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ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PATHOGENESIS OF EXPERIMENTAL GLAUCOMA

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KEY WORDS: glaucoma; intraocular pressure; symptomatic regulation; adrenoblockers.

The study of the complex and still largely debatable problem of the role of the sympathetic nervous system in the pathogenesis of glaucoma is of practical as well as theoretical interest. A transient increase in the intraocular tension and certain forms of glaucoma can be regarded as a model of pathological states belonging to the diseases of regulation [6, 7], which are connected with hyperactivity of structures constituting the apparatus regulating the activity of an affected organ [4, 5]. There is evidence that the sympathetic nervous system participates in the pathogenesis of glaucoma [1, 2, 9-11], but the information is contradictory. The writers have attempted to shed light on this problem by using models of transient ocular hypertension and experimental glaucoma developed previously [3, 8] and to test the effects of lithium and α- and β-adrenoblockers on these models.

EXPERIMENTAL METHOD

Experiments were carried out on 58 adult rabbits of the White Giant breed. A transient increase in intraocular tension was induced by daily intravenous injections of vasopressin in a dose of 0.75 biological unit for 3 months. Experimental glaucoma was produced by intravenous injections of adrenalin in a dose of 0.1 ml of a 1:1000 solution on alternate days for 3 months. Healthy rabbits served as the control. The action of the adrenoblockers was studied during reproduction of experimental glaucoma. The α- or β-blocker was given on alternate days for 3 months a few minutes before injection of adrenalin: a 1% solution of pyrroxan (α-blocker) in a dose of 0.1 ml subcutaneously, a 0.1% solution of obsidan (propranolol; β-blocker) in a dose of 0.2 ml intravenously. The level of the intraocular tension (IOT) was measured by a Maklakov tonometer with a weight of 7.5 g daily or on alternate days in the morning for 1 month before the beginning of the experiment in order to determine the

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TABLE 1. Effect of α- and β-Adrenoblockers on Development of Experimental Glaucoma (M ± m)

Substances injected	No. of animals	IOT, mm Hg				
		initially	during administration of drugs	after end of administration of drugs		
				I quarter	II quarter	III quarter
Adrenalin	8	16,4±0,13	20,6±0,41 (25,6%)	21,6±0,27 (31,7%)	21,7±0,63 (31,8%)	22,7±0,76 (38,4%)
P			<0,001	<0,001	<0,001	<0,001
Adrenalin + pyrroxan	5	17,2±0,09	22,2±0,46 (29,1%)	23,2±0,41 (34,9%)	25,6±0,37 (48,8%)	26,6±0,62 (54,6%)
P			<0,05	<0,01	<0,001	<0,01
Adrenalin + obsidan	6	16,5±0,14	17,1±0,29 (3,6%)	17,6±0,38 (6,7%)	16,7±0,19 (1,2%)	17,3±0,10 (4,8%)
P			<0,1	<0,05	<0,2	<0,01

Legend. Here and in Tables 2-4 changes in IOT at different imes of the experiment are given as percentages and significance of their differences relative to the initial values.

TABLE 2. IOT (in mm Hg) in Rabbits of Different Groups after a Single Injection of 0.1 ml of a 1% Solution of Pyrroxan (M ± m)

Group of animals	No. of animals	IOT								
		initially	at various times after administration of pyrroxan (in min)							
			15	30	45	60	75	90	105	120
Healthy	10	17,0±0,28	18,0±0,34	17,0±0,39	16,0±0,42	17,5±0,30	17,0±0,41	18,0±0,36	17,5±0,46	17,5±0,48
P			<0,5		<0,2	<0,2		<0,5	<0,5	<0,5
With raised IOT	10	21,1±0,78	19,8±0,60	19,4±0,65	18,9±0,70	19,1±0,46	19,2±0,48	18,9±0,62	18,0±0,44	18,1±0,39
P			<0,2	<0,2	<0,05	<0,05	<0,05	<0,05	<0,01	<0,01
With glaucoma	10	23,8±0,61	22,6±0,70	22,7±0,73	21,9±0,78	21,4±0,80	22,5±0,71	23,2±0,54	24,8±0,58	22,9±0,62
P			<0,2	<0,5	<0,2	<0,2	<0,5	<0,5	<0,1	<0,2

TABLE 3. IOT (in mm Hg) in Rabbits of Different Groups after a Single Injection of 0.2 ml of a 0.1% Solution of Obsidan (M ± m)

Group of animals	No. of animals	IOT							
		initially	at various times after injection of obsidan (in min)						
			5	10	20	30	45	60	90
Healthy	17	17,7±0,23	17,1±0,27	17,6±0,24	18,1±0,34	19,3±0,40	2υ,2±0,38	20,3±0,29	19,8±0,32
P			<0,5	>0,5	<0,5	<0,001	<0,001	<0,001	<0,001
With raised IOT	16	20,1±0,45	19,9±0,40	19,7±0,48	18,8±0,60	19,0±0,64	19,8±0,58	19,8±0,55	20,1±0,52
P			<0,5	<0,5	<0,1	<0,2	<0,5	<0,5	
With glaucoma	22	23,9±0,59	21,7±0,55	21,2±0,60	20,5±0,75	20,0±0,78	19,8±0,86	20,4±0,80	20,3±0,82
P			<0,01	<0,001	<0,01	<0,001	<0,001	<0,001	<0,001

TABLE 4. IOT (in mm Hg) in Rabbits of Different Groups after Peroral Administration of a Single Injection of 5 ml of 10% Lithium Chloride Solution (M ± m)

Group of animals	No. of animals	IOT						
		initially	at various times after administration of lithium (in min)					
			30	45	60	75	90	120
Healthy	10	16,5±0,50	18,4±0,49	18,7±0,44	18,2±0,34	17,7±0,46	18,4±0,62	18,1±0,44
P			<0,02	<0,01	<0,01	<0,1	<0,05	>0,05
With raised IOT	10	21,1±0,68	22,1±0,72	22,0±0,85	22,2±0,75	22,6±0,71	21,7±0,56	21,8±0,91
P			>0,2	>0,2	>0,2	>0,1	<0,5	>0,5
With glaucoma	10	24,2±0,50	21,4±1,2	18,8±0,63	17,7±0,79	17,4±0,45	17,4±0,46	17,9±0,44
P			<0,5	<0,001	<0,001	<0,001	<0,001	<0,001

character of the normal fluctuations of this parameter, and later during the period of administration of adrenalin and the adrenoblocker (before injection) and for 9 months after the end of the injections. The action of adrenoblockers and lithium also was studied after a single injection of these substances into rabbits with developed models of glaucoma and increased intraocular tension against the background of a raised IOT, and also on healthy animals. The IOT was measured before injection of the drug and then every 10-15 min for 2 h. The dosage was: pyrroxan 0.1, 0.2, and 0.4 ml of a 1% solution subcutaneously, obsidan 0.2 ml of 0.1% solution intravenously or by instillation of drops into the conjunctival sac, and lithium chloride 1 ml of a 10% solution perorally or in the form of drops.

EXPERIMENTAL RESULTS

Just as in previous investigations [8] repeated intravenous injections of adrenalin caused the development of experimental glaucoma. Disturbance of regulation of IOT with an increase in its level was persistent and continued after administration of adrenalin ceased, and other signs of glaucoma also developed (marginal excavation of the optic disk, trophic disturbances of the eye tissues). The prophylactic use of α- and β-adrenoblockers had different effects on the development and course of experimental glaucoma. The difference between the IOT levels after injection of adrenalin alone and a combination of adrenalin with pyrroxan is statistically significant. Prolonged administration of obsidan prevented the development of disturbances of IOT regulation. The results of this series of experiments are given in Table 1.

The results of the experiments with a single injection of α- and β-blockers also showed that the response of IOT of healthy animals, of animals with experimental glaucoma, and of rabbits with a transient increase in IOT differed. Subcutaneous injection of a 1% solution of pyrroxan in a dose of 0.1 ml did not cause any clear change in the IOT level of healthy animals or of animals with glaucoma. In rabbits with a raised IOT, some decrease in its level was observed (Table 2).

Higher doses of pyrroxan (0.2 and 0.4 ml) led to a fall in IOT not only in animals in which it was raised, but also in healthy rabbits. These doses of pyrroxan in animals with glaucoma raised the IOT level very considerably (by over 30 mm Hg) in some cases.

When instilled into the eyes obsidan caused no change in IOT of healthy animals. Its intravenous injection led to some increase in IOT. In animals with a raised IOT no significant change in its level took place after administration by both methods. In animals with glaucoma instillation of obsidan into the eyes and its intravenous injection caused a distinct fall of IOT (Table 3).

Changes in IOT of rabbits after peroral administration of a single dose of lithium are shown in Table 4. It will be clear from Table 4 that lithium caused a very small increase in IOT of healthy rabbits and of rabbits with transient ocular hypertension. In rabbits with glaucoma administration of lithium caused a significant fall in IOT. This same pattern was preserved when lithium was given by other methods.

It can be concluded from these results that the sympathetic nervous system undoubtedly plays a role in the development of glaucoma. This is shown both by the method of production of the experimental model of glaucoma by the use of a sympathomimetic drug and also by the definite hypotensive effect of lithium, which has a sympatholytic action. However, the results of the experiments with adrenoblockers show that it is not so much the state of the sympathetic nervous system as a change in the function of α- and β-adrenoreceptors which plays the role in the pathogenesis of glaucoma. The β-blocker obsidan not only lowers IOT in the presence of developed glaucoma, but also prevents the experimental production of glaucoma. Pyrroxan, on the other hand, promotes the development of glaucoma and has no hypotensive therapeutic effect. Lowering of IOT under its influence was observed only in healthy rabbits and in rabbits with a transient increase in IOT. The experimental results thus suggest that the state of β-reception plays a special role in the development of glaucoma.

The differences thus revealed in the pathogenetic role of α- and β-adrenoreception are thus important not only for the theoretical analysis of the pathogenesis of glaucoma, but also because of the practical conclusions to which they may subsequently lead. The results of these experiments may lie at the basis of development of methods of early differential diagnosis of transient raised intraocular pressure and glaucoma and they may also lead to the creation of a combined specific pathogenetic treatment of glaucoma.

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MECHANISM OF CHANGES IN POLARIZATION OF SECRETORY CELLS OF THE SUBMANDIBULAR SALIVARY GLANDS IN EXPERIMENTAL BOTULISM

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Nearly all patients with botulism develop a syndrome of xerostomia. This is connected with the development of insufficiency of the secretory function of the salivary glands as a result of injury to their parasympathetic innervation [5, 6].

In view of data showing that parasympathetic decentralization of tissues for a long time is not followed by trophic disturbances, whereas denervation leads to the rapid development of trophic disturbances in them [7], it was decided to study changes in polarization of the acinar and duct cells at different stages of poisoning with botulinus toxin in order to shed light on the problem of the dynamics of injury to the parasympathetic innervation of the submandibular salivary glands.

EXPERIMENTAL METHOD

Noninbred rats of both sexes weighing 50-70 g at different stages of botulinus poisoning were used. To reproduce a general form of botulism, type A botulinus toxin was injected into the region of the left submandibular salivary gland in a dose of 0.2 ml/100 g body weight, and to reproduce the local form of botulism, a dose of 0.09 mg/100 g body weight was given by the same route (1 MLD for an albino mouse in 0.5 μg of the dry toxin). Some animals received two injections of pilocarpine in a dose of 1 mg/kg (24 and 18 h before the acute experiment).

Acute experiments were carried out on animals previously deprived of food for 24 h. The rats were anesthetized with pentobarbital (40 mg/kg, intraperitoneally), the left submandibular salivary gland was isolated, and an immobilizing disk of transparent plastic was inserted beneath it to ensure that the gland did not move when the microelectrode was inserted into its tissue. The temperature of the gland was kept between 37 and 38°C by irrigation with warm Ringer-Locke solution. The resting membrane potential (MP) was investigated by a standard microelectrode technique. Cells with MP of under 36 mV were classed as acinar and those with MP of above 36 mV were classed as duct cells [10].

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