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POTENTIATION BY PROMETHAZINE OF THE HYPOTENSIVE ACTION OF ADRENERGIC DRUGS ON THE INTRAOCULAR PRESSURE

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KEY WORDS: intraocular pressure; hydrodynamics of the eye; timolol; adrenalin; promethazine

The intraocular pressure (IOP) level is determined by dynamic equilibrium between active secretion of the aqueous humor by the ciliary epithelium and its outflow through the drainage system at the angle of the anterior chamber. Stimulators and blockers of adrenergic receptors acting on the epithelium of the ciliary body can modulate production of the humor and thus control the IOP level [6, 7]. It has recently been found that substances stabilizing membrane regions of adrenergic receptors can modify the pharmacological activity of adrenergic agents introduced into the eyes in order to depress IOP [3, 4]. It is also known that the integrity of a cell membrane depends on the potassium ion concentration in the surrounding medium; disturbance of the ionic permeability of membranes, moreover, is calmodulin-dependent in character [8]. One agent with a membranotropic action is promethazine (P; pipolphen). At the same time, this preparation is a calmodulin inhibitor. With respect to its basic pharmacological characteristics P is a histamine antagonist and blocker of H_1-receptors. The action of P on IOP and, in particular, its influence on the hypotensive (relative to IOP) action of adrenergic drugs has not been studied.

In the investigation described below the effect of P together with timolol and adrenalin on IOP and the hydrodynamics of the eyes was studied in experiments on rabbits.

EXPERIMENTAL METHOD

Experiments were carried out on 24 Chinchilla rabbits weighing 2.6-3.5 g. The animals' right eye was experimental, the left — control. IOP was measured with a Maklakov tonometer under local anesthesia with 0.5% amethocaine. The hydrodynamics of the eye was studied by tonography on an electronic tonograph [1]; a 2.5% solution of promethazine [N-(2-dimethylamino-1-propyl)-phenothiazine hydrochloride)], from "Egis" (Hungary) was diluted with Hanks' medium to a 0.5% solution (pH 6.8-7.0). Solutions of the preparations were instilled into the experimental (right) eyes of the rabbits, and Hanks' solution alone into the control (left) eyes of all the animals. After 30 min, a 1% solution of adrenalin (Isoptoepinal, from "Alcon," Belgium) was instilled into both eyes of 12 animals (group 1), and a 0.5% solution of timolol maleate (Optimol, from "Star," Finland) was similarly instilled in group 2; IOP of both eyes was measured immediately before and 30 min after instillation of P, and again 1, 2, 3, 4, and 24 h after instillation of adrenalin or timolol. Tonography was carried out before and 24 h after instillation of the drugs. Altogether 454 tonometric and 108 tonographic investigations were undertaken.

*Deceased.

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TABLE 1. Effect of Combined Use of Promethazine and Adrenalin on IOP of Rabbits

Experimental conditions	n	IOP (M ± m)		p
		right (experimental) eye	left (control) eye	
Initial IOP	22	18,6±0,30	18,6±0,29	—
30 min after instillation of promethazine into right eye	22	19,5±0,33	19,3±0,26	>0,7
1 h after instillation of adrenalin into both eyes	22	15,4±0,40	17,4±0,32	<0,01
2h	22	16,0±0,34	17,8±0,33	<0,01
3h	20	17,0±0,42	18,8±0,40	<0,01
4h	18	15,2±0,46	17,4±0,61	<0,01
24h	20	15,6±0,20	18,2±0,30	<0,01

Legend. M) Arithmetic mean, m) standard deviation, p) coefficient of significance, n) number of experiments.

TABLE 2. Effect of Combined Administration of Promethazine and Timolol on IOP of Rabbits

Experimental conditions	n	IOP (M ± m)		p
		right (experimental) eye	left (control) eye	
Initial IOP	12	18,7±0,5	18,8±0,5	>0,8
30 min after instillation of promethazine into right eye	12	17,9±0,4	18,2±0,4	>0,6
1 h after instillation of timolol into both eyes	12	16,9±0,5	17,9±0,3	>0,1
2 h	12	16,5±0,5	19,0±0,5	<0,01
3 h	12	16,7±0,5	18,7±0,5	<0,02
4 h	12	16,7±0,3	19,1±0,4	<0,01
24 h	9	18,2±0,5	20,5±0,7	<0,02

Legend. M) Arithmetic mean, m) standard deviation, p) coefficient of significance, n) number of experiments.

EXPERIMENTAL RESULTS

A single instillation of P is well tolerated by the rabbit's eye and causes no changes in the conjunctiva or cornea. The effect of P, adrenalin, and combined administration of these two preparations on IOP of the rabbits is illustrated in Table 1.

As Table 1 shows the initial IOP was the same in both eyes. IOP was almost unchanged 30 min after instillation of 0.5% P into the experimental eye. Subsequent instillation of adrenalin into both eyes caused a decrease in IOP; at all times of the experiment (24 h) the decrease in IOP of the experimental eye was much greater than that of the control eye.

According to the results of tonography, parameters of the hydrodynamics of the right and left eyes were virtually identical before instillation of the drugs (Fig. 1a). Instillation of P and adrenalin into the right eye significantly lowered the intraocular pressure (P_0), due to an increase of 61% in the coefficient of ease of drainage (C) ($p < 0.01$). Meanwhile there was a significant increase in production of aqueous humor (F), which was evidently compensatory.

The effect of P and timolol and of a combination of these drugs on IOP of the rabbits is shown in Table 2. It will be clear from Table 2 that subsequent installation of timolol after P significantly lowered IOP in the experimental eye.

Data on the change in parameters of the hydrodynamics of the eyes following combined administration of P and timolol are given in Fig. 1b. The hypotensive effect of these drugs is explained by an increase in the drainage of aqueous humor ($p < 0.01$).

Most substances lowering intraocular pressure, including β-adrenoblockers, inhibit active secretion of aqueous humor. This mechanism of compensation of IOP cannot be regarded as physiological, for under these circumstances the circulation of aqueous humor and the metabolism of the avascular tissue structures of the eye, dependent on it, are

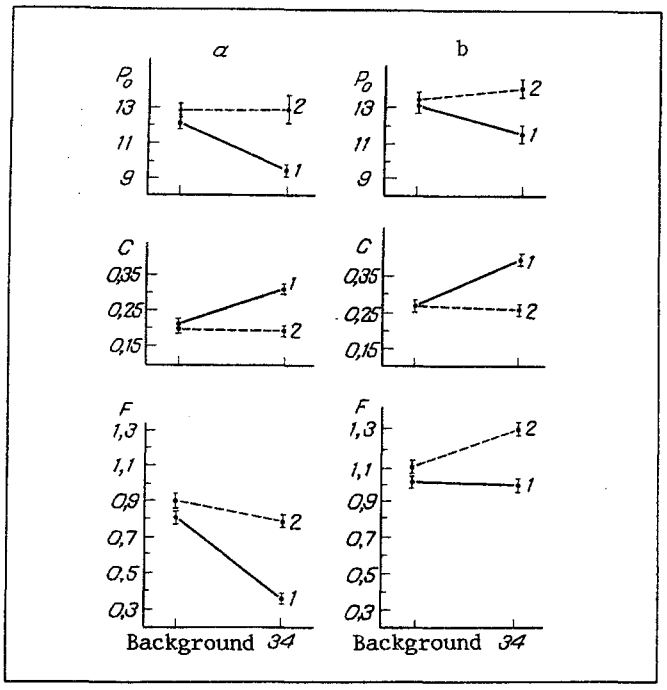

Fig. 1. Effect of combined administration of promethazine and adrenergic drugs on hydrodynamics of rabbits' eyes: a) promethazine + adrenalin, b) + β-adrenoblocker optomol. 1) Experimental eye, 2) control eye. P_0) True intraocular pressure (mm Hg), C) coefficient of ease of flow (relative units), F) production of aqueous humor ($mm^3 \cdot min^{-1}$). Explanation in text.

disturbed, including the drainage system. Accordingly, it is important to note that local administration of P before adrenergic drugs enables the mechanism of their hypotensive action on IOP to be modified, with an increase in drainage of the aqueous humor.

The mechanism of this effect is not sufficiently clear.

There are indications that in experiments on rabbits' eyes binding of molecules of sympathomimetics or β-blockers with the membrane fraction of cells of the iris—ciliary body complex may be increased on account of a decrease in the microviscosity (enhancement of the fluid properties) of the lipid layer of the membranes [5]. We know that P significantly reduces the microviscosity of biomembranes and thereby reduces adenylate cyclase activity [2, 9]. It may be expected that P would increase binding of adrenergic agents introduced into the eyes with membrane receptors of the smooth-muscle cells of the ciliary muscle, thereby increasing their pharmacological activity.

The way of compensating IOP observed with a combination of adrenomimetic (adrenalin) and β-blocker (timolol) is more physiological than inhibition of production of the aqueous humor, characteristically taking place under the influence of adrenomimetics and β-adrenoblockers in the absence of P.

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β-LIPOTROPIN AND β-ENDORPHIN IN MECHANISMS OF COMPENSATION OF FUNCTIONS AFTER DESTRUCTION OF THE LATERAL HYPOTHALAMUS

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KEY WORDS: β-lipotropin; β-endorphin; lateral hypothalamus

Investigations have demonstrated the physiological role of opioids and other oligopeptides in the central mechanisms of hunger and thirst [3, 7, 12, 14]. Of all the neuropeptides, with their broad spectrum of action, one which is particularly interesting is β-lipotropin (β-LPT), which is widely distributed in various structures of the CNS and, in particular, in the hypothalamus [1, 13]. There is also evidence that β-LPT and its derivative β-endorphin can change the character of hunger-motivated food-related instrumental activity in rabbits and drinking behavior in rats [4-10].

Accordingly, in the investigation described below the basic parameters of biological motivations and related physiological functions were studied after destruction of the lateral hypothalamus in order to establish the possible involvement of β-LPT and its derivative, β-endorphin, in the mechanisms of compensation of these functions under the conditions specified, a problem which still remains virtually unstudied.

EXPERIMENTAL METHOD

Experiments were carried out on 45 noninbred male rats weighing 200-250 g. The animals were divided into three groups, with 15 in each group. Group 1 (control) consisted of animals in which the lateral hypothalamus was destroyed and physiological saline injected into the lateral ventricles in a volume of 3-5 μl; in the animals of group 2 the lateral hypothalamus was destroyed and intraventricular microinjections of β-LPT given; in the rats of group 3, after destruction of the lateral hypothalamus, β-endorphin was injected into the lateral ventricles. The lateral hypothalamus of the animals was destroyed by electrical coagulation under general (pentobarbital) anesthesia, using stereotaxic coordinates of an atlas of the rat brain [11]: P = 1.7-2.0 mm, L = 1.5-1.7 mm, H = 8.0-8.5 mm. For electrolytic destruction an anodal current of 50 mA was passed for 5 sec. To inject the substances cannulas 0.84 mm in diameter were inserted into the lateral ventricles in accordance with stereotaxic coordinates: AP = 1.5-1.7 mm, L = 2 mm, H = 4-4.5 mm [17]. These peptides were injected through the implanted cannulas in concentrations of $91.5 \cdot 10^{-6}$ μmoles/μl (for β-LPT) and $269 \cdot 10^{-6}$ μmole/μl (for β-endorphin) in a volume of 3-5 μl (in physiological saline) by means of a microinjector.

β-LPT and β-endorphin were obtained from the Laboratory of Protein Hormones, Research Institute of Experimental Endocrinology and Hormone Chemistry, Academy of Medical Sciences of the USSR, and were isolated from bovine pituitary glands [5].

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