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THE EFFECT OF ANTI-CHOLINESTERASE AGENTS ON THE RAT'S BLOOD PRESSURE

BY

P. DIRNHUBER AND H. CULLUMBINE

From C.D.E.E., Ministry of Supply, Porton, Wilts

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In most species, the effect of systemic intoxication with an anti-cholinesterase—for example, HETP (hexaethyltetraphosphate), TEPP (tetraethyl pyrophosphate), dyflos (di*iso*propylphosphorofluoridate), Tabun (ethyl *NN*-dimethylphosphoramidocyanidate), or neostigmine—is predominantly the production of a profound fall in blood pressure (Modell, Krop, Hitchcock and Riker, 1946; Heymans and Jacob, 1947; Lundholm, 1949; Burgen, Keele and Slome, 1949; Verbeke and Votava, 1949; Salerno and Coon, 1949; Holmstedt, 1951). We have recently noticed that the intravenous administration of the anti-cholinesterase "Sarin" (*iso*propyl methylphosphonofluoridate) to intact rats produces a sharp rise in blood pressure, then one or two oscillations about the point of increased pressure, followed by a very gradual fall in pressure over the next several minutes (10–180 min. in different animals) back to the pre-injection level (Fig. 1). The cause of this sustained rise in blood pressure produced by sarin has been investigated.

METHODS

White rats of homogeneous strain and weighing 350–500 g. were used. They were anaesthetized with urethane (1.25 g./kg. subcutaneously), and polythene cannulae were inserted into the carotid artery, to record blood pressure, and into the femoral vein.

With the doses of sarin used respiratory embarrassment or failure may occur and so may interfere with the blood-pressure recording or response. Therefore, in many experiments, even respiratory exchange was maintained throughout by means of a miniature Starling "Ideal" pump. The same pattern of cardiovascular response has, however, been seen in rats that were not sustained by artificial ventilation.

Spinal preparations were made by transecting the spinal cord between C1 and C2 and destroying the brain.

RESULTS

The hypertensive effect of sarin is best seen following a fairly large dose (40–60 μg./kg.), but is still evident after smaller doses. The effects of rapidly repeated small doses can be summated up to a certain point; then the general blood-pressure level falls, although each successive sarin dose produces a transient, small rise (Fig. 2). With higher single doses (e.g. 90 μg./kg.) the animal dies before the sustained rise in blood pressure has become established.

Bilateral vagotomy does not affect the results, but if sarin is given to a spinal rat only a relatively slow, small and short-lasting increase in blood pressure is caused (Fig. 3). The failure of sarin to produce a sustained elevation of blood pressure in this experiment is not due to the low blood pressure presented by a spinal rat. Thus, if the blood pressure is lowered, by bleeding or by small doses (10–20 mg./kg.) of C6, sarin still produces a typical hypertensive response. This suggests that the hypertensive action is central in origin. Acetylcholine is probably involved as transmitter at some point, since in the previously atropinized rat (intact

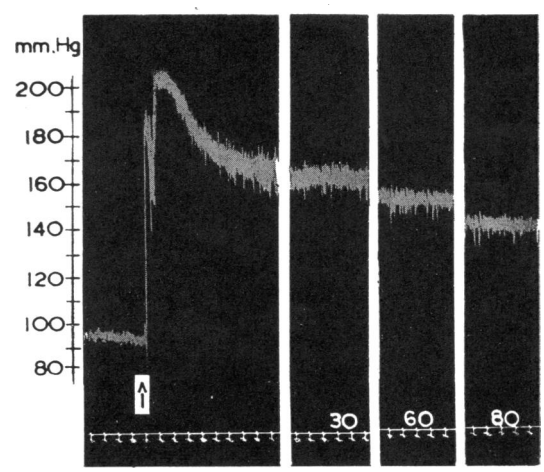

FIG. 1.—Rat 370 g., urethane. Spontaneous respiration. At arrow 40 μg. sarin/kg. i.v. Numerals are times in min. after administration of sarin. (Time scale is 1 min. in all figs.) Shows sustained hypertensive effect of sarin.

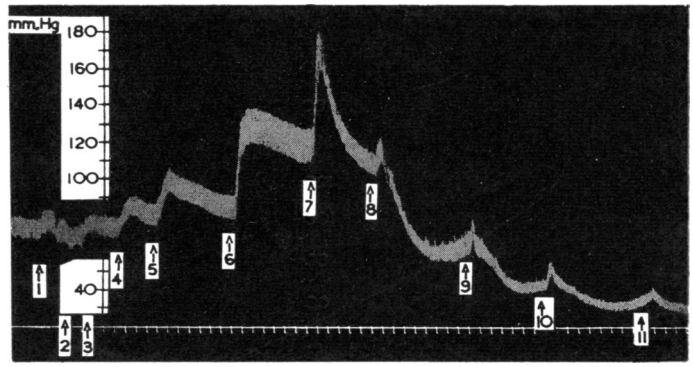

FIG 2.—Rat 400 g., urethane. Artificial ventilation. At each arrow 5 μg. sarin/kg. i.v. (total of 11 doses). Shows effect of repeated small doses of sarin.

or spinal) sarin produces again only a slow and minor rise in blood pressure (Fig. 4). Similarly, if successive doses of atropine are administered after sarin, a step-like depression of the elevated blood pressure is produced.

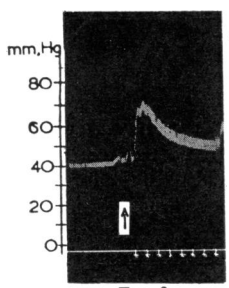

FIG. 3

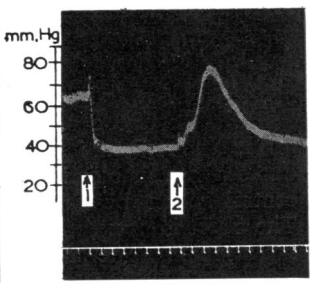

FIG. 4

FIG. 3.—Rat 470 g., urethane. Spine transected, brain pithed. At arrow 40 μg. sarin/kg. i.v. Shows small blood-pressure rise in spinal rat.

FIG. 4.—Rat 310 g., urethane. Artificial ventilation. At 1st arrow 10 mg. atropine/kg.; at 2nd arrow 40 μg. sarin/kg. i.v. Shows small blood-pressure rise in atropinized rat.

If C6 (10–20 mg./kg.) is given to a rat during the sustained pressor response following sarin, the blood pressure is immediately reduced (Fig. 5). Pre-treatment with large doses of C6 (200–400 mg./kg.) prevents the usual pressor response to sarin.

The central stimulant action of sarin is effected, therefore, via the sympathetic nervous system. Liberation of adrenaline from the adrenal glands would not seem to be important, since sarin still raises the blood pressure of adrenalectomized rats, and this rise can be inhibited by small doses of C6.

A sympathetic, peripheral vascular mechanism is probably involved, since peripheral blockade of sympathetic impulses with ergotamine or tolazoline alters the response. If either of these substances is administered before sarin, the latter produces only a preliminary sharp rise, but no sustained elevation, of blood pressure (Fig. 6). If sarin is given first, and then tolazoline during the period of raised blood pressure, the latter is at once temporarily reduced.

The sustained rise in blood pressure induced by sarin is probably due mainly to constriction of the skin arterioles: in the skinned rat only an immediate temporary rise in pressure, with no continued elevation, is seen (Fig. 7). In conformity with this, sarin produces a maintained pressure rise when administered to an eviscerated rat. This rise is not as long-lasting as that occurring in the intact rat, so that some arteriolar constriction may occur in the splanchnic area.

That a direct central action is involved is also suggested by the observation that a small dose (5 μg.) of sarin, injected into the fourth ventricle, causes a similar sustained rise in blood pressure (Fig. 8). An injection of acetylcholine into the same site produces a fall in blood pressure. This dissimilarity in the actions of acetylcholine and sarin may be owing to failure of the former to

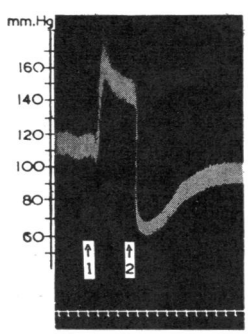

FIG. 5

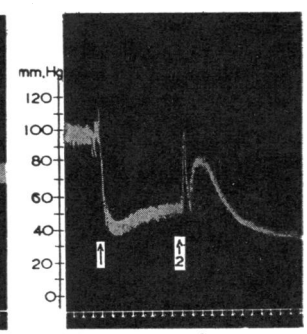

FIG. 6

FIG. 5.—Rat 390 g., urethane. Artificial ventilation. At 1st arrow 40 μg. sarin/kg. At 2nd arrow 10 mg. C6/kg. i.v. Shows that a small dose of C6 after sarin reduces blood pressure.

FIG. 6.—Rat 390 g., urethane. Artificial ventilation. At 1st arrow 10 mg. tolazoline/kg. At 2nd arrow 40 μg. sarin/kg. Shows small pressor effect after treatment with tolazoline.

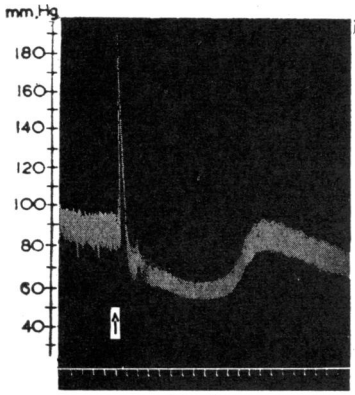

FIG. 7

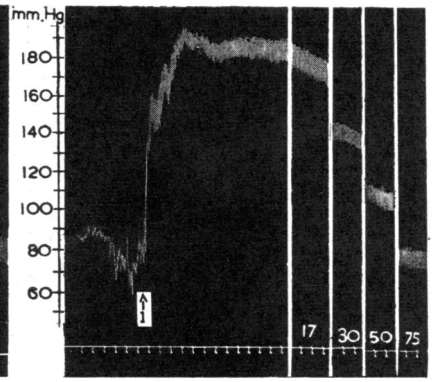

FIG. 8

FIG. 7.—Rat 480 g., urethane. Artificial ventilation. All skin removed (head, feet, and scrotum not skinned). Body placed in saline bath at 37°. At arrow 40 μg. sarin/kg. intravenously. There is no sustained pressor effect in skinned animal.

FIG. 8.—Rat 420 g., urethane. Artificial ventilation. At arrow 5 μg. sarin/rat through atlanto-occipital membrane. Shows effect of small dose of sarin injected to 4th ventricle. Numerals indicate time (min.) after sarin.

penetrate into the brain substance, although some leakage into the systemic circulation occurs. The direct central action of sarin can still be prevented by systemic atropinization.

Another indication of the enhanced sympathetic tone in these rats is that the heart rate (measured from the e.c.g.) is increased during the period of hypertension—in a typical instance the heart rate before sarin (40 μg./kg.) was 270/min.; during the phase of rising blood pressure it was 390/min.; and at the peak of the blood-pressure rise it reached 450/min.

In other species, where a fall of blood pressure is produced by sarin, this is accompanied by a slowing of the heart (Holmstedt, 1951).

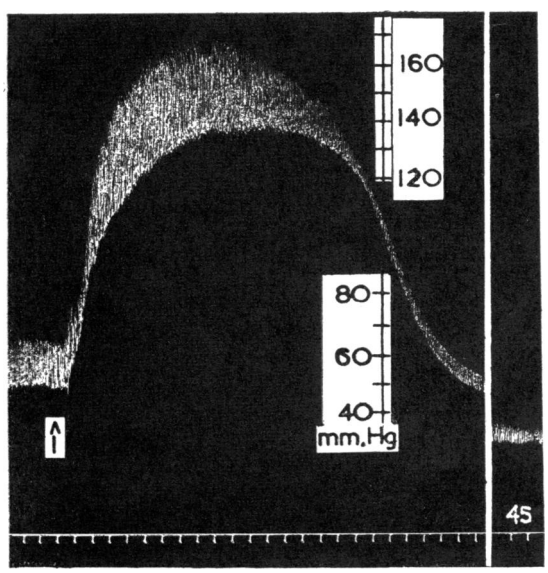

FIG. 9.—Rat 470 g., urethane. Artificial ventilation. At arrow 1 mg. dyflos/kg. intravenously. Shows hypertensive effect of dyflos in ther at.

The hypertensive action of sarin in the rat is not peculiar to that compound, but is shared by other anti-cholinesterases, such as dyflos (Fig. 9), eserine, TEPP, and E.600. Atropine and C6 affect the response to these agents in the manner described for sarin.

DISCUSSION

From the above results we can conclude that sarin, when given intravenously to the rat, produces a rise in blood pressure which is due to a central action, possibly on the vasomotor centre. The effect is not seen in the spinal rat or following atropine. The latter observation suggests that the central phenomenon involves cholinergic transmission.

The central stimulation presumably acts through the sympathetic nervous system, and this sympathetic "drive" can be blocked at the ganglia by hexamethonium bromide and, more peripherally, by ergotamine or tolazoline. It would appear that the vessels of the rat's skin are those chiefly concerned in this sympathetic action.

Other anti-cholinesterases can produce a similar hypertension in the rat, so that the phenomenon presumably has the inhibition of cholinesterase as its basis. The rise in blood pressure is, further, not peculiar to the intravenous route of administration, since it has also been seen after the intraventricular or the intracarotid injection of sarin.

In other species anti-cholinesterases, when administered intravenously, cause a marked lowering of the blood pressure, although a transient rise of pressure is often seen before the profound fall takes place (Holmstedt, 1951). This fall in blood pressure is accompanied by a marked slowing of the heart and by dilatation of the small vessels in the limb muscles; whereas, if sarin is injected in small doses into the vertebral artery or

the cisterna magna of a dog, a rise in blood pressure is the invariable response (Wilson, personal communication). Therefore a central hypertensive action can be seen in another species than the rat. In the dog following intravenous administration, it must be presumed that the peripheral effects on the cardiovascular system predominate over the central hypertensive action.

These varying responses in the different species suggest that there may be corresponding differences in the nature and the sensitivity of the receptor substances and the cholinesterases of the tissues of these species. This is being further investigated.

Summary

1. Sarin, dyflos, eserine, TEPP, and E.600 all produce hypertension when administered to rats in near-lethal doses.

2. This hypertension is apparently effected by a central mechanism acting through the sympathetic nervous system on the blood vessels of the skin.

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