Injection of phentolamine into the control animals caused adrenoreceptor sensitivity to fall by two-thirds (Table 2). Consequently, both intact animals and animals receiving the drug served as the control.

Because of exposure to EPS the adrenoreactivity of the smooth muscle was reduced by more than 12 times (Table 2), in agreement with data obtained previously [2]. Preliminary injection of phentolamine increased the adrenoreactivity of the portal vein by four times; the value of K under these circumstances almost reached the control level. Administration of inderal had no significant effect on sensitivity of the smooth-muscle adrenoreceptors of both control and stressed animals.

One result of exposure to severe stress is known to be catecholamine-induced damage to myocytes, due to excessively strong and prolonged activation of the sympathicoadrenal system [3]. Since in the present experiments disturbances of the contractile function and adrenoreactivity of the portal vein were prevented only by the α-adrenoblocker phentolamine, it can be postulated that the damaging effect of high concentrations of catecholamines is realized in stress through α-adrenoreceptors which, according to data obtained by other workers [8, 9], predominate in the receptor apparatus of the portal vein.

Preliminary injection of the α-adrenoblocker phentolamine thus largely abolishes the damaging effect of high concentrations of catecholamines arising as a result of previous exposure to stress on spontaneous contractility and adrenoreactivity of the smooth muscle of the portal vein.

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# EFFECT OF β-ADRENOBLOCKERS ON PROSTAGLANDIN-INDUCED OCULAR HYPERTENSION IN RABBITS


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KEY WORDS: intraocular pressure; prostaglandins; β-adrenoblockers.


Prostaglandins (PG) of various groups ($E_1$, $E_2$, $F_2$), if instilled into the conjunctival sac or injected subconjunctivally, cause an acute rise of intraocular pressure (IOP) in rabbits and monkeys — prostaglandin-induced ocular hypertension [1, 2, 9, 12]. There is reason to suppose that PG participate in the pathogenesis of acute increases of IOP in man.

Reports of the hypotensive action of β-adrenoblockers on normal and raised IOP under experimental and clinical conditions have recently been published [4, 6-8, 11, 13, 15]. Propranolol and Timolol have found wide application as drugs lowering IOP in glaucoma.

The problem of the effect of β-adrenoblockers on ocular hypertension induced by PG has received little study. Only Waitzman [14] and Green and Kim [10] have shown that propranolol


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TABLE 1. Effect of β-Adrenoblockers on Normal IOP in Rabbits (M ± m)

| Preparation | Number of experiments | Before instillation | | Time after instillation of drug, h | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | | 2 | | 3 | | 4 | |
| | | OD | OS | OD | OS | OD | OS | OD | OS | OD | OS |
| Propranolol (2% solution | 9 | 20,1±0,4 | 20,1±0,5 | 19,1±0,4*** | 21,5±0,4 | 17,8±0,3*** | 20,4±0,5 | 18,0±0,5*** | 20,4±0,5 | 18,4±0,7* | 20,6±0,7 |
| Timolol (0,5% solution) | 12 | 19,7±0,4 | 19,5±0,4 | 18,7±0,5* | 20,1±0,5 | 18,3±0,6* | 19,6±0,4 | 18,0±0,5 | 19,4±0,6 | 18,4±0,5 | 19,5±0,7 |
| Atenolol (3% solution) | 6 | 20,3±0,5 | 19,8±1,2 | 19,4±0,4 | 20,1±0,6 | 18,1±0,5** | 19,8±0,2 | 16,7±0,5 | 18,0±0,6 | 17,3±0,5 | 18,3±0,6 |
| Oxprenolol (2% solution) | 8 | 20,4±0,7 | 20,3±0,9 | 20,3±0,3** | 21,9±0,3 | 19,4±0,6 | 21,1±0,8 | 19,3±0,5 | 20,6±0,9 | 19,6±0,6 | 20,8±1,0 |
| Talinolol (2% solution) | 8 | 20,5±0,7 | 19,5±0,9 | 21,0±0,7 | 21,6±0,4 | 20,8±1,0 | 22,2±0,9 | 21,6±0,7 | 21,8±0,9 | 20,5±0,8 | 21,7±0,8 |

Legend. *P < 0.05; **P < 0.02; ***P < 0.01 compared with control. Here and in Table 2, OD signifies right eye (experiment), OS left eye (control).

TABLE 2. Effect of β-Adrenoblockers on IOP in Rabbits with Prostaglandin-Induced Ocular Hypertension (M ± m)

| Experimental conditions | Propranolol | | | Atenolol | | | Timolol | | | Oxprenolol | | | Talinolol | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | number of experiments | OD | OS | number of experiments | OD | OS | number of experiments | OD | OS | number of experiments | OD | OS | number of experiments | OD | OS |
| Control | 7 | 21,1±0,8 | 20,9±0,8 | 4 | 19,3±1,0 | 18,8±0,3 | 8 | 21,0±0,7 | 20,6±0,6 | 11 | 22,1±0,5 | 22,0±0,5 | 4 | 21,6±0,4 | 21,8±0,5 |
| After instillation of drugs | | | | | | | | | | | | | | | |
| 15 min | 7 | 25,3±1,4 | 27,7±1,1 | 4 | 26,0±0,9 | 28,9±1,1 | 8 | 28,1±0,8 | 28,7±0,9 | 11 | 29,4±0,3 | 32,1±0,9 | 4 | 35,3±2,5 | 30,8±3,1 |
| 30 min | 7 | 27,6±1,5 | 30,7±1,5 | 4 | 26,5±1,9 | 30,4±0,8 | 8 | 33,0±1,0 | 31,1—1,3 | 11 | 31,2—1,0 | 33,2—0,9 | 4 | 37,0—3,4 | 34,5—4,5 |
| 45 min | 7 | 27,1±0,8* | 30,9±1,3* | 4 | 27,1±2,0 | 29,5±0,3 | 8 | 31,3±1,2 | 30,8±1,2 | 11 | 29,1±1,1 | 31,8±1,0 | 4 | 35,5±3,2 | 30,1±3,3 |
| 1 h | 7 | 25,4±0,8 | 29,7±1,0** | 4 | 24,9±1,9 | 26,1±0,9 | 8 | 29,0±1,6 | 27,9±1,5 | 11 | 25,2±1,2 | 28,0±1,3 | 4 | 32,3±2,0 | 29,5±2,5 |
| 1 h 15 min | 7 | 21,6±0,8** | 26,6±1,2 | 4 | 22,3±0,7 | 25,3±2,0 | 8 | 26,0±1,7 | 26,1±1,6 | 11 | 23,9±1,3 | 26,6±1,2 | 4 | 27,4±2,6 | 25,9±3,1 |
| 1 h 30 min | 7 | 19 9±0,6*** | 25,1±1,3 | 4 | 22,4±1,1 | 24,5±1,7 | 8 | 24,9±1,4 | 23,7±1,4 | 11 | 21,6±1,1 | 23,7±1,3 | 4 | 26,4±2,9 | 24,8±3,2 |
| 2 h | 7 | 19,1±1,3 | 19,8±1,0 | 4 | 18,0—0,9 | 17,5—1,1 | 8 | 23,7—3,4 | 23,0—3,1 | 11 | 19,7—0,8 | 20,2—1,0 | 4 | 26,0±4,1 | 24,7±4,4 |
| 2 h 30 min | 7 | — | — | | — | — | 8 | 19,8±0,2 | 20,8±1,3 | | — | — | | 23,0±3,0 | 22,5±4,6 |

has no significant effect of prostaglandin-induced ocular hypertension in anesthetized cats and rabbits.

This paper describes a comparative study of the effect of β-adrenoblockers (propranolol, timolol, atenolol, oxprenolol, and talinolol) on IOP of normal rabbits' eyes and in $PGE_2$-induced ocular hypertension.

## EXPERIMENTAL METHOD

Experiments were carried out on chinchilla rabbits weighing 2.5-3 kg under local anesthesia (instillation of 0.5% amethocaine into the conjunctival sac). IOP was measured by means of Maklakov's tonometer. The β-adrenoblockers were instilled into the conjunctival sac in concentrations used clinically for the treatment of glaucoma (2% propranolol, 0.5% timolol, 3% atenolol, 0.5% oxprenolol, and 0.5% talinolol).

A solution of $PGE_2$ (from Upjohn, USA) was diluted in distilled water in the ratio 1:3 and instilled in a dose of 4 drops (15-20 μg). Tonometry was carried out 1, 2, 3, and 4 h after instillation of the drugs. In the experiments with ocular hypertension the β-adrenoblockers were instilled into the conjunctival sac of the right (experimental) eye 60 min before injection of PG. The animals' left eye served as the control. IOP of both eyes was measured before instillation of the β-adrenoblockers and 60 min after instillation, after which PG was instilled into both eyes and IOP was measured every 15 min for 90 min, and then every 30 min for 1 h. Altogether 77 experiments were carried out on 32 rabbits.

## EXPERIMENTAL RESULTS

In rabbits with normal IOP instillation of 2% propranolol caused a significant fall of IOP (by 2.2-2.6 mm Hg) in the course of all 4 h of the investigation (Table 1). Timolol as a 0.5% solution, caused a significant fall of IOP (by 1.3-1.4 mm Hg) after 1 and 2 h. Atenolol (3% solution) caused IOP to fall by 1.7 mm Hg only after 2 h. Oxprenolol and talinolol (2% solutions) did not significantly lower IOP.

Instillation of $PGE_2$ caused IOP to rise in all experiments by between 6 and 16 mm Hg. Preliminary instillation of propranolol lead to a significant decrease in the rise of IOP caused by subsequent instillation of PG (Table 2). The difference between IOP in the experimental and control eyes was 3.8-5.2 mm Hg in the course of 45 min to 1.5 h. Unlike propranolol, the other β-adrenoblockers tested had no significant effect on the course of prostaglandin-induced hypertension.

The investigations confirmed data obtained previously showing reduction of IOP under the influence of propranolol in rabbits with prostaglandin-induced hypertension, and also the role of adrenoreceptors in the development of pathology of IOP [5]. Meanwhile the results also show that this effect is not given by all β-adrenoblockers. Timolol, atenolol, oxprenolol, and talinolol (in the concentrations used) had no such action. However, timolol and atenolol caused the normal IOP to fall.

Thus not all β-adrenoblockers modify the effects of PG. Propranolol is not a direct antagonist of PG. The action of propranolol on the course of PG-induced hypertension is evidently connected with its normalizing action on permeability of the microvessels of the eye when disturbed by administration of PG. It is also possible that the effect of propranolol may be due to the stabilizing influence of the drug on cell membranes of the ciliary epithelium, which participate in the formation of the aqueous humor.

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# TRIALS OF CHOLINESTERASE REACTIVATORS AS NEOSTIGMINE ANTAGONISTS

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KEY WORDS: neostigmine; cholinesterase reactivators; prevention of carbamate poisoning.

Neostigmine is an anticholinesterase drug of the carbamate group. The highest decurarizing dose of the drug, 0.05 mg/kg [12], is more than three times greater than the dose sufficient to give rise to marked symptoms of poisoning in a normal individual [9], and for that reason, during its clinical use, signs of overdosage appear relatively often, sometimes terminating in death [7]. The use of atropine to prevent complications does not abolish disturbances associated with excitation of nicotinic acetylcholine receptors [8].

Since carbamylation leads to the formation of a less stable complex with the enzyme than phosphorylation, it can be postulated that cholinesterase reactivators used in cases of poisoning by organophosphorus insecticides will be more effective against carbamate poisoning. It has been found in practice that only single preparations are effective, and they vary, moreover, in their effectiveness against poisoning by different carbamates [13].

Reactivators (HS-3, HI-6, HGG-12, etc.) distinguished by ability to act on acetylcholine receptors have recently been described [6]. Accordingly in the investigation described below an attempt was made to chose a reactivator which, in conjunction with cholinolytics, could give a high protective effect against neostigmine poisoning. The pyridinaldoxime derivatives were provided by Yu. V. Lupandin.

## EXPERIMENTAL METHOD

Lethal ($LD_{50}$), toxic ($TD_{50}$), and effective ($ED_{50}$) doses of the preparations were determined by the tabular method [3] on 250 male albino mice. To prevent poisoning, cholinolytics were injected subcutaneously 15 min before, and cholinesterase reactivators intraperitoneally 1 min before subcutaneous injection of neostigmine.

The reactivating action of HI-6 and TMB-4 in concentrations of $10^{-5}$-$10^{-4}$ M was estimated in experiments *in vitro* after incubation for 30 min with purified acetylcholinesterase, inhibited by neostigmine ($5 \cdot 10^{-8}$ M) in a medium of 0.08 M KCl at 37.4°C and pH 7.4. The velocity of enzymic hydrolysis of acetylcholine iodide was determined by the method of continuous potentiometric titration [1]. The affinity constant ($K_a$), velocity constant of carbamylation ($K_c$), and the pseudomonomolecular inhibition constant ($K_i$) were determined graphically [11].

## EXPERIMENTAL RESULTS

To choose a reactivator the index of effectiveness (the ratio of $LD_{50}$ to $ED_{50}$), the dose necessary to prevent death of half of the animals poisoned with $LD_{99}$ of neostigmine, was determined. The experimental results (Table 1) showed that reactivator HI-6 had an index of effectiveness 1.5 times higher than that of TMB-4 and twice as high as the other preparations.

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