Chapter

Neuropathology in Hypertensive Glaucoma

Jan Lestak and Martin Fůs

Abstract

Hypertensive glaucoma is still defined as a disease where, at high intraocular pressure, retinal ganglion cell axons are impaired with excavation at the optic disc and changes in the visual field. In single cases, the study highlights the importance of knowledge of neuropathology not only at the level of the retina but the entire visual pathway, including the visual centres in the brain. It uses the issue of neurotransmission in the visual analyser and its pathology, but mainly the results of electrophysiological examinations and functional imaging of the brain using Positron Emission Tomography and Functional Magnetic Resonance. It does not overlook the imaging methods of the eye (nerve fibre layer, vessel density). On the basis of this information, therapy is recommended as well.

Keywords: physiology and pathology of neurotransmission in the visual pathway, hypertensive glaucoma, neuropathology, electrophysiology, fMRI, PET, therapy

1. Introduction

For correct and early diagnosis of glaucoma, it is useful to know the processes that occur in the eye during pathological intraocular pressure (IOP). In a chronic condition, when the nerve structures are no longer able to cope with this cause, the process also expands vertically. Subsequently, even following compensation of IOP, the disease progresses. In this study, you will read about the processes explaining the pathology in the entire visual pathway and the treatment options consisting not only of the reduction of IOP.

2. Electrophysiology in the visual analyser

One of the first stimuli that led us to examine glaucomas was the simultaneous measurement of pattern electroretinogram (PERG) and pattern visual evoked potentials (PVEP) in a 20-year-old healthy individual –firstly at IOP of 15 mmHg and then after increasing it to 40 mmHg. To our surprise, neurotransmission was blocked at the retinal ganglion cell level, while PVEPs changed slightly (**Figure 1**). With the blockade of transmission at the level of ganglion cells, we also expected an unequivocal or at least abnormal PVEP response (measurements were performed in 1988). This fact did not fit into the existing definitions of glaucoma regarding retinal ganglion cell axon dysfunction with excavation at the optic disc and changes in the visual field [1, 2].

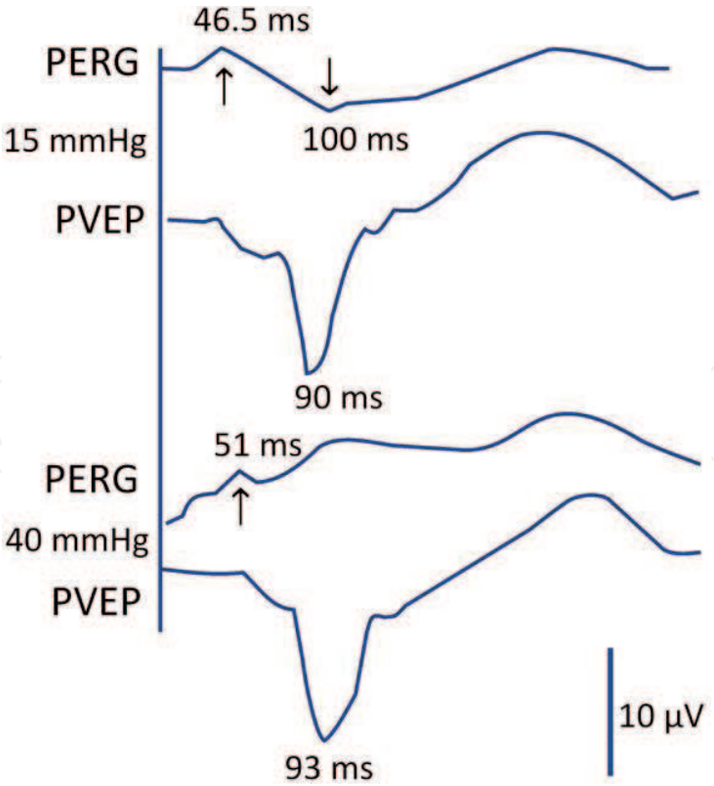

Figure 1.
Upper curve (PERG) and below it PVEP at normal IOP. The arrows indicate the latencies of oscillations, the amplitude of which arises from the responses of retinal ganglion cells. The lower curves - following increase of IOP to 40 mmHg [3].

Therefore, we tried to find an answer to this reaction of the visual analyser. Several questions remained unanswered. Why did the retinal ganglion cells not respond? What happened to the central visual pathway when, following the blockade at the retinal ganglion cell level, we elicited an almost "normal response" from the brain? To an electrophysiologist, there was only one explanation. After stabilisation of binocular functions, the visual cortex is set to receive a certain amount of action potentials. When it is reduced at any level, from photoreceptors to cortical cells of the brain, it begins to stimulate the visual pathway through feedback processes in order to restore their numbers to their original values [4–7].

Before elucidating the above mechanisms, we briefly explain the process of transmitting electrical changes in the visual pathway, from photoreceptors to the visual centres in the brain.

3. Neurotransmission in the visual analyser

After the impact of light on the retina, the cis-retinal chemically changes its outer form in the outer segments of photoreceptors, leading to their hyperpolarisation [8].

Hyperpolarisation of photoreceptors causes the release of glutamate from the presynaptic neuron into the synaptic cleft during synaptic transmission and subsequent binding to receptors located on the membrane of the postsynaptic neuron [9]. Glutamate binds to receptors that have been named after their selective agonists. A typical agonist for NMDA receptors is N-methyl-D-aspartate. For AMPA receptors, α-amino-3-hydroxy-5-methyl-4-8 isoxazole propionate (AMPA), and for the third type, kainate receptors, kainate. AMPA and kainate receptors are also referred to as non-NMDA. NMDA receptors are ion channels permeable to calcium (Ca) ions. The flow of Ca through the NMDA receptors is blocked by magnesium

(Mg) ions at normal membrane potential. This block can be eliminated by strong depolarisation [10, 11]. Excessive flow of Ca into the cell through NMDA voltage-gated channels can cause hypoxia, hypoglycaemia, etc. Under these conditions, glutamate levels in the synaptic cleft remain elevated for a long time, with NMDA receptors being permanently activated, leading to intracellular Ca concentrations that are cytotoxic [12]. The concentration of free glutamate in the synaptic cleft reaches approximately 1.1 mM during the synaptic transmission. However, its concentration decreases rapidly and breaks down at NMDA receptors within 1.2 ms. However, glutamate dissociates much faster from the AMPA receptors. Thus, the time course of free glutamate predicts that dissociation contributes to AMPA receptor-mediated postsynaptic current breakdown. Otherwise, voltage-gated channels would open [9].

In the mammalian central nervous system, glutamate is primarily removed from the synapse by the excitatory amino acid transporter (EAAT) glutamate transporters and the glutamate aspartate transporter (GLAST as a glutamate transporter to Muller cells (MB) and glutamine synthetase (GL) as an enzyme that converts glutamate to glutamine in MB) [13, 14]. In the glial cells (MB), glutamate is subsequently converted to glutamine, which no longer acts as a neurotransmitter and can thus be released back into the synapse, from where it is subsequently taken up by a presynaptic neuron, which converts it back to glutamate [15]. To date, there is no evidence of the presence of an enzyme that converts glutamate directly in the synapse [16].

The glutamate receptors are expressed not only in retinal ganglion cells but also in the photoreceptors, as well as in the horizontal and bipolar cells [17]. Glutamate is the predominant excitatory neurotransmitter, not only in the retina, but also in the mammalian brain [18].

In this way, the processes are clarified that function in the transmission of electrical changes in voltage in the visual path.

4. Efforts to restore the amount of action potentials entering the brain

We have two options for restoring the amount of action potentials entering the brain to their original values. The first is to flush out a larger amount of neurotransmitter at the level of the "damaged" cell, and the second is to leave this neurotransmitter in the synaptic cleft for a longer period of time. Both variants have been experimentally demonstrated in glaucoma.

In the vitreous body of the glaucoma eyes of experimental animals, the value of glutamate was up to three times higher in comparison with the control group. These values are toxic to both the ganglion cell layer and the inner plexiform layer. The GLAST and GS values did not increase until 3 weeks after an increase in IOP in rats. The number of ganglion cells decreased from 4 to 60 days from an increase in IOP to 6 to 44% [19, 20].

Another important discovery is that the glutamate transporter can begin to function in reverse and transfer glutamate and sodium from the cell back to the synaptic cleft. Thus, the flushed glutamate comes only in a small part from the synaptic vesicles; most of it comes from the cytosol, where it was previously pumped to [21].

The long-term action of glutamate on non-NMDA receptors increases the postsynaptic potential and opens up the voltage-bound receptors which are normally closed by Mg, and the entry of Ca into the cell. This process takes place in all cells with glutamate receptors. Therefore, glaucoma damages not only retinal ganglion cells, but also cells in the inner nuclear layer and the photoreceptor layer [22].

Nerve cells do not die immediately following the entrance of Ca into the cells. As mentioned above, their size will first be reduced. If they have a sufficient energy supply, they will cope with this situation. Once the energy is consumed, an apoptotic or necrotic process begins and the cell dies [23].

With regard to the first of the above questions: why did the retinal ganglion cells not respond? - we found the answer in the study of Morgan et al., Naskar et al. and others who experimentally studied retinal cells after an acute increase in IOP. They found primary changes in the ganglion cells [23–26].

What happened to the central visual pathway when, after blockade at the retinal ganglion cell level, we elicited an almost "normal response" from the brain?

If the visual pathway, including the visual cortex, is also involved in the process of hypertensive glaucoma, then we should also find changes in the brain. Standard structural examination techniques do not allow this diagnosis.

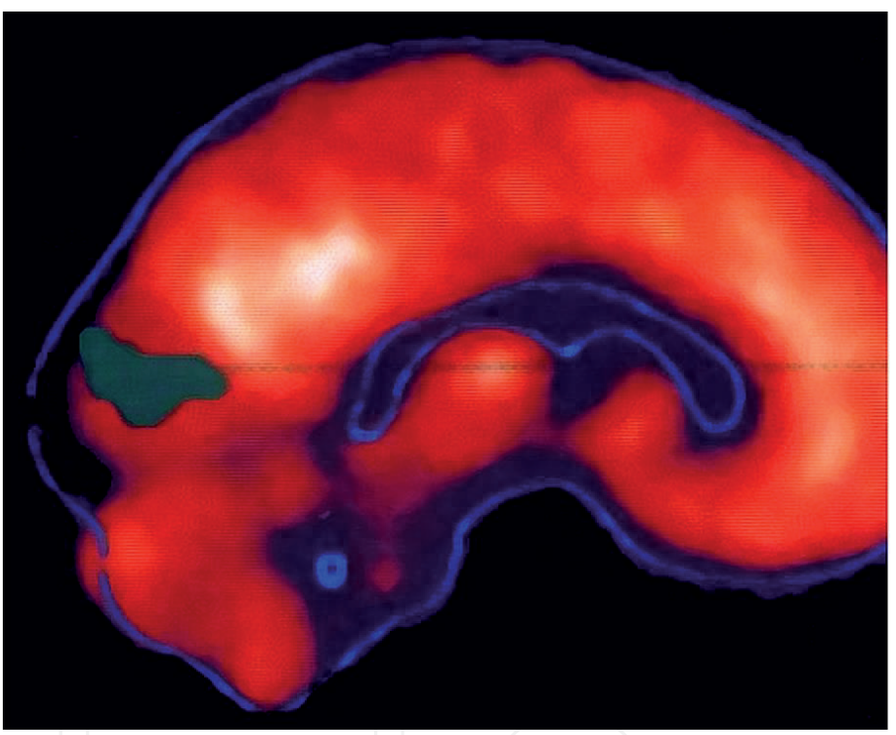

Figure 2.
Sagittal section of the brain of a 58-year-old patient with secondary glaucoma. VOD: 0.05, correct light projection, VOS: 1.0 naturally. c/d = 1.0. The green colour indicates fluorodeoxyglucose deficiency in the visual Centre [27].

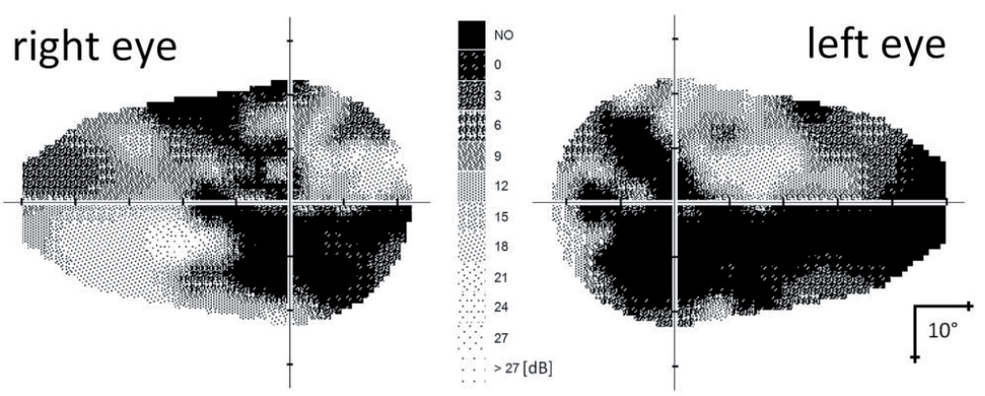

Figure 3.
Field of view of the same patient as in ***Figure 2*** *from the same period [27].*

For this reason, we sought a solution in Positron Emission Tomography. Radioactive glucose (18-fluororodeoxyglucose) is used to examine brain activity, which is taken up in healthy cells. **Figure 2** shows the absence of glucose radioactivity in the occipital lobe and **Figure 3** shows the field of view of the same patient. We performed the examination in 2001.

Because it was necessary to verify this finding in a larger group of patients with HTG and we did not want to burden the patients with radioactive material, we performed the further examination using Functional Magnetic Resonance Imaging (fMRI) on the visual paradigm (**Figure 4**). As an example, we present the result of the fMRI examination in the same patient, in whom we also performed the PET examination **Figure 5**.

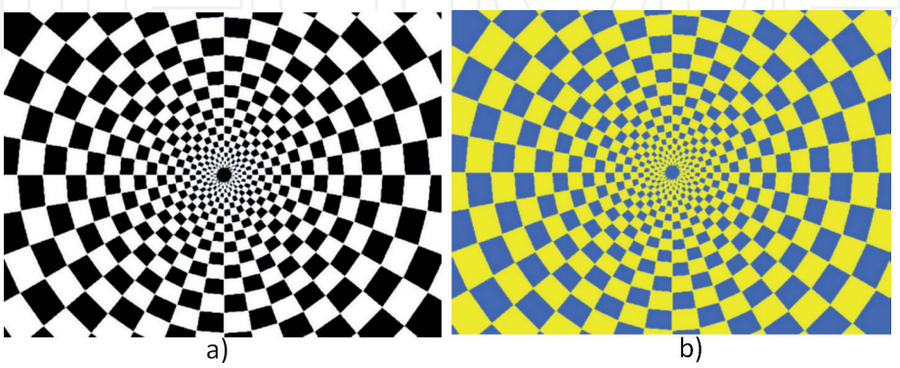

Figure 4.
Chessboard field of black and white stimulation (a) and yellow-blue stimulation (b). During stimulation, the chessboard field alternates with its inversion at a frequency of 2 Hz.

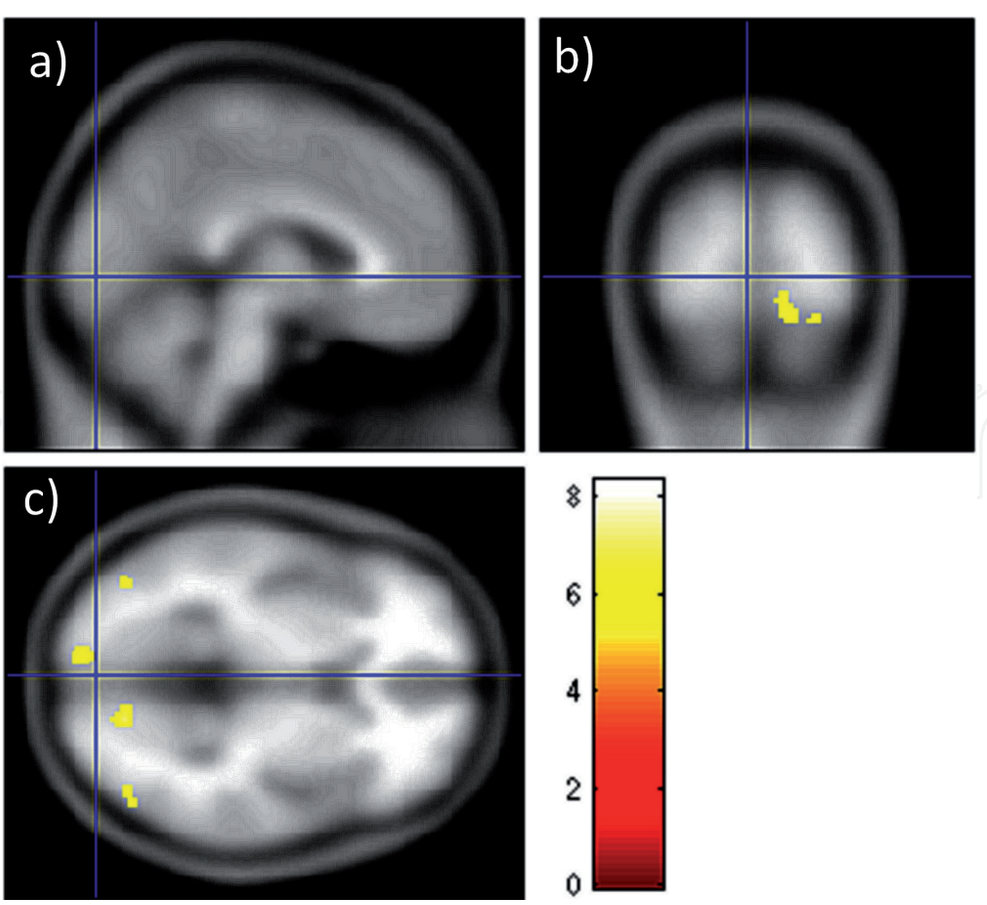

Figure 5.
*Functional magnetic resonance imaging (fMRI) following the visual paradigm of a black and white chessboard in the same patient as in **Figure 2**. We performed the examination in 2010. Sagittal (a), coronary (b) and transverse (c) section [27].*

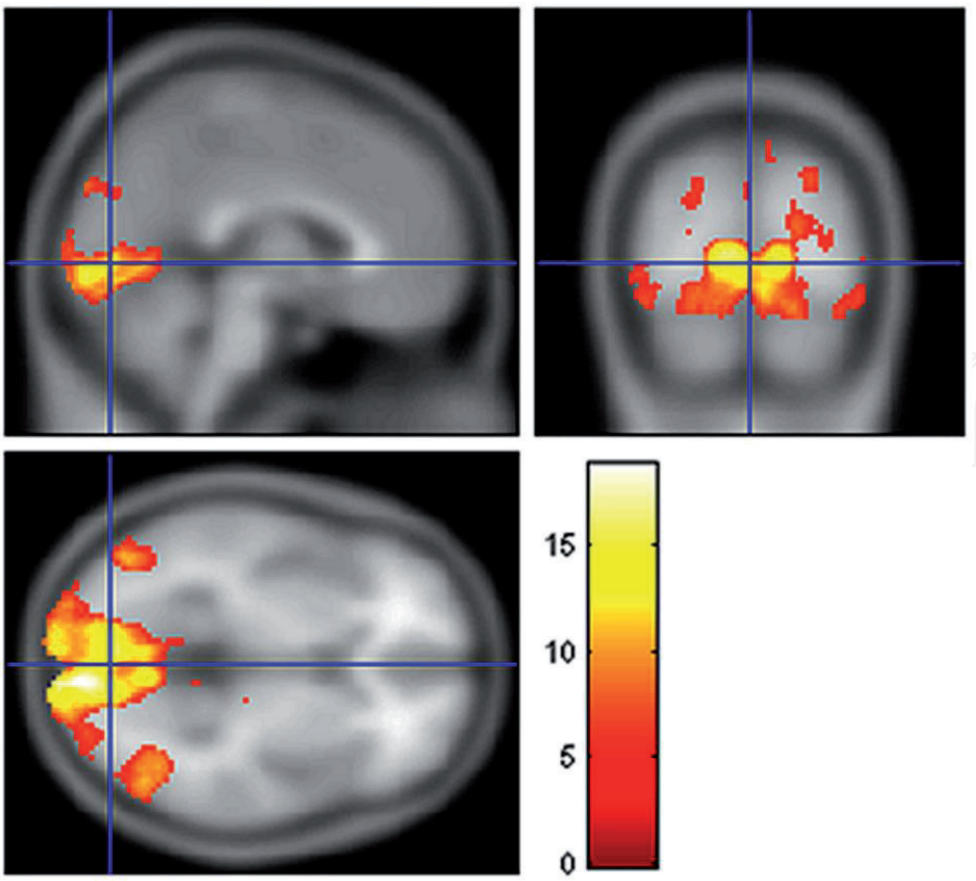

Figure 6.
fMRI in a patient with normotensive glaucoma (61 years), V: 1.0 without correction. c/d = 1 [27].

For comparison, we also present a normal fMRI finding in a patient with normotensive glaucoma (**Figure 6**).

With the use of Positron Emission Tomography and fMRI, we have shown that hypertensive glaucoma also damages the visual centres in the brain. The finding was surprising in patients with HTG following stimulation with both black-white and yellow-blue stimulation, which has not been used in any of the cited work (**Figure 4**). We examined 8 patients with HTG (various stages) and compared their results with the results of 8 healthy people. We found that the difference in the number of activated voxels in patients using black and white versus yellow-blue stimulation was 59%. It was only 2% in a control group. We consider that the ganglion cell damage will be greater than normally expected [27].

5. Electrophysiology in hypertensive glaucoma

We now return to electrophysiological eye examinations.

In experimental glaucoma, electroretinographic changes (decrease in amplitudes of up to 50%) preceded changes in the retinal nerve fibre layer [28].

These facts, as well as the conclusions of other authors, [29–31] led us to use the electrophysiological methods (PERG and PVEP) to determine the level and depth of damage in various types of hypertensive glaucoma. Based on these examinations, we concluded that the changes in PERG and PVEP in HTG indicate that not only the retinal ganglion cells and subsequently their axons, but also the visual centres in the brain are damaged [32].

At the neuronal membrane level, the relationship between the two neurotransmitter systems is supported by the direct inhibition of the NMDA receptor by

dopamine and the inhibitory effect of glutamate on dopamine release. This means that a higher dopamine level blocks the NMDA receptor and, conversely, glutamate blocks the release of dopamine [33, 34].

To verify this biochemical information, we used the examination of the oscillating potentials of the electroretinogram. Amacrine cells are divided into dopaminergic and GABAergic according to the neurotransmitter. Dopaminergic cells generate oscillating potentials in the electroretinogram, and GABAergic cells participate in the formation of the threshold scotopic potential [35].

We performed the examination in 2001 on a Primus device (Lacce Elettronica) according to the ISCEV methodology (1989). After a 30-minute adaptation to darkness, we examined the oscillating potentials. Retinal stimulation in artificial mydriasis (tropicamide) was performed with a 5 ms flash light with a luminous flux of 2.5 cd/m^2/s. An average of 10 responses (stimuli after 15 seconds) were averaged, using 80 to 500 Hz filters. We evaluated latency and amplitude of the P2 oscillation.

The first group consisted of 23 eyes of healthy people. In the second group, there were 36 glaucoma eyes with incipient changes in visual field with compensated IOP. Persons included in the groups had an average age of 40.3 years (35–56). The results showed a statistically significant prolongation of the latency of the P2 oscillation ($p = 0.049$) and a reduction of the amplitude of the P2 oscillation ($p = 0.001$) in the glaucoma eyes, compared to the healthy group. In this way, we indirectly demonstrated increased levels of glutamate in glaucoma eyes.

We were also interested in how retinal ganglion cells (PERG) will behave when adjusting antiglaucoma treatment, and subsequently the whole visual analyser (PVEP). We performed PERG and PVEP examinations (according to the ISCEV - 2012 methodology on the Roland Consult Germany device) in a patient (64 years old)

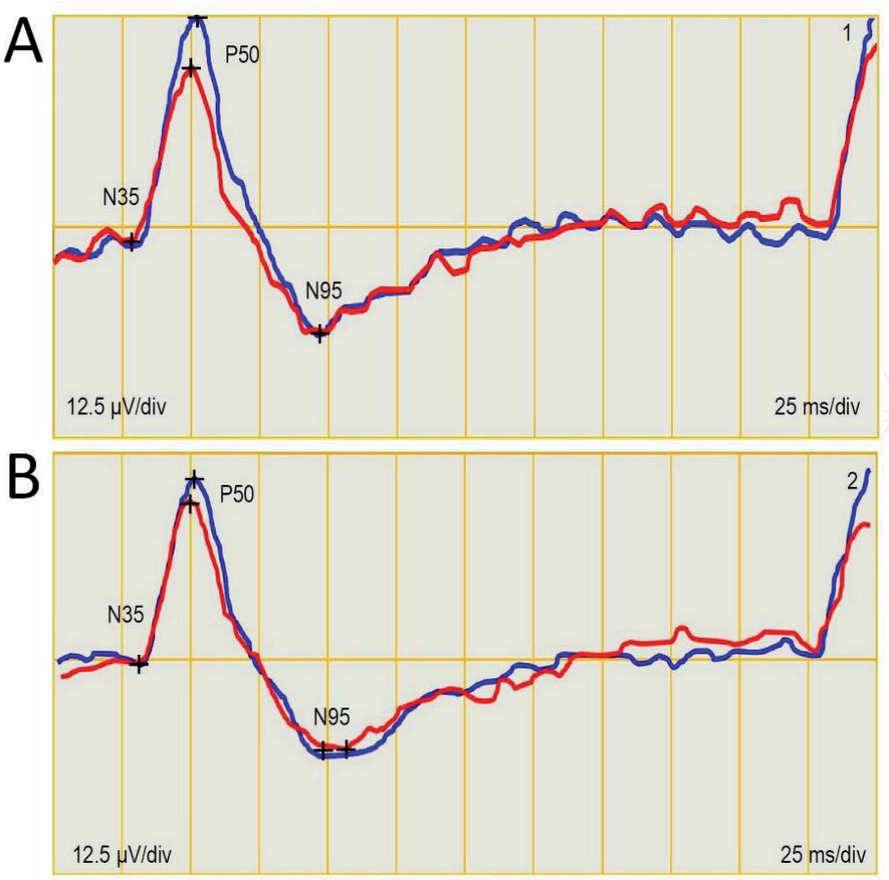

Figure 7.
PERG before discontinuation (blue curve) and after discontinuation of antiglaucoma medications (red curve). Right eye (A), left eye (B).

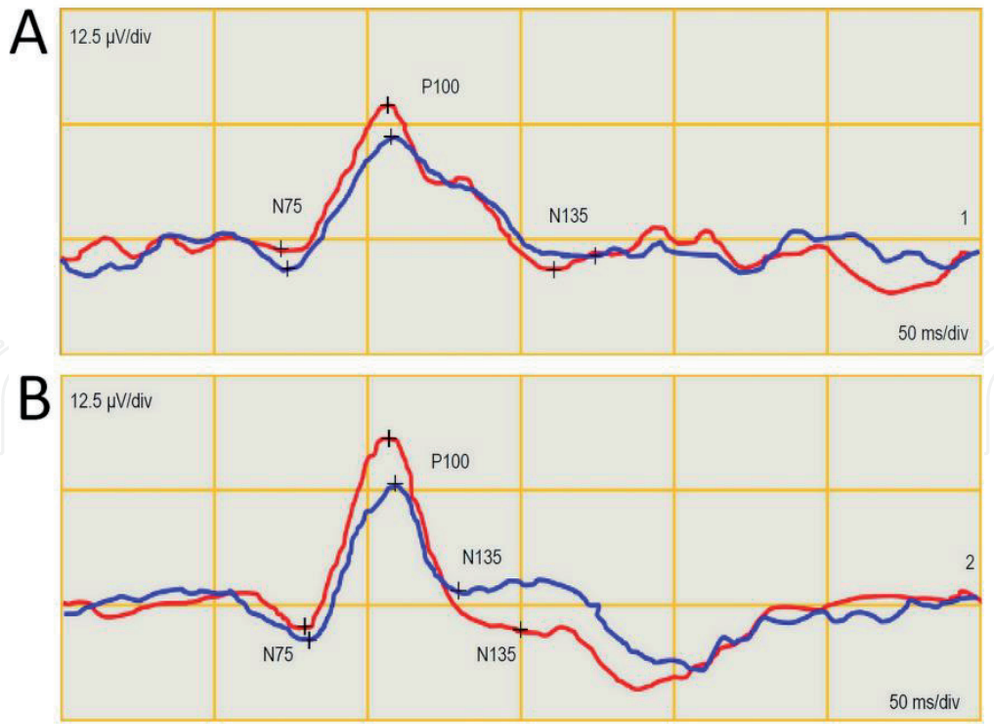

Figure 8.
PVEP before discontinuation (blue curve) and following discontinuation of antiglaucoma medicines (red curve). Following stimulation of the right eye (A) and left eye (B).

with glaucoma, compensated by Cosopt and Lumigan to IOP of 18/18 mmHg. The perimeter was normal in this patient, c/d = 0.4 and GDX 11/20. Due to these values, we repeated the examination one month after discontinuation of both antiglaucoma medicines. IOP increased to 23/29 mmHg. The amplitude of the PERG oscillations P50 and N95 decreased by 3.2uV and 1.1uV, respectively, after discontinuation of the medications (**Figure 7**), and conversely, it was increased in PVEP by 1.4 and 4.7uV, respectively (**Figure 8**).

This finding also indicates an alteration of the retinal ganglion cells and, conversely, a potentiation of the visual pathway by glutamate [36].

Because, even with compensated IOP, the amount of action potentials is reduced due to the loss of cells involved in the processing of electrical changes in the visual pathway, these cells are "bombarded" by feedback mechanisms to a higher response. Excessive flushing and reduced resorption of glutamate from the synaptic cleft increases the postsynaptic potential. Subsequently, the voltage-gated channels for the entry of Ca into the cells are unblocked and the whole process progresses. As the disease progresses, the response to flushing of more neurotransmitters is higher. We also confirmed this in our study, where we monitored the progression of changes in the visual fields in compensated glaucoma eyes over a 5-year period. We found that the greater the baseline perimeter changes were, the greater was their progression in 5 years [37].

6. The role of vascular supply of the posterior pole of the eye in hypertensive glaucoma

Another issue is that of the vascular supply to the posterior pole of the eye and its relationship to the retinal nerve fibre layer (RNFL). We also investigated the relationship between RNFL, vessel density (VD) and visual field (VF) in HTG. The results showed a moderate correlation between RNFL and VD in the same

altitudinal halves of the retina. We did not find any dependence between RNFL and VF [38]. When we compared VD from the whole measured area to the sum of sensitivities in the central part of the visual field (0–22 degrees), we found a strong correlation (0.64–0.65) [39].

The relationship of VD in different stages of HTG was also studied by other authors. They all found that, with the progression of glaucoma, a reduction in VD occurs [40–45].

The IOP value also plays an important role in the value of VD. By decreasing IOP in young individuals with high IOP, Holló noted an increase in VD [46]. Conversely, after its increase above 20 mmHg, the vascular density (VD) in the macula and peripapillary decreased significantly [47].

Another important fact is the finding that glutamate can also affect blood vessels of the posterior pole of the eye. Tsuda et al. studied the effect of intravitreal NMDA in an experiment and found that NMDA induced retinal vessel loss. After blocking NMDA with nafamostat mesylate, there was a significantly lower loss of these vessels [48].

This means that, even after compensation of the IOP, the progression of changes in HTG may occur, as through the feedback, glutamate constantly bombards the neurons which have receptors for this neurotransmitter. And merely the high levels of glutamate can cause ischaemia in the eye [4–7].

Already in 1974, Hayreh [49] summarised the pathogenesis of optic disc excavation as three factors that are probably the most responsible for this abnormality:

1. Destruction of the nerve tissue in the prelaminar area;

2. Distortion of the cribriform plate (lamina cribriformis) rearwards that occurs due to retrolaminar fibrosis and a lack of normal support in the back part of the lamina due to its loss;

3. Weakening of the cribriform plate. These changes, however, are not characteristic only for optic disc glaucoma atrophy, but also have other (mainly vascular) causes.

Notwithstanding these conclusions, it is also worth noting that some local antiglaucoma medicines may lead to the progression of changes in visual fields, even following a decrease in IOP [50].

Based on this knowledge, effective antiglaucoma treatment is also offered. We emphasise the reduction of IOP in the first place. We draw attention to the unsuitability of antiglaucoma medications which can cause ischaemia of the posterior pole of the eye. This is followed by a reduction in glutamate in the synaptic cleft and blockade of its binding to NMDA receptors. The supply of energy substrates to altered nerve cells is also suitable. Because the entire visual pathway is damaged, this treatment should be systemic.

7. Conclusion

In hypertensive glaucomas, the entire visual pathway is damaged. Therefore, early diagnosis of this disease is important. Treatment should consist not only of the reduction of IOP, but also of reducing the levels of glutamate in the synaptic cleft and their binding to glutamate receptors. An important element of treatment is the supply of energy substrate to nerve cells with the ability to cope with intracellular processes. This therapy should be systemic.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-8 isoxazolpropionate c/d, cup/disc ratio
CGL	corpus geniculatum laterale (lateral geniculate body)
EEAT	excitatory amino acid transporter
FMRI	functional magnetic resonance imaging
GS	glutamine synthetase
GLAST	glutamate aspartate transporter
HTG	hypertensive glaucoma;
IOP	intraocular pressure
NMDA	N-methyl-D-aspartate
MB	Muller cells
PERG	pattern electroretinogram
PET	positron emission tomography
PVEP	pattern visual evoked potential
RNFL	retinal nerve fibre layer
VD	vessel density

Author details

Jan Lestak[1,2*] and Martin Fůs[1]

1 Eye Clinic JL Faculty of Biomedical Engineering Czech Technical University in Prague, Prague, Czech Republic

2 Faculty of Biomedical Engineering, CTU in Prague, Kladno, Czech Republic

*Address all correspondence to: lestak@seznam.cz

References

[1] Lešták J, Tintěra J, Kynčl M, Svatá Z. Rozsíval P: High Tension Glaucoma and Normal Tension Glaucoma in Brain MRI J Clin Exp Ophthalmol 2013, 4: 4 DOI:10.4172/2155-9570.1000291.

[2] Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014 Nov;121(11):2081-90. DOI: 10.1016/j.ophtha.2014.05.013. Epub 2014 Jun 26. PMID: 24974815.

[3] Lešták J, Tintěra J, Kynčl M, Svatá Z. Rozsíval P: High Tension Glaucoma and Normal Tension Glaucoma in Brain MRI. J Clin Exp Ophthalmol 2013, 4:4 DOI: 10.4172/2155-9570.1000291.

[4] Sherman SM, Guillery RW. Exploring the Thalamus and Its Role in Cortical Function. 2nd Ed MIT Press; Boston: 2006.

[5] Shou TD. The functional roles of feedback projections in the visual system. Neurosci Bull. 2010 Oct;26(5):401-10. doi: 10.1007/s12264-010-0521-3. PMID: 20882067; PMCID: PMC5560353.

[6] Briggs F, Usrey WM. Corticogeniculate feedback and visual processing in the primate. J Physiol. 2011 Jan 1;589(Pt 1):33-40. doi: 10.1113/jphysiol.2010.193599. Epub 2010 Aug 19. PMID: 20724361; PMCID: PMC3039257.

[7] Thompson AD, Picard N, Min L, Fagiolini M, Chen C. Cortical Feedback Regulates Feedforward Retinogeniculate Refinement. Neuron. 2016 Sep 7;91(5):1021-1033. doi: 10.1016/j.neuron.2016.07.040. Epub 2016 Aug 18. PMID: 27545712; PMCID: PMC5156570.

[8] Kiser PD, Golczak M, Maeda A, Palczewski K. Key enzymes of the retinoid (visual) cycle in vertebrate retina. Biochim Biophys Acta. 2012 Jan;1821(1):137-51. doi: 10.1016/j.bbalip.2011.03.005. Epub 2011 Apr 5. PMID: 21447403; PMCID: PMC3158816.

[9] Clements JD, Lester RA, Tong G, Jahr CE, Westbrook GL. The time course of glutamate in the synaptic cleft. Science. 1992 Nov 27;258(5087):1498-501. doi: 10.1126/science.1359647. PMID: 1359647.

[10] Kew JN, Kemp JA. Ionotropic and metabotropic glutamate receptor structure and pharmacology. Psychopharmacology (Berl). 2005 Apr;179(1):4-29. doi: 10.1007/s00213-005-2200-z. Epub 2005 Feb 25. Erratum in: Psychopharmacology (Berl). 2005 Oct;182(2):320. PMID: 15731895.

[11] Johnson JW, Ascher P. Voltage-dependent block by intracellular Mg2+ of N-methyl-D-aspartate-activated channels. Biophys J. 1990 May;57(5):1085-90. doi: 10.1016/S0006-3495(90)82626-6. PMID: 1692749; PMCID: PMC1280813.

[12] Choi DW, Koh JY, Peters S. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. J Neurosci. 1988 Jan;8(1):185-96. doi: 10.1523/JNEUROSCI.08-01-00185.1988. PMID: 2892896; PMCID: PMC6569373.

[13] Rothstein JD, Martin L, Levey AI, Dykes-Hoberg M, Jin L, Wu D, Nash N, Kuncl RW. Localization of neuronal and glial glutamate transporters. Neuron. 1994 Sep;13(3):713-25. doi: 10.1016/0896-6273(94)90038-8. PMID: 7917301.

[14] Amara SG, Fontana AC. Excitatory amino acid transporters: keeping up with glutamate. Neurochem Int. 2002 Nov;41(5):313-8. doi: 10.1016/s0197-0186(02)00018-9. PMID: 12176072.

[15] Danbolt NC. Glutamate uptake. Prog Neurobiol. 2001 Sep;65(1):1-105. doi: 10.1016/s0301-0082(00)00067-8. PMID: 11369436.

[16] Huang YH, Bergles DE. Glutamate transporters bring competition to the synapse. Curr Opin Neurobiol. 2004 Jun;14(3):346-52. doi: 10.1016/j.conb.2004.05.007. PMID: 15194115.

[17] Shen Y, Liu XL, Yang XL. N-methyl-D-aspartate receptors in the retina. Mol Neurobiol. 2006;34:163-179. doi: 10.1385/MN:34:3:163.

[18] Olney JW, Sharpe LG. Brain lesions in an infant rhesus monkey treated with monsodium glutamate. Science. 1969 Oct 17;166(3903):386-8. doi: 10.1126/science.166.3903.386. PMID: 5812037.

[19] Vorwerk CK, Naskar R, Dreyer EB. Die exzitotoxische Hypothese der Glaukomgenese [The excitotoxicity theory of glaucoma]. Klin Monbl Augenheilkd. 1999 Jan;214(1):2-11. German. doi: 10.1055/s-2008-1034740. PMID: 10198875.

[20] Woldemussie E, Wijono M, Ruiz G. Müller cell response to laser-induced increase in intraocular pressure in rats. Glia. 2004 Aug 1;47(2):109-19. doi: 10.1002/glia.20000. PMID: 15185390.

[21] Grewer C, Gameiro A, Zhang Z, Tao Z, Braams S, Rauen T. Glutamate forward and reverse transport: from molecular mechanism to transporter-mediated release after ischemia. IUBMB Life. 2008 Sep;60(9):609-19. doi: 10.1002/iub.98. PMID: 18543277; PMCID: PMC2632779.

[22] Pavlidis M, Stupp T, Naskar R, Cengiz C, Thanos S. Retinal ganglion cells resistant to advanced glaucoma: a postmortem study of human retinas with the carbocyanine dye DiI. Invest Ophthalmol Vis Sci. 2003 Dec;44(12):5196-205. doi: 10.1167/iovs.03-0614. PMID: 14638717.

[23] Shou T, Liu J, Wang W, Zhou Y, Zhao K. Differential dendritic shrinkage of alpha and beta retinal ganglion cells in cats with chronic glaucoma. Invest Ophthalmol Vis Sci. 2003 Jul;44(7):3005-10. doi: 10.1167/iovs.02-0620. PMID: 12824245.

[24] Morgan JE, Uchida H, Caprioli J. Retinal ganglion cell death in experimental glaucoma. Br J Ophthalmol. 2000 Mar;84(3):303-10. doi: 10.1136/bjo.84.3.303. PMID: 10684843; PMCID: PMC1723413.

[25] Naskar R, Wissing M, Thanos S. Detection of early neuron degeneration and accompanying microglial responses in the retina of a rat model of glaucoma. Invest Ophthalmol Vis Sci. 2002 Sep;43(9):2962-8. PMID: 12202516.

[26] Soto I, Oglesby E, Buckingham BP, Son JL, Roberson ED, Steele MR, Inman DM, Vetter ML, Horner PJ, Marsh-Armstrong N. Retinal ganglion cells downregulate gene expression and lose their axons within the optic nerve head in a mouse glaucoma model. J Neurosci. 2008 Jan 9;28(2):548-61. doi: 10.1523/JNEUROSCI.3714-07.2008. PMID: 18184797; PMCID: PMC6670511.

[27] Lestak J, Tintera J, Svata Z, Ettler L, Rozsival P. Glaucoma and CNS. Comparison of fMRI results in high tension and normal tension glaucoma. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014;158(1):144-53. doi: 10.5507/bp.2013.038. Epub 2013 Jun 4. PMID: 23733146.

[28] Fortune B, Bui BV, Morrison JC, Johnson EC, Dong J, Cepurna WO, Jia L, Barber S, Cioffi GA. Selective ganglion cell functional loss in rats with experimental glaucoma. Invest Ophthalmol Vis Sci. 2004 Jun;45(6):1854-62. doi: 10.1167/iovs.03-1411. PMID: 15161850.

[29] Holder GE. Pattern electroretinography (PERG) and an

integrated approach to visual pathway diagnosis. Prog Retin Eye Res. 2001 Jul;20(4):531-61. doi: 10.1016/s1350-9462(00)00030-6. PMID: 11390258.

[30] Parisi V, Miglior S, Manni G, Centofanti M, Bucci MG. Clinical ability of pattern electroretinograms and visual evoked potentials in detecting visual dysfunction in ocular hypertension and glaucoma. Ophthalmology. 2006 Feb;113(2):216-28. doi: 10.1016/j.ophtha.2005.10.044. Epub 2006 Jan 10. PMID: 16406535.

[31] NEBBIOSO, Marcella, Fabio De GREGORIO, Laura PRENCIPE a Irene PECORELLA. Psychophysical and Electrophysiological Testing in Ocular Hypertension. Optometry and Vision Science [online]. 2011, 88(8), E928-E939 [cit. 2020-12-30]. ISSN 1040-5488. Dostupné z: doi:10.1097/OPX.0b013e31821c6ca4

[32] Lešťák, J., Nutterová, E., Pitrová, Š., Krejčová, H., Bartošová, L., Forgáčová, V.: High tension versus normal tension glaucoma. A comparison of structural and functional examinations. J Clinic Exp Ophthalmol 2012, S:5, doi: 10.4172/2155-9570.S5-006.

[33] Castro NG, de Mello MC, de Mello FG, Aracava Y. Direct inhibition of the N-methyl-D-aspartate receptor channel by dopamine and (+)-SKF38393. Br J Pharmacol. 1999 Apr;126(8):1847-55. doi: 10.1038/sj.bjp.0702479. PMID: 10372829; PMCID: PMC1565957.

[34] Wu Y, Pearl SM, Zigmond MJ, Michael AC. Inhibitory glutamatergic regulation of evoked dopamine release in striatum. Neuroscience. 2000;96(1):65-72. doi: 10.1016/s0306-4522(99)00539-4. PMID: 10683411.

[35] Kaneko M, Sugawara T, Tazawa Y. [Electrical responses from the inner retina of rats with streptozotocin-induced early diabetes mellitus]. Nippon Ganka Gakkai Zasshi. 2000 Nov;104(11):775-8. Japanese. PMID: 11530366.

[36] Lestak J, Fus M: Neuroprotection in glaucoma – a review of electrophysiologist. Exp Ther Med. 2020 Apr;19(4):2401-2405. doi: 10.3892/etm.2020.8509. Epub 2020 Feb 10

[37] Lešťák, J., Rozsíval, P.: The Influence of Corneal Thickness on Progression of Hypertensive Glaucoma. J Clin Exp Ophthalmol 2012, 3:8, doi: 10.4172/2155-9570.1000245.

[38] Zakova M, Lestak J, Fus M, Maresova K. OCT angiography and visual field in hypertensive and normotensive glaucomas. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.2020, 164, DOI: 10.5507/bp.2020.044

[39] Lešťák J, Fůs M, Benda A, Marešová K. OCT ANGIOGRAPHY AND DOPPLER SONOGRAPHY IN NORMAL-TENSION GLAUCOMA. Ceska a Slovenska Oftalmologie: Casopis Ceske Oftalmologicke Spolecnosti a Slovenske Oftalmologicke Spolecnosti. 2020 ;76(3):120-123. DOI: 10.31348/2020/20.

[40] Mammo Z, Heisler M, Balaratnasingam C, et al. Quantitative Optical Coherence Tomography Angiography of Radial Peripapillary Capillaries in Glaucoma, Glaucoma Suspect, and Normal Eyes. Am J Ophthalmol. 2016;170:41-49.

[41] Yarmohammadi A, Zangwill LM, Diniz-Filho A, Suh MH, Yousefi S, Saunders LJ, Belghith A, Manalastas PI, Medeiros FA, Weinreb RN. Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma. Ophthalmology. 2016 Dec;123(12):2498-2508.

[42] Hou H, Moghimi S, Zangwill LM, Shoji T, Ghahari E, Manalastas PIC,

Penteado RC, Weinreb RN. Inter-eye Asymmetry of Optical Coherence Tomography Angiography Vessel Density in Bilateral Glaucoma, Glaucoma Suspect, and Healthy Eyes. Am J Ophthalmol. 2018;190:69-77.

[43] Hollo G. Comparison of Peripapillary OCT Angiography Vessel Density and Retinal Nerve Fiber Layer Thickness Measurements for Their Ability to Detect Progression in Glaucoma. J Glaucoma. 2018;27:302-305.

[44] Penteado RC, Zangwill LM, Daga FB, Saunders LJ, Manalastas PIC, Shoji T, Akagi T, Christopher M, Yarmohammadi A, Moghimi S, Weinreb RN. Optical Coherence Tomography Angiography Macular Vascular Density Measurements and the Central 10-2 Visual Field in Glaucoma. J Glaucoma. 2018;27:481-489.

[45] Mangouritsas G, Koutropoulou N, Ragkousis A, Boutouri E, Diagourtas A. Peripapillary Vessel Density In Unilateral Preperimetric Glaucoma. Clin Ophthalmol. 2019;13:2511-2519. doi: 10.2147/OPTH.S224757.

[46] Holló G. Influence of Large Intraocular Pressure Reduction on Peripapillary OCT Vessel Density in Ocular Hypertensive and Glaucoma Eyes. J Glaucoma. 2017 Jan;26(1):e7-e10. doi: 10.1097/IJG.0000000000000527.

[47] Ma ZW, Qiu WH, Zhou DN, Yang WH, Pan XF, Chen H. Changes in vessel density of the patients with narrow antenior chamber after an acute intraocular pressure elevation observed by OCT angiography. BMC Ophthalmol. 2019 Jun 21;19(1):132. doi: 10.1186/s12886-019-1146-6

[48] Uchiba M, Okajima K, Murakami K, Okabe H, Takatsuki K. Effect of nafamostat mesilate on pulmonary vascular injury induced by lipopolysaccharide in rats. Am J Respir Crit Care Med. 1997 Feb;155(2):711-8. doi: 10.1164/ajrccm.155.2.9032217. PMID: 9032217.

[49] Hayreh SS. Pathogenesis of cupping of the optic disc. Br J Ophthalmol. 1974 Oct;58(10):863-76. doi: 10.1136/bjo.58.10.863. PMID: 4375487; PMCID: PMC1215042.

[50] Maresova K, Lestak J, Fus M, Weisova, Effect of prostaglandins and beta blockers on progression of hypertensive and normotensive glaucoma. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2020 Mar 26. doi: 10.5507/bp.2020.011