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Abstract

From the results of various experiments in an attempt to investigate the relationship between the intraocular pressure and the ophthalmic nerve, the author has come to the conclusion that the ophathalmic nerve is one of the afferent pathways transmitting the various impulses caused by the changes in the intraocular pressure to the autonomic eye pressure center, and the impulses created by these stimuli in the eye pressure center are in turn transmitted to the eyeball by way of the autonomic nerves and thus the eye pressure is autonomically regulated by these reflexes.

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STUDIES ON THE ETIOLOGY OF GLAUCOMA PART 3. STUDIES ON THE EFFERENT AND AFFERENT PATHWAYS OF AUTONOMIC EYE-PRESSURE ADJUSTMENT REFLEX

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In previous reports, it has been demonstrated that the diencephalon is the site at which the eye pressure is regulated. However, the efferent tracts actually carrying the impulses of the adjustment center of eye pressure to the eyeball and the afferent tracts transmitting the variations of intraocular pressure to the center regulating eye pressure still remain to be solved. With a view to clarify these, the author conducted the present experiment.

A. STUDIES ON THE EFFERENT PATHWAYS OF EYE PRESSURE REFLEX.

As is well known, many autonomic functions such as blood pressure, pupillary activity, body temperature, pulsations, and respiratory rate, gastric and intestinal motility are regulated by the autonomic nervous system. This being so, for the clarification of the mechanism of autonomic eye pressure reflex, the autonomic nervous system seems to be the first point of approach.

EXPERIMENTS AND RESULTS

1. The relation between eye pressure and sympathetic nerve[10].

Among the literatures concerning this problem, there are reports by such investigator as HENDERSON a. STARLING[1], ADAMÜCK[2], WESSELY[3], STOCK[4], YADA[5], COLLE a. DUKE-ELDER[6], JAFFE[7], DAVSON a. MATCHETT[8], GREAVES a. PERKINS[9] and others, but their results do not necessarily concur with each other. Therefore, with an intention to re-examine this point, observations were made on the changes in the intraocular and the systemic blood pressures and on the behavioral patterns of pupils and exophthalmus by stimulating the cervical sympathetic nerve electrically under various conditions. All the experiments were carried on normal adult rabbits. In the following the results are described dividing into 4

Table 1

No. of rabbit	Sex	Intensity of stimulus	Duration of stimulation	Mydriasis	Exopththal-mos	Eye pressure (mm.Hg)			Blood pressure (mm.Hg)		
						Initial	Min. or max.	Differ-ence	Initial	Min. or max.	Differ-ence
1	♂	Weak	27	+	±	29	26	−3.0	90	80	−10
2	♀	〃	10	−	−	31	29	−2.0	80	65	−15
3	〃	〃	25	−	−	24	22	−2.0	79	63	−16
4	♂	〃	3	−	−	26	24.5	−1.5	77	65	−12
5	〃	〃	10	−	±	22	21	−1.0	90	76	−14
6	〃	Strong	20	+	+	28	29	+1.0	90	60	−30
7	〃	〃	10	+	±	25.5	26	+0.5	88	64	−22
11	♀	〃	10	+	+	18	19	+1.0	76	57	−19
12	♂	〃	10	+	−	30	28	−2.0	98	75	−23
14	♀	〃	15	±	+	25	25.5	+0.5	83	65	−18
15	〃	〃	10	−	−	27	24.5	−2.5	102	88	−14
16	〃	〃	15	±	−	21	18.0	−3.0	93	75	−18

min.: minimum, max.: maximum

Table 2

No. of rabbit	Sex	Intensity of stimulus	Duration of stimuation	Mydriasis	Exophthal-mos	Eye pressure (mm.Hg)			Blood pressure (mm.Hg)		
						Initial	Min. or max.	Differ-ence	Initial	Min. or Max.	Differ-ence
3	♀	Weak	25	—	—	24	24	0	82	64	−18
4	♂	〃	3	—	—	26	26	0	75	65	−10
6	〃	〃	20	—	—	29	28.5	−0.5	82	63	−19
7	〃	Strong	10	—	—	26	25.5	−0.5	87	75	−12
10	♀	〃	15	—	—	23	23	0	90	78	−12
11	〃	〃	10	—	—	18.5	18.5	0	73	56	−19
12	♂	〃	10	—	—	29	28	−1.0	99	77	−22
14	♀	〃	15	—	—	25	24.5	−0.5	83	62	−21
15	〃	〃	10	—	—	25	25	0	100	85	−15
16	〃	〃	15	—	—	19	19	0	92	79	−13

sections.

i. Relationship between the stimulation in sympathetic nerve and the eye pressure.

As showns in Table 1, the results on the 12 rabbits differ somewhat according the changed intensity of stimuli. In cases of weak stimulation, the eye and the systemic blood pressures decreased as a rule, but in the majority of them mydriasis or exophthalmus could not be found. On the other hand, in the cases of strong stimulation the eye pressure either decreased or increased although systemic blood pressure fell in all cases. In the cases showing an increase in both blood pressure and eye pressure, marked mydriasis and exophthalmus were generally recognized.

ii. The relationship between the stimulation of sympathetic nerve and the intraocular pressure on the unstimulated side.

In order to confirm whether or not the changes of eye pressure occurring at the time of the stimulation of cervical sympathetic nerve are effected by the changes of the systemic blood pressure, the changes of the eye pressure on the unstimulated side have been investigated at the time of unilateral stimulation of cervical sympathetic nerve. As shown in Table 2, the intraocular pressure of the eye on the unstimulated side showed little or no change, and even in the cases showing a slight decrease, the decreasing grade was far less comparing to those on the stimulated side. Therefore, the fall of the eye pressure at the time of the stimulation of cervical sympathetic nerve seems to be not effected solely by the changes of systemic blood pressure.

iii. The effects of the resection of cervical sympathetic nerve on the eye pressure.

The resection of cervical sympathetic nerve, including superior cervical ganglion, caused the rise in both the intraocular and the systemic blood pressures (Table 3).

iv. Influences of the resection of cervical sympathetic nerve on the rise of the eye pressure caused by the compression of jugular vein.

By a mechanical compression of jugular vein, the eye pressure usually tends to rise; and the rate of the rise in the case of the rabbits with prior resection of cervical symathetic nerve is more marked than that of the untreated ones (Table 4). This fact seems to suggest that the cervical sympathetic nerve possesses the functions inhibiting abnormal rise of the eye pressure.

Table 3

No. of rabbit	Sex	Eye pressure (mm.Hg)			Blood pressure (mm.Hg)		
		Initial	Min. or max.	Difference	Initial	Min. or max.	Difference
6	♂	28	28	0	81	95	+14
10	♀	26	29	+3.0	92	103	+11
12	♂	28	30	+2.0	91	83→100	+ 9
24	〃	16.5	16.5	0	98	103	+ 4
25	〃	29	28.5→33	+4.0	109	82→106	− 3

Table 4

No. of rabbit	Sex	Eye pressure of nomal animals (mm.Hg)			Eye pressure of animals resected their cervical sympathetic nerves (mm.Hg)		
		Initial pressure	Vriation of eye pressure	Difference	Initial pressure	Variation of eye pressure	Difference
23	♀	19	19.5	+0.5	21	23.5	+2.5
24	♂	21.5	22.0	+0.5	23	27.0	+4.0
25	〃	24.5	24.5	0	26	34.0	+8.0
26	♀	29.0	29.5	+0.5	30	33.5	+3.5
27	〃	24.0	24.0	0	27.5	27.5	+1.5

Summarizing these results, it will be said that the excitation of the cervical sympathetic nerve seems to serve essentially in the lowering of the eye pressure by transmitting the impulses inhibiting abnormal rise of the eye pressure. However, when the stimulus is so intense as to cause the contraction of intraorbital smooth muscles, the eye pressure seems to rise by being effected by the muscular contraction itself.

2. The relationship between the oculomotor nerve and the eye pressure[17].

Extensive studies on this subject have been undertaken by numerous investigators such as IMACHI[11, 12], SAITO[13], SCHMERL a. STEINBERG[14], GREAVES a. PERKINS[15], AGARWAL[16] and others, but their results do not necessarily coincide with each other. Recently, SCHMERL and STEINBERG[14] report that an electric stimulation in ciliary ganglion causes a rise of the eye pressure of rabbits, while the cauterization of it resulted in a fall. GREAVES and PERKINS[15] claim that the stimulation of the oculomotor

nerve induces a rise in the eye pressure, but the resection itself does not affect the pressure. AGARWAL[16] asserts that the 3rd cranial nerve is not responsible to the regulation of eye pressure. In order to clarify the rôle of the oculomotor nerve in the regulation of eye pressure the author has conducted the following experiment.

By anesthetizing rabbits with urethan, the skull was opened to expose the oculomotor nerve, and then by dividing the animals into two groups; one group with the brains removed, the other group with the brains intact, the exposed oculomotor was electrically stimulated. Now, the changes in the intraocular and the systemic blood pressures occurring at the time of stimulation, the behavioral patterns of pupils, and the width of lid fissures were recorded simultaneously; and the differences between the changes in the animals with brains removed and with those left intact have been studied comparing respective factor in each. The fluctuations of the eye pressure at the time of the stimulation in the oculomotor are shown in Table 5. Marked rise of the eye pressure has

Table 5

No. of rabbit	Intensity of stimulus	Variation of eye pressure (mm.Hg)	Variation of systemic blood pressure (mm.Hg)	Miosis	Widening of lid fissures	Systemic spasm	Procedure
91	Weak	+3.0	−18	++	+	++	
	Strong	+4.5	−10	++	+	+	
92	Weak	+5.0	0	+	+	±	Removing brain
	Strong	+7.5	0	++	+	−	,,
93	Weak	+4.0	0	+	+	−	,,
94	,,	+1.0	0	±	+	±	,,
	Strong	+15.0	−8	+	++	+	,,
95	,,	+6.0	0	+	+	−	
	Weak	+3.0	0	±	±	−	

been observed in all cases; namely, the eye pressure rises rapidly simultaneous with stimulation of the oculomotor, whereas it falls quite swiftly immediately after the cessation of stimulation. The falling pattern of eye pressure has proceeded in two steps falling rather rapidly at first then slowly reaching the original level. Miosis and the widening of lid fissures have been seen in all cases. The systemic blood pressure is kept in the normal range showing a slight fall. As for the eye on the unstimulated

side, hardly no change of pressure can be recognized. From the above observations, as the rapid rise of the eye pressure seen immediatly after the stimulation seems to be in a large measure due to the contraction of ocular muscles, a similar experiment was conducted with a rabbit whose extrinsic ocular muscles had been cut and subjected to akinesy (Table 6).

Table 6

No. of rabbit	Intensity of stimulus	Variation of eye pressure (mm.Hg)	Variation of systemic blood pressure (mm.Hg)	Miosis	Widening of lid fissures	Systemic spasm	Procedure
91	Weak	+2.0	−10.0	+	±	+	
93	„	+2.0	0	+	−	−	Removing brain
94	„	+0.5	0	±	−	−	„
	Strong	+5.0	0	+	+	+	„
95	Weak	+2.0	0	±	−	−	

In this experiment, miosis was found in every case; however, the widening of lid fissures could not be observed except in one case. The rise and the fall of the eye pressure in this experiment were similar to those of the preceding experiment, though the amplitude of the rise and fall was less. From these results, it seems that the excitation of the oculomotor is responsible for the rise of the eye pressure, and that its mechanism is mainly dependent on the contraction of ocular muscles, though other factors can not be entirely ignored.

3. Influences of ganglion blocking agents on the changes of eye pressure caused by the compression of eyeball[17].

In the previous papers, the author has demonstrated that the mechanical compression of eyeball brought about a sudden elevation of eye pressure, but after a while the eye pressure began to descend, slowly reaching to the original level after 5—10 minutes, on the average of 6.6 minutes. The author, however, has found that in the rabbits administered venously with ganglion blocking agents such as Teabrom (tetraethylammonium bromide) or Imidalin (benzyl-imidazolin) prior to the compression of eyeball, the consequential decrease did not occur. These results suggest that the regulation of the eye pressure are performed likely through the autonomic nerve fiber.

4. The influences of ganglion blocking agents upon consensual ophthalmotonic reaction[17].

The author has mentioned in his previous report that when the intraocular pressure is artificially elevated unilaterally by the mechanical compression, the pressure of the unstimulated eye in contrast falls. The author in this experiment has been able to prove that no such consensual ophthalmotonic reaction appears if the superior cervical ganglion on the side opposite to the side to be stimulated is coated with 1% nicotin solution or the cervical sympathetic nerve including its superior cervical ganglion is removed prior to the stimulation (Table 7). On the contrary, in the cases

Table 7

No. of rabbit	Procedure	Eye pressure of l. eye	Variation of eye pressure of r. eye (mm.Hg)	Variation of systemic blood pressure
28	Coated with nicotin-solution	60	–	–
29	„	80	–	–
30	„	80	–	Slightly descended
31	„	80	Slightly ascended	Descended (−20mmHg)
33	Resection of superior cervical ganglion	80	–	–
34	„	80	–	Slightly descended
35	„	80	–	„
36	„	80	–	–

My: Yydriasis, Mi: Miosis

resected of their cervical sympathetic nerve on the same side of the eye to be stimulated, this reaction remained unaffected. From the present experiment, it may be interpreted that when the eye pressure of one eye rises, its regulating center is excited; and then the regulating center in turn creates an impulse to lower the eye pressure. This impulse, however, seems to be transmitted to the other eye by way of the sympathetic nerve of the opposite side, thus resulting in the decrease of the intraocular pressure of another eye.

5. The influences of ganglion blocking agents on the changes of eye pressure caused by the stimulation of the diencephalon[17].

It has already been indicated that the diencephalon is the site of the

regulating center of eye pressure, but as for its efferent pathways, we have no exact knowledge as yet. SCHMERL and STEINBERG[14] claim that this impulse is transmitted by way of autonomic nerve, but their experiment seems to give not enough proof to support their claim. If the impulse from the regulating center travels by way of the autonomic nerve to the eyeball, it is to be expected that the changes of eye pressure caused by the stimulation of diencephalon should disappear by a prior blocking of the autonomic nerve. To ascertain this assumption, the author has introduced ganglion blocking agents, namely, 20 mg. of 2-benzyl-imidazolin or 200 mg. of tetraethylammonium bromide, intravenously into the adult rabbits and observed how the intraocular and the systemic blood pressures, the behavioral pattern of the pupils, and the width of lid fissures might be affected at the time of stimulation of the diencephalon (Table 8).

Table 8

No. of rabbit	Stimulation point	Variation of eye pressure (mm.Hg)		Variation of blood pressure (mm.Hg)		Pupillary change	
		Before injection	After injection	Before injection	After injection	Before injection	After injection
101	Sympathetic area	−2.0	0	+10→−10	+ 5	My	My(±)
102	„	+2.0	0	+10→−15	0	„	−
103	„	−0.2→+4	+1.0	+12	+ 3	„	My
104	„	−1.5	−0.2	+ 4	0	„	„
106	Parasympathetic area	+4.5	+1.5	+45	+20	Mi→My	−
107	„	+2.5	+0.1	+10	+ 2	Mi	−
108	„	+3.0	0	−10	0	„	−
109	„	+0.1	0	−10	0	„	−

(My: Mydriasis, Mi: Miosis)

As the results, the changes of the intraoculalar and the systemic blood pressures which occurred in the stimulation of diencephalon before the injection, either disappeared or diminished after the injection. From this fact, it may be assumed that the impulse from interbrain seems to be transmitted by way of the autonomic nerve to the eyeball.

Conclusion; From these experimental findings, it may be concluded that the autonomic nerves have an important rôle in the regulation of the eye pressure, and that the impulses in eye pressure adjustment center seem to be transmitted by way of efferent pathways of the autonomic nervous system; namely, the sympathetic nerve the impulse to lower the

eye pressure while the parasympathetic nerve the impulse to raise the eye pressure.

B. STUDIES ON THE AFFERENT PATHWAYS OF AUTONOMIC EYE PRESSURE REFLEX[17].

HENDERSON and STARLING[1] point out that the 5th cranial nerve participates to a great degree in the regulation of eye pressure. More recently, many investigators such as MOREU[18], COURTIS and NUNEZ[19], PERKINS[20], and others report that trigeminal nerve plays an important rôle in the development of glaucoma. Lately, PERKINS[20] proves that a mechanical stimulation of trigeminal nerve causes a marked increase of the eye pressure by dilating uveal vessels as well as by raising the temperature of the ciliary body.

The author has investigated from various angles whether or not the 5th cranial nerve might be involved in the regulation of eye pressure and attempted to prove that this cranial nerve might be one of the afferent tracts of the "autonomic eye-pressure reflex".

EXPERIMENTS AND RESULTS

By making an incision of the skin of rabbit the point half way between the ear-hole and the external ocular angle, and by advancig deeper while parting the subcutaneous muscles right and left, the condyloid process of submaxillary bone was uncovered. By removing a part of this bone and advancing still deeper while separating the muscles, the tympanum of temporal bone was exposed. The branch of ophthalmic nerve was easily found in the anterior part of the tympanum. Then, after cutting this nerve, its proximal or its distal end was electrically stimulated and the reactions of the intraocular and the systemic blood pressures, changes of pupils, and the responses of nictitating membrane were simultaneously recorded and traced continuously. Observations were carried on with rabbits with or without treatment by curare.

1. Results on the untreated rabbits.

i. Stimulation at the proximal end of the nerve.

The electric stimulation of the proximal end resulted in the decrease of the systemic blood pressure in all cases. The eye pressure decreased in some and increased in other, i. e. a weak stimulation resulted in the lowering of the eye pressure in most of animals, but a strong stimulation caused an elevation of the eye pressure, mydriasis and systemic spasm in every case (Table 9).

Table 9

No. of rabbit	Intensity of stimulus	Variation of eye pressure (mm.Hg)	Variation of systemic blood pressure (mm.Hg)	Mydriasis	Systemic spasm
37	Weak	+2.5	−12	+	±
	Strong	+29.0	−13	+	##
38	„	+16.0	−8	+	##
39	Weak	−0.5	−10	−	−
	Strong	+1.5	−15	−	±
43	„	+2.5	−18	−	+
50	Weak	+2.0	−2	−	−
	Strong	+11.0	−10	±	+
51	Weak	+0.5	−2	−	−
	Strong	+15.0	−8	+	+
53	Weak	−0.5	−5	−	−
	Strong	+4.0	−9	±	+
55	Weak	+1.0	0	−	±
	Strong	+1.5	−5	±	±
56	Weak	+1.0	−5	−	±
	Strong	+2.0	−14	+	+
57	Weak	+1.0	−5	−	±
	Strong	+10.0	−12	±	+
58	Weak	−0.4	−4	−	−
	Strong	+15	−13	−	+

ii. Electric stimulation at the distal end of the nerve.

The stimulation on the distal end resulted in no change of the intraocular and the systemic blood pressures and the width of pupils. From the fact that the stimulation at the proximal end of trigeminal nerve induces the rise or fall in the eye pressure while the stimulation at its distal end elicits no change, it is possible to deduce that the trigeminal nerve is considered to be one of the afferent tracts of the "autonomic eye pressure reflex".

In order to make this deduction more conclusive, however, the question, to what degree and in what way the simultaneous changes of syste-

mic spasms and the systemic blood pressure are involved in the changes of the eye pressure, needs to be solved.

2. Results on the rabbits paralyzed with curare.

A similar experiment has been carried out on the rabbits previously given Amelizol (d-tubocurarine chloride pentahydrate) intravenously. As shown in Table 10, the intravenous injection of Amelizol did inhibit

Table 10

No. of rabbit	Intensity of stimulus	Variation of eye pressure (mm.Hg)	Variation of systemic blood pressure (mm.Hg)	Mydriasis	Systemic spasm
40	Weak	−1.0	−7	−	−
	Strong	−4.0	−35	±	±
41	Weak	−0.5	−5	−	−
	Strong	+15.0	−35	+	++
42	Weak	−2.0	−15	−	±
43	„	0	0	−	−
	Strong	+1.0	−6	−	−
50	Weak	0	0	−	−
	Strong	+0.5	−8	−	−
51	Weak	+0.5	−3	−	−
	Strong	+4.0	−10	±	±

the systemic spasms quite markedly though not completely. Even in the cases whose systemic spasm was highly inhibited, the rise or fall of the eye pressure was induced as markedly as in the case of the untreated ones, and moreover, there was no evidence of parallel fluctuations of the intraocular and the systemic blood pressures. Therefore, the changes of eye pressure caused by the trigeminal stimulation are not the complimentary phenomenon solely caused by the changes of the systemic blood pressure and the systemic spasm.

3. The influences of the ophthalmic nerve on consensual ophthalmotonic reaction.

The author has previously demonstrated that when the intraocular pressure of one eye has raised by the mechanical compression, the eye pressure of the other eye in contrast has fallen. In the present experiment it

was proven that when the ophthalmic nerve had previously been cut on one side, the consensual reaction on the other eye stated above did not appear as shown in Table 11. These results also suggest that the trigeminal nerve may be the afferent pathway of autonomic adjustment reflex of eye pressure.

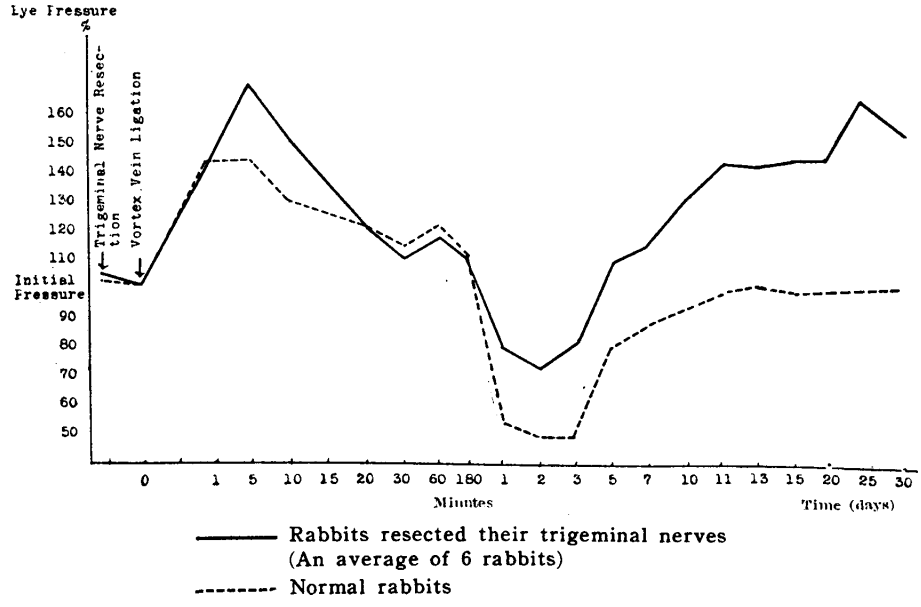
Table 11

No. of rabbit	Value of increased I. O. P. (mm.Hg)	Duration of increased I. O. P. (minutes)	Variation of I. O. P. of the other eye	Variation of systemic blood pressure
46	80	3	—	—
47	80	3	Slight drop	Slight drop
48	80	3	—	—
53	80	2	—	—
54	80	2	—	—

4. Influences of the trigeminal nerve on the eye pressure changes caused by ligation of vortex vein.

As shown in Fig. 1, the ligation of the vortex vein of normal rabbit brought about a rapid elevation of the eye pressure, but after a while the eye pressure began to descend and on the following day it was found to

Fig. 1. Variation of eye pressure



have fallen below the initial level. Subsequently, however, the eye pressure began to ascend again gradually and finally reached the initial level within two weeks without passing beyond the normal level. While in the rabbits with their ophthalmic nerves cut, the fluctuation of eye pressure took a greatly different pattern from those of the normal, i. e. the fluctuation of the former was more extensive than that of the latter, and yet the subsequent elevation of the eye pressure did not stop at the initial level but elevated passing far beyond it.

CONCLUSION

From the results of various experiments in an attempt to investigate the relationship between the intraocular pressure and the ophthalmic nerve, the author has come to the conclusion that the ophathalmic nerve is one of the afferent pathways transmitting the various impulses caused by the changes in the intraocular pressure to the autonomic eye pressure center, and the impulses created by these stimuli in the eye pressure center are in turn transmitted to the eyeball by way of the autonomic nerves and thus the eye pressure is autonomically regulated by these reflexes.

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