Br. J. Pharmac. Chemother. (1968), 33, 199–201.

THE PRESSOR EFFECT OF LARGE DOSES OF PHYSOSTIGMINE ON THE PITHED RAT

BY

J. E. McEWEN

From the Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge

(*Received January* 30, 1968)

Varagić (1955) showed that small doses of physostigmine (eserine) injected into the anaesthetized rat produced a long-lasting rise in blood pressure. This effect of eserine was not observed in spinal rats and it was blocked by atropine or α-receptor blocking agents (Varagić, 1955). It seemed therefore to be caused by a centrally elicited release of catecholamines into the circulation. On the other hand, the same author stated that large doses of eserine injected into the perfused hind leg of the rat resulted in vasoconstriction (Varagić, 1955). Such a peripheral action of eserine was also suggested by an observation reported by Dixon & Ransom (1924); after a dose of nicotine which paralysed the ganglia, an injection of eserine 10 mg caused a rise in blood pressure in the atropinized cat.

The present paper was prompted by the observation that large doses of eserine caused pressor effects in the atropinized pithed rat. Its purpose was to decide whether these pressor responses were entirely the result of a direct constrictor effect on blood vessels, or whether stimulation of the adrenal medulla or of sympathetic ganglia might be involved.

METHODS

Rats of 200–240 g body weight were injected with atropine sulphate (10 mg/kg body weight, subcutaneously), anaesthetized with ether and pithed according to Shipley & Tilden (1947). A femoral vein was cannulated, heparin (1,000 u./kg body weight) injected and a carotid artery cannulated for recording the blood pressure on a mercury manometer.

Bilateral adrenalectomy, by dorsal approach, was performed under ether anaesthesia.

The following drugs were used: physostigmine sulphate (B.D.H.); *l*-noradrenaline (Hoechst); hexamethonium bromide (May & Baker); phentolamine (Rigitine, Ciba); phenoxybenzamine hydrochloride (Dibenyline, Smith, Kline & French); atropine sulphate (B.D.H.); neostigmine methyl sulphate (Koch-Light).

RESULTS

Typical responses of the blood pressure of the pithed rat to 100 μg and to 300 μg of eserine are shown in Fig. 1A. The pressor effect was short-lasting and the responses were dose-dependent and reproducible.

In two rats bilateral adrenalectomy was performed 24 hr before the experiment. One such experiment is shown in Fig. 2. The pressor response to 1 mg eserine was apparently not reduced in the adrenalectomized rat (Fig. 2A). After the administration of phenoxybenzamine, and at a time when the responses to noradrenaline were blocked (Fig. 2B and

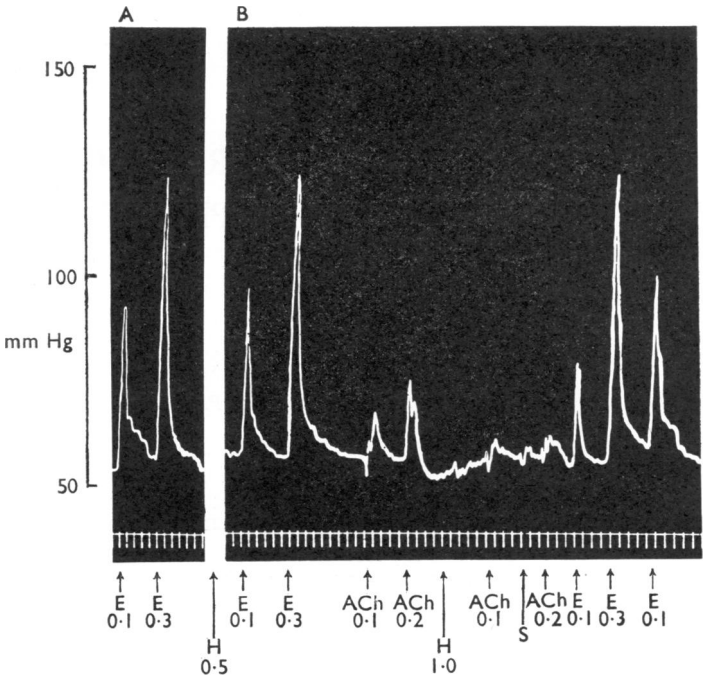

Fig. 1. Pithed rat (200 g), atropine (10 mg/kg). Effect of intravenous injections of eserine (E) and acetylcholine (ACh) on the carotid blood pressure. Hexamethonium was injected intravenously at H. All doses are in mg. Saline (0.3 ml.) was injected intravenously at S. Between A and B there was an interval of 15 min. Time signal: 30 sec.

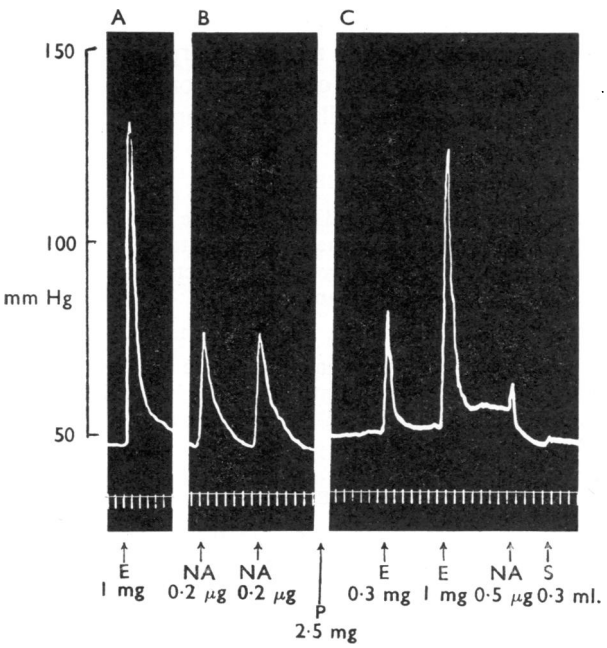

Fig. 2. Pithed rat (200 g), adrenalectomized, atropine (10 mg/kg). Effect of intravenous administration of eserine (E), noradrenaline (NA) and saline (S) on the carotid blood pressure. Between B and C, phenoxybenzamine was injected intravenously (P). There is a 20 min interval between A and B and a 36 min interval between B and C. Time signal: 30 sec.

C) the pressor effect of eserine remained unaffected (Fig. 2C). Phenoxybenzamine also failed to antagonize the pressor effect of eserine in the pithed rat with intact adrenals. Similar results were obtained when phentolamine (5 mg/kg intravenously) was used instead of phenoxybenzamine.

Hexamethonium did not reduce the pressor effect of eserine, at a time when ganglionic blockage had abolished the nicotinic effect of acetylcholine (Fig. 1B). In another experiment eleven doses of 1 mg of nicotine were injected intravenously until ganglionic block was achieved. The pressor effect of eserine remained unchanged when the response to nicotine had disappeared.

Neostigmine in doses from 20 μg to 500 μg had no pressor effects in the pithed rat.

DISCUSSION

The pressor effect of large doses of physostigmine reported in the present publication is an entirely different phenomenon from that of smaller doses described by Varagić (1955) for the following reasons: (1) it is a peripheral effect (obtained in pithed rats); (2) it is unaffected by either atropine or α-receptor blocking agents. With regard to the nature of this peripheral pressor effect of physostigmine, several possibilities have been excluded. The persistence of the pressor effects in adrenalectomized rats shows that it is not mediated through the release of catecholamines from the adrenal medulla. Furthermore, the inability of hexamethonium to reduce the effect of physostigmine demonstrates that it is not caused by stimulation of sympathetic ganglia by physostigmine.

The failure of phenoxybenzamine to antagonize the pressor effect is consistent with the results in adrenalectomized rats and it also excludes as mechanisms the release of endogenous noradrenaline by physostigmine and stimulation of the α-receptors of the arterial smooth muscle by physostigmine.

Consequently the results obtained show that this pressor effect of physostigmine is the result of a direct action on the smooth muscle of the arterial wall.

SUMMARY

1. Doses of 100 μg to 1 mg of physostigmine injected intravenously produce an increase in arterial blood pressure of the pithed, atropinized rat.

2. This pressor effect of physostigmine is not affected by bilateral adrenalectomy, α-receptor blocking agents (phenoxybenzamine or phentolamine), or ganglion-blocking drugs (hexamethonium or nicotine).

3. It is concluded that the pressor action of large doses of physostigmine is the result of a direct effect on the smooth muscle of the arterial wall.

I wish to thank, most sincerely, Dr. M. Vogt, F.R.S., and Dr. S. Z. Langer for their kind encouragement and helpful advice. I am also greatly indebted to Dr. Vogt for performing the adrenalectomies.

REFERENCES

DIXON, W. E. & RANSOM, F. (1924). *Heffter's Handbuch der Experimentellen Pharmakologie II*, 2 Hälfte, 786–812. Berlin: Springer.

SHIPLEY, R. E. & TILDEN, J. H. (1947). A pithed rat preparation suitable for assaying pressor substances. *Proc. Soc. exp. Biol. Med.*, **64**, 453–455.

VARAGIĆ V. (1955). The action of eserine on the blood pressure of the rat. *Br. J. Pharmac. Chemother.* **10**, 349–353.