видниот нерв и смртта на ретиналните ганглиски клетки.

Фармаколошката интервенција има за цел да ги неутрализира некои од ефектите на невротоксичните фактори, преку зголемување на способноста на преостанатите неврони да се справат со стресните услови. Од друга страна, имунолошката реакција ги стимулира сопствените телесни репараторни механизми за спречување на токсичните ефекти од различни хемиски агени генерирани во тек на каскадата на настани.

Ключни зборови: невропротекција, глауком, интраокуларен притисок, невропротективни агени, ретинални ганглиски клетки.

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