

# PHARMACOLOGY

## THE ACTION OF TROPAPHEN ON THE PERIPHERAL VESSELS

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The adrenolytic properties of the tropine ester of  $\beta$ -methoxyphenyl- $\alpha$ -phenylpropionic acid and of the tropine ester of  $\beta$ -acetoxyphenyl- $\alpha$ -phenylpropionic acid have previously been described [3]. The latter compound has been called tropaphen. Clinical trials have shown that tropaphen has a beneficial effect on hypertension [2]. The therapeutic effect of this preparation is more constant in diseases accompanied by spasm of the peripheral vessels. The more detailed study of the action of tropaphen on the peripheral vessels accordingly appeared warranted.

### EXPERIMENTAL METHOD

The action of tropaphen on the tone of the vessels of the hind limbs was studied in cats anesthetized with urethane, by means of the technique of resistography [4]. The effect of tropaphen on the ear vessels of the intact rabbit was judged by the changes in the temperature of the ear. The temperature was measured by means of an electrothermometer, the detector of which was fixed to the internal surface of the ear. The dilation of the auricular vessels was also examined under the microscope, observations being made on the lumen of the marginal artery and vein.

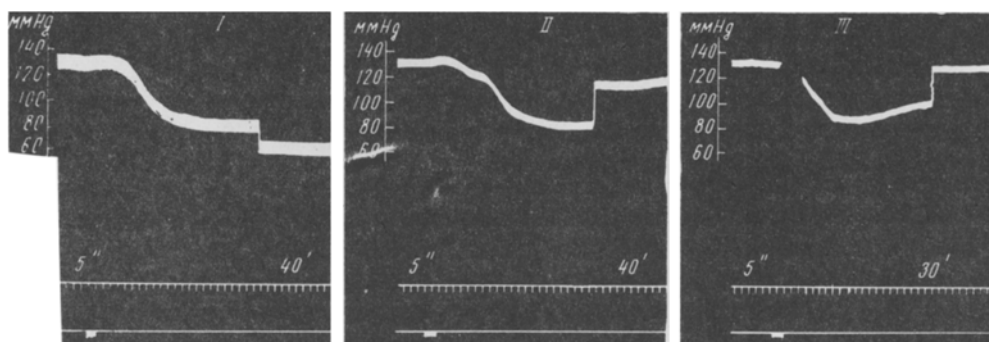


Fig. 1. Changes in the tone of the hind-limb vessels of cats after intravenous injection of tropaphen (I), regitin (II), and benzolin (III) in a dose of 0.25 mg/kg.

The drug was injected intravenously into cats and rabbits. Experiments on the isolated ears of the rabbits were carried out by the Kravkov-Pisemskii method.

The action of tropaphen was compared with that of other adrenolytic substances: regitin (phentolamine; [2-N-p-tolyl-N(m-oxyphenyl)-aminomethylimidazoline]) and benzolin (priscot, tolazolin, 2-benzyl-2-imadazoline). In addition to the investigation of the action of tropaphen itself, its interaction with sympathicomimetic vasoconstrictor drugs—adrenalin, noradrenalin, phenylephrine, and naphazoline—was studied. Further, the action of tropaphen was studied on the tone of the peripheral vessels of the perfused limb of the cat during stimulation of the paravertebral sympathetic chain by the method suggested by V. M. Avakyan and A. A. Chilingaryan [1].

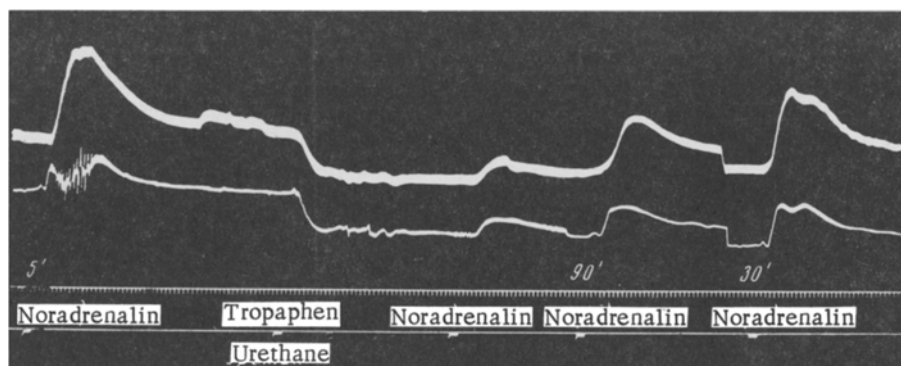


Fig. 2. Effect of noradrenalin on the tone of the peripheral vessels of a cat before and after injection of tropaphen. Significance of curves (from top to bottom): re-sistogram of hind-limb vessels, pressure in common carotid artery, time marker (5 sec) and marker of stopping of kymograph drum, marker of injection of noradrenalin ( $20 \mu\text{g/kg}$ ) and tropaphen ( $0.1 \text{ mg/kg}$ ).

### EXPERIMENTAL RESULTS

The experiments showed that tropaphen has a very marked adrenolytic and vasodilator action. Experiments in which the hind limb of the cat was perfused revealed that tropaphen greatly lowers the tone of the peripheral vessels. The preparation is effective starting with a dose of  $0.1 \text{ mg/kg}$ . After injection of the drug in a dose of  $0.25 \text{ mg/kg}$ , a considerable and gradually progressive decrease in the perfusion pressure took place (Fig. 1). The pressure fell by 30-35% and remained at a low level for 90-100 min. With a dose of tropaphen of  $0.5 \text{ mg/kg}$ , the perfusion pressure fell by 40-45% and remained low for 120 min or more. By comparison with regitin and benzolin, tropaphen has a much more powerful and prolonged action. Regitin, for instance, when injected intravenously in a dose of  $0.5 \text{ mg/kg}$ , lowered the perfusion pressure by 25-30% for 60-90 min. The action of benzolin in a dose of  $0.5 \text{ mg/kg}$  on the tone of the peripheral vessels was ill defined and of brief duration.

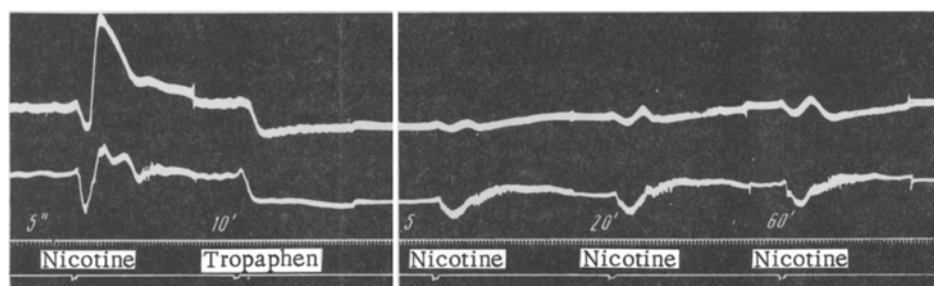


Fig. 3. Action of nicotine on the tone of the peripheral vessels in a cat before and after injection of tropaphen. Significance of the curves (from top to bottom): resistogram of the hind-limb vessels, pressure in the common carotid artery, time marker (5 sec) and marker of stopping of the kymograph drum, marker of injection of nicotine ( $50 \mu\text{g/kg}$ ) and tropaphen ( $0.25 \text{ mg/kg}$ ).

Strong vasodilatation was also observed after injection of tropaphen into intact rabbits. With a dose of  $2 \text{ mg/kg}$ , during the first 5 min the temperature of the ear rose by  $10-12^\circ$  (from  $22$  to  $34^\circ$ ). After 1 h it remained  $2-3^\circ$  above the initial level, and it returned to normal 1.5 h after injection of the compound. Regitin, in the same dose, raised the temperature of the ear by  $8-10^\circ$ , and its action was less prolonged. Benzolin caused no increase in temperature, even in a dose of  $10 \text{ mg/kg}$ . After administration of tropaphen, a considerable increase in the lumen of the vessels of the ear was observed under the microscope.

In the isolated rabbits' ears, tropaphen in a concentration of 1:5000 caused an increase of 16-18% in the outflow

of drops; regitin and benzolin, in the same concentration, gave only a slight vasoconstrictor effect. Hence, tropaphen caused a marked and prolonged fall in the tone and dilatation of the peripheral vessels.

The study of the interaction between tropaphen and the sympathomimetic drugs showed that, starting from a dose of 0.1 mg/kg, the compound clearly diminished the action of adrenalin and noradrenalin on the peripheral vascular tone (Fig. 2). After injection of tropaphen in a dose of 0.25-1.0 mg/kg, the pressor action of adrenalin and noradrenalin and their action on the tone of the vessels diminished or was completely abolished. When tropaphen was given in a dose of 0.25 mg/kg its effect lasted 1.5-2 h, and in a dose of 1 mg/kg—3-3.5 h. In a dose of 0.25 mg/kg tropaphen also completely abolished the action of phenylephrine (0.2 mg/kg) and naphazoline (0.2 mg/kg). By comparison with regitin, tropaphen showed much stronger activity. The adrenolytic action of regitin, when injected intravenously in a dose of 0.25 mg/kg, lasted 1 h; benzoline was inactive in this dose.

Experiments on cats showed that tropaphen, in a dose of 1 mg/kg, abolished the spasm of the vessels of the perfused limb caused by stimulation of the paravertebral sympathetic chain. In a dose of 0.25 mg/kg, tropaphen abolished and prevented for a long time spasm of the vessels caused by injection of cytisine (20  $\mu$ g/kg) and nicotine (50  $\mu$ g/kg) (Fig. 3).

#### SUMMARY

The hydrochloride of the tropine ester of  $\beta$ -acetoxyphenyl- $\alpha$ -phenylpropionic acid (tropaphen) causes reduction in resistance and dilatation of the peripheral vessels and is a highly active adrenolytic agent. By the power and the length of its action it exceeds regitin (phentolamine) and benzolin (tolazoline).

#### LITERATURE CITED

1. V. M. Avakyan and A. A. Chilingaryan. *Farmakol. i toksikol.* 6, 750 (1962).
2. Ts. A. Levina and A. I. Romanovskaya, *Sov. med.* 4, 67 (1961).
3. M. D. Mashkovskii and K. A. Zaitseva. *Byull. éksper. biol.* 1, 56 (1956).
4. V. M. Khayutin et al. *Byull. éksper. biol.* 2, 117 (1958).

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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.

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