NEUROTRANSMISSION IN VISUAL ANALYSER AND BIONIC EYE. A REVIEW

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Sworn declaration
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SUMMARY

Aims: The aim of the work is to point out the transmission of electrical voltage changes in the visual analyser and thus the efficiency of the bionic eye.
Material and methods: The review deals with the question of the transmission of electrical changes in visual path voltage under physiological and pathological conditions. In particular, it points to feedback autoregulatory damage not only of primarily altered cellular structures, but of all other, both horizontally and vertically localized. Based on the results of functional magnetic resonance imaging and electrophysiological methods, it shows the pathology of the entire visual pathway in three eye diseases: retinitis pigmentosa, age-related macular degeneration and glaucoma.
Results: The thesis also provides an overview of possible systems that are used to replace lost vision, from epiretinal, subretinal, suprachoroidal implants, through stimulation of the optic nerve, corpus geniculatum laterale to the visual cortex.
Conclusion: Due to the pathology of neurotransmission, bionic eye systems cannot be expected to be restored after stabilization of binocular functions.
Key words: neurotransmission, retinitis pigmentosa, age related macular degeneration, bionic eye

INTRODUCTION

The question of restoration of damaged sight is nothing new, and has been occupying professionals for several decades. In our periodical also we can find several studies on this theme. Their conclusions have been based on the results of other authors [1,2,3]. In this study we attempt to clarify a number of aspects which have been overlooked not only by our own, but above all by foreign experts.

Neurotransmission in the visual pathway – physiology.

A chemical change takes place following the impact of light on the retina in the outer segments of the photoreceptors (cis-retinal is converted into trans-retinal). This generates hyperpolarisation [4]. During the course of synaptic transmission, hyperpolarisation of the photoreceptors causes the release of glutamate from the pre-synaptic part into the synaptic cleft and its subsequent binding to the receptors, which are located on the membrane of the post-synaptic neurone [5].

Glutamate binds to receptors, which were named according to their selective agonists. For NMDA (N-methyl-D-aspartate) receptors the typical agonist is N-methyl-D-aspartate. For AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors the typical agonist is α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, and for the third type, kainate receptors, kainate. AMPA and kainate receptors are also known as non-NMDA receptors [6]. Glutamate receptors are present not only in photoreceptors but also in horizontal and bipolar cells, as well as in the retinal ganglion cells [7]. Glutamate is also the predominant excitatory neurotransmitter in the retina and in the brain of mammals [8].

After generating post-synaptic excitatory potential, glutamate must be immediately removed from the synaptic cleft. In the mammalian central nervous system glutamate is removed from the synapse primarily by glutamate transporters of the type of excitatory amino acid transpor-

ter and glutamate aspartate transporter (GLAST) into the Müller cells (MC). The enzyme glutamine synthetase (GS) converts glutamate into glutamine in the MC [9,10].

Glutamine then does not act as a neurotransmitter, and so may be released back into the synapse, from where it is subsequently uptaken by the pre-synaptic neuron, which converts it back into glutamate [11].

To date there is no evidence concerning the presence of an enzyme that would convert glutamate directly in the synapse [12].

The concentration of free glutamate in the synaptic cleft during synaptic transmission is approximately 1.1 mmol, although its concentration rapidly decreases and breaks down by the NMDA receptors within 1.2 ms. However, glutamate separates far more rapidly from the AMPA receptors. The time course of free glutamate therefore predicts that separation contributes to the breakdown of the post-synaptic current mediated by the AMPA receptors [5].

Neurotransmission in the visual pathway – pathology

One of the first impulses that led us to examine the processes in the visual pathway was simultaneous measurement of pattern electroretinogram (PERG) and pattern visual evoked potentials (PVEP) in a young, healthy individual, first with intraocular pressure (IOP) of 15 mm Hg and subsequently after its increase to 40 mm Hg. To our surprise, a blockade of neurotransmission occurred on the level of the retinal ganglion cells, whereas PVEPs changed only imperceptibly. This finding did not fit the existing definitions of glaucoma upon breach of the axons of the retinal ganglion cells, with excavation on the optic nerve papilla and changes in the visual field. With the blockade of transmission on the level of the ganglion cells, we had also expected an absent or at least abnormal response of PVEP [13].

Immediately two questions remained unanswered. Why did the retinal ganglion cells not respond, and what happened with the central visual pathway, when following a blockade on the level of the retinal ganglion cells we obtained an almost normal response? How is it possible that the first changes we recorded were not on the level of the axons of the retinal ganglion cells, when this is stated by all the hitherto available definitions of glaucoma?

We found an answer to the first question in the study conducted by Morgan et al., Nakar et al. and others, who studied the retinal cells following an acute increase of IOP. They determined primary changes precisely in the ganglion cells [14,15, 16, 17].

For an electrophysiologist, only one explanation can be provided for the second question, concerning what happened with the visual pathway upon the increase of IOP. Following stabilisation of the binocular functions, the visual cortex is configured for the intake of a certain quantity of action potentials. When it is reduced on any level from the photoreceptors to the cortical cells, it begins to determine the level on which this lesion has occurred by means of feedback processes [18,19,20,21].

Two possibilities exist for the restoration of the quantity of action potentials reaching the brain to their original values. The first is the flooding of a larger quantity of the neurotransmitter, and the second is to leave this neurotransmitter in the synaptic cleft for a longer time. Both possibilities have been experimentally demonstrated in the case of glaucoma. In the vitreous body of glaucomatous eyes of experimental animals, the value of glutamate is up to three times higher in comparison with a control group. These values are toxic both for the layer of the ganglion cells and for the internal plexiform layer [22].

Following an increase of IOP in rats, the GLAST and GS values did not increase until after 3 weeks. The number of ganglion cells within the period of 4-60 days from the increase of IOP decreased by 6 to 44 % [23].

Another significant discovery is the fact that the glutamate transporter may additionally begin to operate in reverse, and transport glutamate and sodium back to the synaptic cleft. The washed out glutamate therefore originates only in small part from the synaptic vesicles, and mostly originates from the cytosol, to where it was previously discharged [24].

Upon the long-term action of glutamate on the non-NMDA receptors, an increase of post-synaptic potential occurs, with the opening of voltage-gated receptors, which under normal conditions are closed by magnesium (Mg), preventing the penetration of Calcium (Ca) into the cell. This takes place in all cells with glutamate receptors. As a result, in glaucoma not only the retinal ganglion cells are damaged, but also the cells in the internal core layer and the layer of the photoreceptors [25]. Upon the binding of glutamate, the NMDA receptor begins to release calcium into the cell. This may have a dual effect on the cell. Under physiological conditions it may provide a signal necessary for the survival of the nerve cell, whereas in pathological states, by contrast, it may have an excitotoxic effect. This is caused by the fact that excessive activation of the glutamate receptors has several harmful impacts on the cell, including reduced capacity to buffer inflowing calcium, to produce oxygen radicals and activate synthesis of nitric oxide, which may lead to a degradation of the cytoskeleton and excessive activation of calcium-dependent enzymes [26].

Excessive flow of Ca into the cell may also generate hypoxia, hypoglycaemia etc. Under these conditions, a raised level of glutamate remains in the synaptic cleft over the long term, in which long-term activation of the NMDA receptors occurs, leading to an increase of intracellular concentrations of Ca to cytotoxic levels. This process is therefore not only typical of glaucomatous damage [27].

For these reasons it is necessary to drain off free cytosolic Ca, which is ensured by the mitochondria and partially also the endoplasmic reticulum. Above all, the mitochondria are important for maintaining a low concentration of cytosolic Ca, and their dysfunction may lead to cell death due to a disruption of homeostasis of Ca, a release of proapoptotic factors or an increase in

the production of oxygen radicals [28].

It is precisely excessive production of oxygen radicals that leads to the onset of oxidative stress, which causes damage to nucleic acids, proteins and lipids, and may lead also to an opening of the mitochondrial channels, which is subsequently the cause of the generation of further oxygen radicals, energy failure and release of proapoptotic factors. Oxidative stress is the main factor of pathological damage to neurons, contributing to acute and chronic damage to the central nervous system in several neurodegenerative diseases [26].

In the case of activation of the signal pathways that lead to the death of a nerve cell, the energy reserves of the cell shall decide on the manner of cell death. If the cell has sufficient energy, a cascade of reactions may be triggered, leading to programmed cell death – apoptosis, in which an alteration of cellular morphology occurs, as well as condensation and fragmentation of DNA, proteolysis of the cytoskeleton and exposure of other antigens on the surface of the cell. The neuron is therefore removed in such a manner as to minimise inflammatory reaction and ease its liquidation for the glial cells. By contrast, if a cell does not have sufficient energy for programmed cell death to occur, it dies by means of necrosis. However, sufficient energy is not decisive only with regard to the manner of cell death, but also regarding whether this occurs at all, because if there is insufficient energy together, a concentration of glutamate which would normally not be excitotoxic may have an excitotoxic effect. This is because the neurons and glial cells removing glutamate from the synapse require a sufficient quantity of energy [29,30,31].

However, neurons are not passive, and prevent excitotoxicity in a number of ways. One of these is the active removal of glutamate from the synapse and Ca from the cytosol. Another mechanism is ensuring a larger energy supply to the nervous system. Defensive hyperpolarisation of neurons also takes place with the aid of potassium channels, the opening of which is triggered by the exhaustion of adenosine triphosphate or an excess of cytosolic Ca. Furthermore, they may increase the synthesis of antioxidant enzymes destroying the oxygen radicals that are generated in excitotoxicity [32].

Whether or not activation of an NMDA receptor leads to excitotoxicity or neuroprotection is most probably influenced, besides the intensity of stimulation, also by its localisation, since NMDA receptors may appear both synaptically and extrasynaptically. It appears that activation of synaptic NMDA receptors has a predominantly neuroprotective effect, whereas activation of extrasynaptic NMDA receptors triggers the signal pathways leading to cell death [33].

The most common ocular pathologies for which a bionic eye is indicated

As indicated above, any lesion of the nerve cells in the visual pathway can damage not only the cellular nerve structures located horizontally, but also vertically. Another significant finding ensuing from this information, as well as from the anatomy of the visual pathways is that a unilateral lesion damages also contralateral nerve structures [34,35,36].

As a result it is also not possible to predict an improvement of visual functions to usable values upon implantation of visual neuroprostheses. It is evident that even despite damaged visual structures, a non-specific electrical impulse can be transmitted to the brain, the content of which is a phosphene or flash perceived by the given person.

Because a bionic eye is most often indicated for patients with pigmentary retinal dystrophy (PRD) and age-related macular degeneration (ARMD), we focus mainly on these two diagnostic groups. The prerequisite for the effectiveness of this system is the preservation of the integrity of the central and internal retinal structures, the visual pathway and the subcortical and cortical centres in the brain [37].

PRD is a disease which primarily affects the rods and cones, as well as the retinal pigment epithelium located beneath them. The internal core, plexiform layer, the ganglion cells and their fibres also succumb to degeneration, and are replaced by gliotic tissue. These changes may not be visible until the later stage of the disease [38]. The electrophysiological findings of sight indicate that, already in the early phases of the disease, not only rods are altered, but also macular retinal structures, including the ganglion cells. As a consequence, damage also occurs to the optic nerve and visual cortex of the brain. The electrophysiological findings were also verified by tractography of the visual pathway [39,40].

In a man aged 63 years with PRD [vision in right eye (VRE): 0.2, vision in left eye (VLE): 0.3, perimeter manifested concentric constriction of the visual fields to ten and five degrees respectively], with the aid of functional magnetic resonance (fMR) and upon such "good" visual functions, we did not record any voxel activity of the visual cortex. An electrophysiological examination demonstrated absence of a response bilaterally, both flash electroretinogram and PERG and PVEP [41]. Similarly, in a man aged 38 years with Usher syndrome (VRE: 0.5, VLE: 0.3), in whom a perimetric examination demonstrated concentric constriction of the visual fields to ten and five degrees respectively, we recorded a pronounced decrease of fMR activity to 950 and 290 voxels respectively [42]. The values in healthy individuals are 9200 ± 2700 activated voxels [34].

In ARMD, damage to the cones leads also to a diminution of the retinal ganglion cells. It has been demonstrated that the number of retinal ganglion cells is significantly lower in ARMD than in eyes in a control group. In wet form ARMD their number was as much as 47 % lower in comparison with a control group [43]. Isolated central retinal lesions such as ARMD also lead to damage to the visual cortex of the brain. With the aid of fMR, we demonstrated a pronounced reduction of voxel activity in ten patients with wet form ARMD in comparison with a control group [44,45].

In hypertensive glaucomas, damage occurs to the retinal ganglion cells and subsequently also to the visual pathway, including the visual centres of the brain [46,47]. Damage is similarly caused also to the lower retinal structure (bipolar cells and photoreceptors) [25].

From these case reports it is evident that retinal malfunction, whether on the level of the photoreceptors or the retinal ganglion cells, leads to damage also to the visual centres in the brain, most markedly in the case of PRD. It is precisely this pathology that is most frequently indicated for implantation of visual neuroprostheses.

BIONIC EYE

At present four bionic eye systems have obtained a permit for introduction onto the European and American market. This advance indicates the endeavour to provide blind patients with genuine and measurable help [48]. In the last quarter of a century, attention has been focused mainly on retinal neuroprostheses with an external energy source. In terms of construction this concerns a system of a small camera placed on the glasses which transmits recorded information to a video chip. This converts the information into electrical changes of voltage and transmits it to a retinal implant composed of a certain number of electrodes which are intended to stimulate the retinal cells. Instead of a camera it is possible to use also photo diodes built directly into the microchip. However, these also require an external energy source. The microchip with electrodes may be implanted epiretinally, subretinally or suprachoroideally. With the aid of a sleeve it is possible to stimulate the optic nerve, corpus geniculatum laterale or the visual cortex directly [49,50].

In 2019 the American neurosurgeon Pouratian referred to the first patient in whom an Orion cortical prosthesis from the Second Sight Medical Products company had been implanted. The author himself states that this prosthesis provides artificial vision, but does not restore vision, which is an important fact [51].

CONCLUSION

In the case of advanced malfunctions of vision acquired after stabilisation of binocular functions, pathologies of neurotransmission in the visual pathway do not enable the effective use of a bionic eye. The perception of phosphenes after successful stimulation does not correspond to standard visual perceptions. As a result, development should focus on other possible solutions.

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