THE MECHANISM OF ACTION OF EPHEDRINE

UDC 615.711.7-017.8

I. V. Komissarov

Department of Pharmacology, Faculties of Pediatrics and Hygiene (Head – Docent I. V. Komissarov), Donetsk Medical Institute
(Presented by Active Member AMN SSSR V. V. Zakusov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 4, pp. 66-69, April, 1964
Original article submitted April 5, 1963

The hypothesis that ephedrine acts as a monoamine oxidase inhibitor [7, 13] conflicts with the facts of the pharmacology of hydrazine derivatives [17] and with the results of investigations [6] showing the presence of inhibition of monoamine oxidase in experiments in vitro but its absence in experiments in vivo. The assertion that ephedrine has a direct action on adrenergic structures [14] is likewise debatable, for in contrast to the catecholamines ephedrine has no effect on organs after division and degeneration of the sympathetic nerves supplying them [18].

In the present paper we describe facts providing a new interpretation of the mechanism of action of ephedrine.

The action of ephedrine was studied on the sympatheticolytic effect and the neuromuscular block caused by bretylium. The latter drug blocks sympathetic nerves but does not affect the action of injected catecholamines [8]. The sympatheticolytic effect of bretylium is due to its ability to depress the liberation of acetylcholine by the endings of adrenergic nerves, and thereby to prevent the liberation of the stocks of catecholamines deposited in the region of these endings [5, 9]. Meanwhile, bretylium also suppresses the liberation of acetylcholine by the endings of cholinergic nerves. This action, in particular, lies at the basis of the neuromuscular block produced by this preparation [12].

EXPERIMENTAL METHOD

Experiments were carried out on cats and rabbits, anesthetized with urethane (1 g/kg intraperitoneally) and chloralose (0.05 g/kg intravenously). In the experiments of series I, on 6 cats, recordings were made of the contractions of the gastrocnemius muscle during stimulation of the sciatic nerve with rectangular pulses with a frequency of 0.5 cps and duration of 0.5 millisec. In the experiments of series II, on 5 cats, the tone of the nictitating membrane was recorded during constant stimulation of the postganglionic trunk with a frequency of 15 cps and duration 0.5 millisec. In the experiments of series III the effect of ephedrine was studied on the level of the arterial pressure in 6 rabbits receiving reserpine. Reserpine was injected into the animals intrapertioneally in a dose of 4 mg/kg 24 h before the experiment.

EXPERIMENTAL RESULTS

Intravenous injection of bretylium into cats in a dose of 2.5-5 mg/kg caused no change in neuromuscular conduction. In a dose of 10 mg/kg, the drug lowered the amplitude of the contractions of the gastrocnemius muscle in response to indirect stimulation by 10-15%, and in a dose of 15-20 mg/kg, by 40-60%. The duration of the neuromuscular block in this case was 7-13 min.

Potassium chloride and calcium chloride, in a dose of 20 mg/kg, and also ephedrine in doses of 1-5 mg/kg diminished or totally abolished the neuromuscular block produced by bretylium (Fig. 1). The effect of ephedrine in abolishing the presynaptic block caused by bretylium can only be accounted for by the action of ephedrine on the synthesis or liberation of acetylcholine in the motor nerve endings. Hence, the action of ephedrine and of calcium ions [10] on a neuromuscular conduction is evidently similar in principle.

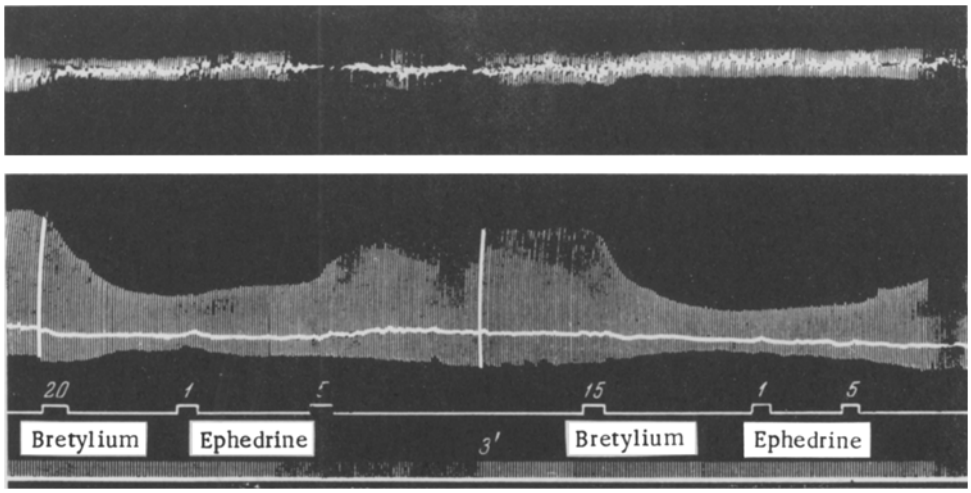

Fig. 1. Effect of ephedrine on neuromuscular block caused by bretylium in a cat weighing 2.2 kg. Significance of curves (from top to bottom): respiration, contractions of gastrocnemius muscle, markers of injection and time (3 sec).

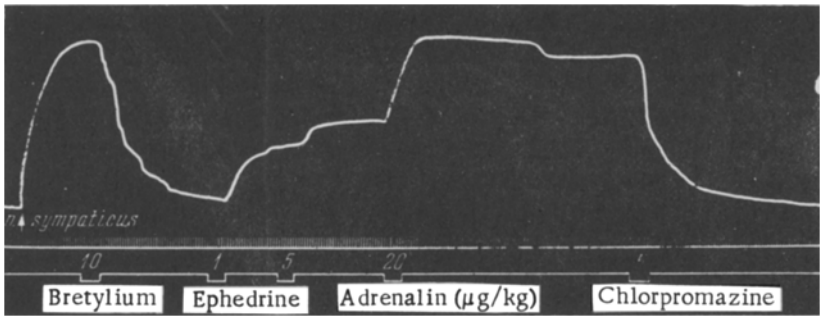

Fig. 2. Effect of ephedrine on the sympatheticolytic effect of bretylium in a cat weighing 2.8 kg. Significance of the curves (from top to bottom): contraction of the nictitating membrane, marker of injection, time, marker (3 sec).

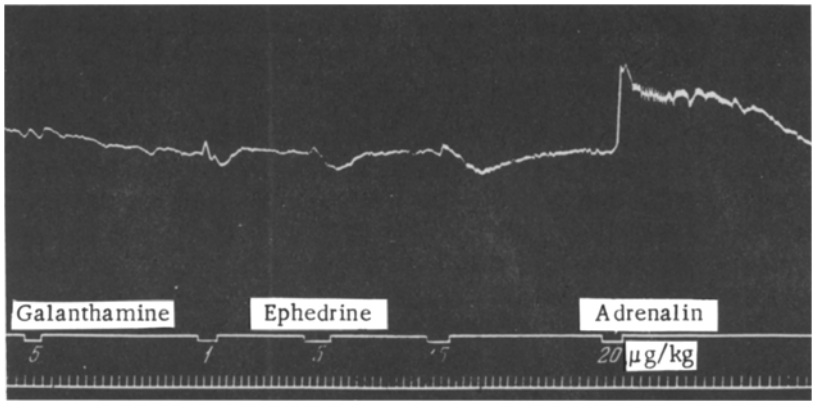

Fig. 3. Effect of ephedrine on level of arterial pressure in a rabbit weighing 2.3 kg receiving reserpine. Significance of the curves (from top to bottom): arterial pressure, marker of injection, time marker (5 sec).

Ephedrine appreciably reduced, but did not completely abolish, the sympatheticolytic effect of bretylium.

Usually after a short latent period, but sometimes immediately after injection, bretylium in doses of 2.5-5 mg/kg sharply depressed the contracture of the nictitating membrane due to constant stimulation of the cervical postganglionic sympathetic nerve. Injection of ephedrine (1-5 mg/kg) against this background clearly increased the tone of the nictitating membrane, although its contraction never regained its initial magnitude (Fig. 2). The subsequent injection of adrenalin (20 g/kg) increased, and injection of chlorpromazine (5-8 mg/kg) decreased the tone of the nictitating membrane.

The action of ephedrine, described above, on the sympatheticolytic effect of bretylium may be the result of the direct action of ephedrine on the adrenergic structures, and also of the stimulant action of ephedrine on the liberation of acetylcholine by the endings of the postganglionic sympathetic nerves. The latter mechanism seems more likely, bearing in mind the data cited showing the effect of ephedrine on the depth of the neuromuscular block caused by bretylium.

With the depletion of the catecholamine depots resulting from administration of reserpine, the direct action of ephedrine on the adrenergic receptors (if such exists) must be preserved, but the adrenomimetic effect, if due to stimulation of the liberation of acetylcholine by ephedrine from the endings of the adrenergic nerves, must be absent. With these considerations in mind, experiments were carried out on rabbits receiving injections of reserpine. Rabbits were chosen because reserpine produces total depletion of the catecholamine depots in these animals, whereas in cats the catecholamines persist in the adrenals [1]. It was found that in intact rabbits ephedrine, in doses of 1 and 5 mg/kg, raised the arterial pressure by 15-20 and 30-35 mm respectively, while in rabbits receiving reserpine, ephedrine in doses of 1-15 mg/kg did not give a pressor effect.*

It was also found that in the rabbits receiving reserpine and which, to block cholinesterase, received an intravenous injection of galanthamine (4-5 mg/kg) [4] 2-3 min before the injection of ephedrine, the injection of the latter in doses of 1, 5, 10, and 15 mg/kg was accompanied every time by a depressor effect (Fig. 3).

The results demonstrate that the adrenomimetic action of ephedrine is due mainly to the liberation of acetylcholine by the endings of the adrenergic nerves. From the standpoint of this hypothesis regarding the mechanism of action of ephedrine it becomes clear why ephedrine has no effect on organs deprived of their sympathetic nerve supply. Ephedrine causes liberation of acetylcholine also by the endings of the cholinergic nerves, which explains its effect in abolishing the postsynaptic block to the conduction of impulses in the ganglia and neuromuscular synapses [2, 3], and also its muscarine-like cholinomimetic effects [11, 15, 16].

SUMMARY

As demonstrated in experiments on cats, ephedrine reduced or completely eliminated the neuromuscular block, caused by bretylium and weakened the sympatholytic effect of the latter. In reserpinized rabbits ephedrine provoked no peculiar pressor effect. After ephedrine administration to reserpinized rabbits in which cholinesterase block was attained by giving galanthamine, a regular depressor effect was noted, which correlated with the dose of ephedrine.

The effects mentioned are attributed to the capacity of ephedrine to stimulate acetylcholine liberation by the postganglionic sympathetic nerve endings, as well as by the cholinergic nerve endings.

LITERATURE CITED

1. M. L. Belen'kii and M. A. Vitolinya. In the book: Proceedings of the Tenth All-Union Conference on Pharmacologists, Toxicologists, and Chemotherapists [in Russian], Volgograd (1962), p. 42.
2. A. F. Danilov, In the book: The Physiological Role of Acetylcholine and the Search for New Therapeutic Substances [in Russian], Leningrad (1957), p. 406.
3. A. I. Mitrofanov, In the book: Gangliolytics and Blocking Agents of Neuromuscular Synapses [in Russian], Leningrad (1958), p. 130.
4. D. S. Paskov, Nivalin. Its Pharmacological Characteristics [in Russian], Sofia (1959).
5. D. M. Aviado, Am. J. med. Sci., Vol. 241 (1961), p. 650.
6. J. Axelrod, Pharmacol. Rev., Vol. 11 (1959), p. 402.

* After the completion of our investigations there appeared the paper by N. M. Kostygov [Farmakologiya i toksikologiya, 26, 1, 28 (1963)], who showed that ephedrine does not give a pressor effect in cats receiving injections of Octatensin (guanethidine), leading to depletion of the catecholamine depots.

7. H. Blaschko, D. Richter, and H. Schlossmann, Biochem. J., Vol. 31 (1937), p. 2187.
8. A. L. A. Boura and A. F. Green, Brit. J. Pharmacol., Vol. 14 (1959), p. 536.
9. J. H. Burn, Brit. med. J., Vol. 1,(1961), p. 1623.
10. J. Del Castillo and L. Stark, J. Physiol. Vol. 116 (Lond.) (1952), p. 507.
11. K. K. Chen, Proc. Soc. exp. Biol. Vol. 22 (1925), p. 570.
12. B. N. Dixit, O. D. Gulati, and S. D. Gokhale, Brit. J. Pharmacol., Vol. 17 (1961), p. 372.
13. J. H. Gaddum and H. Kwiatkowski, J. Physiol., Vol. 94 (Lond.) (1938), p. 87.
14. L. S. Goodman and A. Gilman, The Pharmacological Basis of Therapeutics, New York (1955).
15. H. Kreitmair, Arch. exp. Path. Pharmak., 1927, Bd. 120, S. 189.
16. I. Marcou and A. Savulesco, Compt. rend. Soc. Biol., Vol. 98 (1928), p. 243.
17. A. Pletscher, K. F. Gey and P. Zeller, Fortschr. Arzneimittelforsch., 1960, Bd. 2, S. 417.
18. O. Schaumann, Arch. exp. Path. Pharmak., 1928, Bd. 138, S. 208.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.