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PHARMACOLOGICAL ACTIONS OF PSEUDOSCOPINE AND SOME OF ITS DERIVATIVES

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Pseudoscopine is an amino-alcohol which has the same relation to scopine as has pseudo-tropine to tropine. Its pharmacological properties have not so far been studied and it seemed interesting to compare them with those of scopine, pseudotropine and related compounds to try to establish how changes in chemical structure alter activity.

METHODS

Conscious mice were used to study the effects of the compounds on behaviour, and conscious cats for the effects on behaviour and on electroencephalographic patterns obtained from two animals with recording electrodes implanted in the skull.

Cats of either sex (2–3.5 kg in weight) anaesthetized with sodium pentobarbitone (35 mg/kg intraperitoneally) were used to assess effects on blood pressure, respiration and nictitating membrane, as described previously (Monti & Vidal-Beretervide, 1966) and on the electrocardiogram. Conscious rabbits and pigeons were used to test the ability of compounds to cause paralysis.

Pseudoscopine was tested as the base and as the hydrochloride and the doses refer to the base. All other doses refer to the salts.

RESULTS

In doses up to 450 mg/kg intraperitoneally in mice, and up to 30 mg/kg in cats, pseudoscopine had no apparent effect on behaviour, nor did it affect the electroencephalographic pattern in cats, conscious or anaesthetized.

In doses of 15 mg/kg, pseudoscopine produced a brief fall in blood pressure. Large doses produced a greater fall but no significant changes in electrocardiogram were observed. A fall in blood pressure was also produced in cats in which the vagi had previously been cut. The doses of pseudoscopine did not modify the fall in blood pressure produced by acetylcholine.

When injected into the lingual artery, pseudoscopine neither caused a contraction of the nictitating membrane nor modified the responses to electrical stimulation of the preganglionic nerve to the superior cervical ganglion. Pseudoscopine methobromide, on the other hand, reduced the effects of preganglionic stimulation and also of dimethylphenylpiperazinium without affecting the responses to adrenaline. To reduce the contraction by half, a dose of pseudoscopine methobromide of about 6.5 mg/kg was needed, which is about 20–25 times the amount of hexamethonium chloride producing the same effect. The block in ganglionic transmission was accompanied by a transient fall in blood pressure (Fig. 1). Pseudoscopine methiodide produced similar effects.

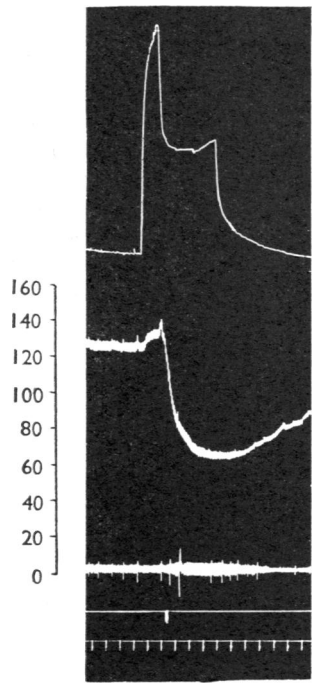

Fig. 1. Male cat weighing 3.2 kg. Sodium pentobarbitone 35 mg/kg, intraperitoneally. From top to bottom, contraction of the nictitating membrane preganglionically stimulated at a rate of 10 pulses/sec, each pulse 1 msec in duration, for 2 min at 7 V; arterial blood pressure; respiration; signal of injection; time (30 sec intervals). At the signal pseudoscopine methobromide 6 mg/kg was injected into the femoral vein. Notice the relaxation of the nictitating membrane (about 50%) and the fall in blood pressure.

The xylylene-*bis*-pseudoscopinium compounds produced a flaccid paralysis in mice, rabbits and pigeons, and these effects were rapidly reversed by the injection of neostigmine 125–250 μg/kg. Full paralysis was produced in rabbits by doses of the *p*-xylylene compounds 16–18 mg/kg, the *m*-xylylene compound 8 mg/kg, and (+)-tubocurarine chloride 0.18 mg/kg. In pigeons the dose of the P-compound needed was 15 mg/kg and of the M-compound 7 mg/kg.

The *p*-xylylene compound produced a transient fall in blood pressure in anaesthetized cats but doses up to 20 mg/kg, necessitating the use of artificial respiration, were without effect on the contractions of the nictitating membrane in response either to preganglionic stimulation or to the injection of dimethylphenylpiperazinium.

DISCUSSION

Pseudoscopine seems to possess weak vasodilatory properties but is otherwise virtually devoid of pharmacological activity. This contrasts with the nicotine-like stimulant and blocking actions of pseudotropine on autonomic ganglia (Hazard, 1939). Pseudoscopine methobromide seems to be a weak ganglion-blocking agent and in this resembles the metho derivatives of scopine and scopoline (Vidal-Beretervide & Monti, 1965).

The xylylene-*bis*-scopinium compounds seem to be neuromuscular blocking agents devoid of ganglion-blocking activity. In this they resemble the xylylene *bis* tropinium salts described by Nádor, Kuttel-Issekutz & Kovatsits (1950), Gyermek & Nádor (1952) and Haining & Johnston (1962) and *p*-xylylene *bis* hyoscinium bromide (Vidal-Beretervide, Monti, Dominguez & Trinidad, 1967). They further resemble these compounds in that their actions resemble those of tubocurarine rather than those of decamethonium but differ from them in that they are much weaker. Although *m*-xylylene bis-pseudoscopinium is 2–2.5 times as active as the *p*-compound, it is only 1–2% as active as (+)-tubocurarine, whereas *p*-xylylene *bis*-hyoscinium bromide is about twice as active as (+)-tubocurarine.

The presence of the epoxide ring and the position of the hydroxyl group seems, therefore, to be important for the activity (or inactivity) of these compounds.

SUMMARY

1. Pseudoscopine injected intravenously in cats anaesthetized with pentobarbitone produces a brief fall in arterial blood pressure, presumably caused by peripheral vasodilatation. It is devoid of action on the central nervous system, the heart and the autonomic ganglia. It does not antagonize the action of acetylcholine on the blood pressure nor the effects of pre-ganglionic stimulation on the contracture of the nictitating membrane.

2. Pseudoscopine monoquaternary methosalts produce a short-lasting blockade of transmission in the superior cervical ganglion.

3. Pseudoscopine *bis*quaternary *p*- and *m*-xylylene derivatives produce flaccid paralysis in mice, rabbits and pigeons. Their effects are reversed by neostigmine but are only feeble, the compounds being between 1 and 2 per cent as active as (+)-tubocurarine chloride.

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