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THE PERIPHERAL ACTION OF HEXAMETHONIUM AND OF PENTOLINIUM

BY

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The influence of hexamethonium and pentolinium on the responses of certain peripheral effector cells to adrenaline, noradrenaline or postganglionic stimulation was studied in the cat. The actions of adrenaline and noradrenaline on the blood vessels of a limb and of adrenaline and postganglionic stimulation on the nictitating membrane were increased after the administration of hexamethonium and pentolinium. This effect was considered to be due to sensitization of the peripheral effector cells. The possible significance of these findings is discussed.

Hexamethonium and pentolinium are quaternary ammonium compounds which block transmission in autonomic ganglia by competition with acetylcholine. From animal experiments it is known that, under standard conditions, these substances are extremely consistent in their behaviour and that the ganglionic synapse, no matter which ganglionic pathway is tested, shows an increasing sensitivity to subsequent doses. Repeated doses of hexamethonium and pentolinium, however, produce decreasing responses from the blood pressure (Zaimis, 1956). The same discrepancy between blood pressure and ganglionic responses is seen in man during the intravenous administration of these drugs for the reduction of blood pressure in operations; the first dose usually produces a good fall of blood pressure, but the pressure returns quite rapidly to its initial level and any subsequent doses are practically without effect (Enderby, personal communication). Also it has been the experience of clinicians that a daily increase in the dose of hexamethonium or pentolinium is necessary for the first few weeks if the initial rate of reduction in blood pressure is to be maintained. This is usually described as the development of "tolerance." In addition, there is the much discussed potentiation of adrenaline and noradrenaline which always occurs in the presence of hexamethonium or pentolinium, and which cannot be attributed only to the abolition of the normal compensatory mechanisms as it is found both after vagotomy and after section of the spinal cord at a high level (Bartorelli, Carpi and Cavalca, 1954; Salerno, 1955; Maengwyn-Davies, Walz and Koppanyi, 1958). All these factors taken together suggested the possibility of a peripheral action of hexamethonium and pentolinium in the form of a sensitization of the effector cells to adrenaline and noradrenaline (Zaimis, 1955). This hypothesis has been tested in the experiments reported in the present paper. Some of these results have already been reported briefly (Zaimis, 1956).

METHODS

Cats were anaesthetized with a mixture of chloralose (80 mg./kg.) and pentobarbitone (6 mg./kg.) injected into the cephalic vein of the fore limb or the saphenous vein of the hind limb. The addition of pentobarbitone prevented the initial stage of excitement which normally follows the intravenous injection of chloralose alone.

Recording of the Venous Outflow from the Hind Limb.—An incision was made in the skin of the medial surface of the thigh to expose the femoral artery and vein, and all branches of both femoral artery and vein down to the popliteal space, including the saphenous vein, were ligated and cut, with the exception of the artery chosen for the intra-arterial administration of the drugs. In order to maintain a regular blood-flow through the limb, the muscles were stimulated indirectly by the application of electrical shocks to the sciatic nerve at a frequency of 6 stimuli/min. Heparin (1,000 units/kg.) was administered intravenously 10 min. before any vessels were opened. The method described by Hilton (1952, 1953) was used for recording the venous outflow. In the tracings the height of the record measures the time interval between successive drops.

The drugs were injected either *close-arterially* by means of a cannula made from a No. 18 hypo-

dermic needle tied into the cut central end of a branch of the femoral artery, usually the small artery supplying the gracilis muscle; or *distant-arterially* into the external iliac artery of the non-operated leg, the cannula in which pointed towards the bifurcation of the aorta.

Contractions of the Nictitating Membrane.—These were elicited either by rectangular pulse stimuli of 0.3 msec. duration and applied at 10/sec. to the pre- or post-ganglionic cervical sympathetic nerve trunk; or by intra-arterial injections of adrenaline into the cut central end of the lingual artery.

Drugs.—(−)-Adrenaline tartrate, (−)-noradrenaline bitartrate, hexamethonium iodide and pentolinium bitartrate were used throughout these experiments and are referred to as adrenaline, noradrenaline, hexamethonium and pentolinium respectively.

RESULTS

Blood-flow.—In the first group of experiments, 0.1 μg. of noradrenaline was injected close-arterially at intervals of 10 to 15 min. This dose produced a local vasoconstriction with no change of the general blood pressure. After the intravenous administration of hexamethonium, or pentolinium, the vasoconstrictor effect of noradrenaline became more pronounced and more prolonged. Fig. 1 illustrates the results of two such experiments. In Fig. 1*a* 1 mg. of hexamethonium and in Fig. 1*b* 1 mg. of pentolinium was administered intravenously. This potentiating effect lasted for 10 to 15 min. with hexamethonium and somewhat longer with pentolinium.

In a second series of experiments noradrenaline was administered intravenously and hexamethonium or pentolinium distant-arterially. Fig. 2 illustrates such an experiment in which 1 μg. of noradrenaline administered intravenously produced a rise in blood pressure and a diphasic effect on the blood-flow through the limb, an increase to begin with because of the rise in the general blood pressure, followed by a decrease due to the direct vasoconstrictor effect of noradrenaline on the limb vessels. After the distant-arterial administration of 200 μg. of hexamethonium both the local vasoconstriction and

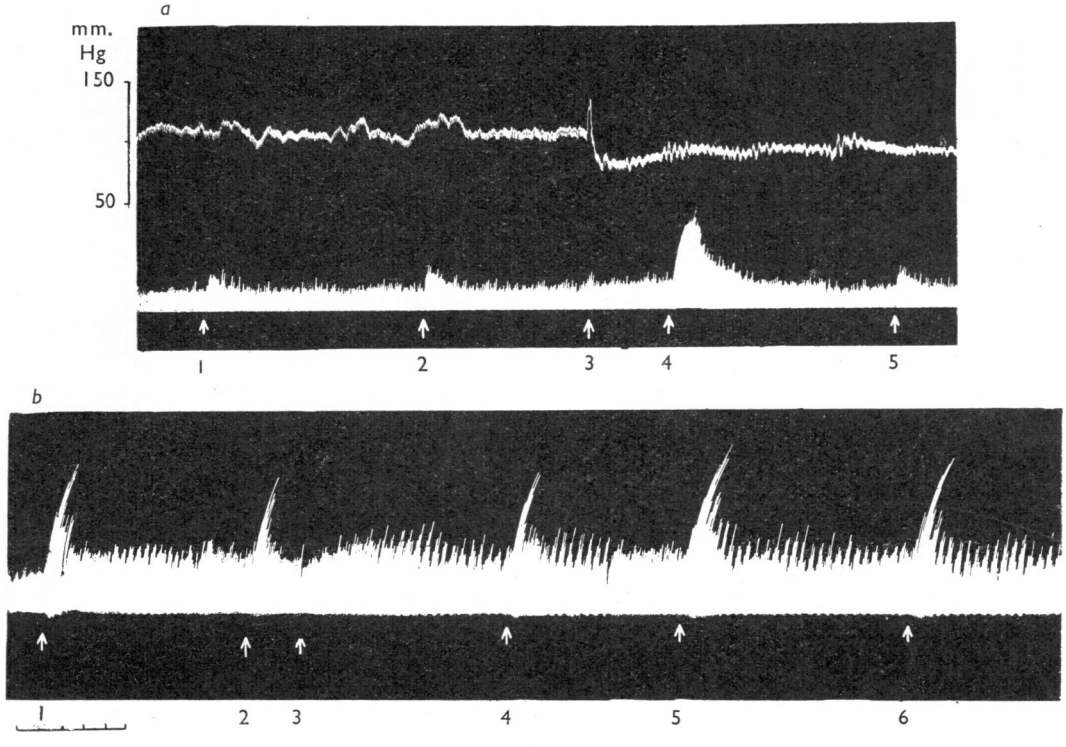

FIG. 1.—(*a*) Cat: 2 kg. Blood pressure upper trace. Venous outflow from hind limb lower trace. At 1, 2, 4 and 5, close-arterial injections of 0·1 μg. of noradrenaline. At 3, intravenous injection of 1 mg. of hexamethonium. (*b*) Cat: 3·2 kg. Venous outflow from hind limb. At 1, 2, 4, 5 and 6, close-arterial injections of 0·1 μg. of noradrenaline. At 3, intravenous injection of 1 mg. of pentolinium. Time, min.

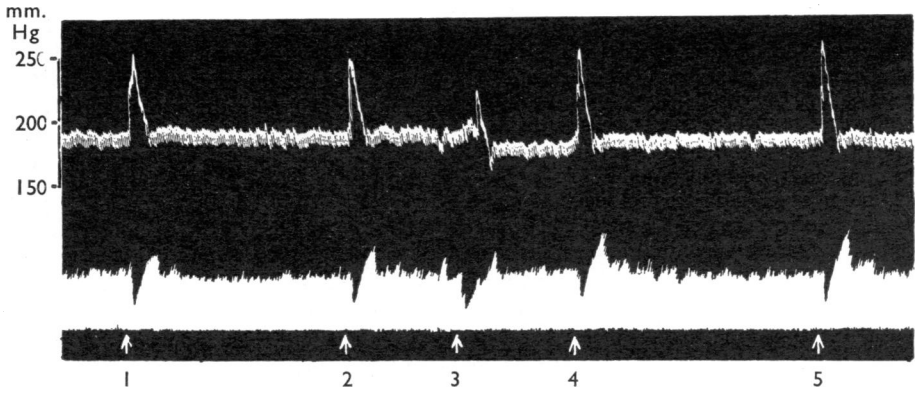

FIG. 2.—Cat: 2·6 kg. Blood pressure upper trace. Venous outflow from hind limb lower trace. At 1, 2, 4 and 5, intravenous injections of 1 μg. of noradrenaline. At 3, distant-arterial injection of 200 μg. of hexamethonium.

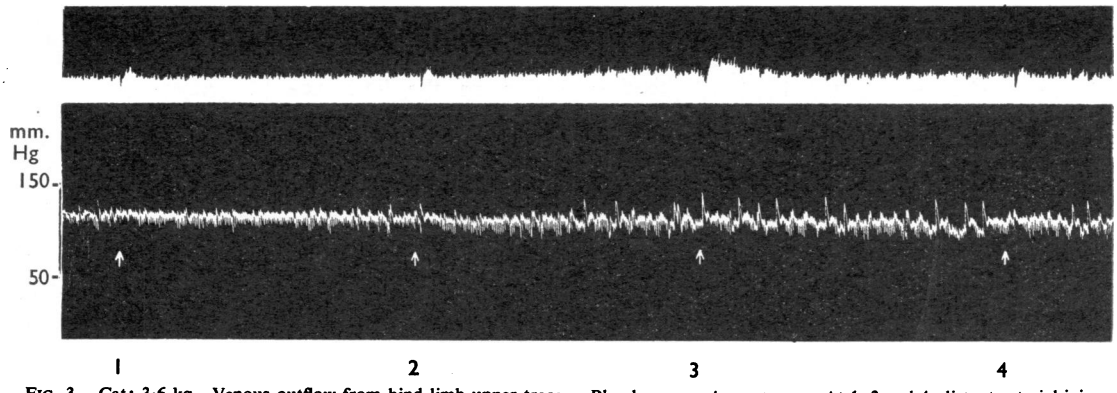

FIG. 3.—Cat: 3·6 kg. Venous outflow from hind limb upper trace. Blood pressure lower trace. At 1, 3 and 4, distant-arterial injections of 1 μg. of noradrenaline. At 2, distant-arterial injection of 1 μg. of noradrenaline together with 100 μg. hexamethonium.

blood pressure responses produced by noradrenaline were increased. In a third series of experiments both drugs were administered distant-arterially and similar results were obtained. After 100 μg. of hexamethonium, noradrenaline produced a more pronounced vasoconstriction (Fig. 3).

In a few experiments in which adrenaline was used, both hexamethonium and pentolinium increased its vasoconstrictor action.

Nictitating Membrane.—In the first group of experiments, a series of submaximal contractions of the nictitating membrane were elicited at regular time intervals by the electrical stimulation of the postganglionic cervical sympathetic trunk. After a number of control contractions hexamethonium or pentolinium was administered intravenously. The contractions increased after the administration of either drug. The onset of the effect was usually rapid, attained its maximum in about 3 to 6 min. and lasted for

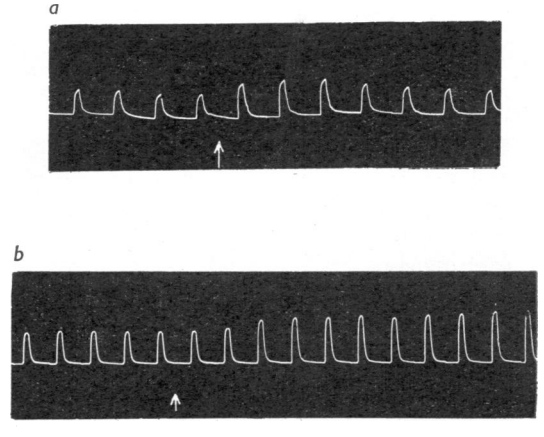

FIG. 4.—(*a*) Cat: 2·2 kg. Contractions of nictitating membrane elicited every 3 min. by submaximal postganglionic stimulation at 10 shocks/sec. Period of stimulation 30 sec. At arrow, intravenous injection of 2 mg. of hexamethonium. (*b*) Cat: 2·8 kg. Similar experiment. At arrow, intravenous injection of 2 mg. pentolinium.

10 to 15 min. for hexamethonium and somewhat longer for pentolinium. Fig. 4 illustrates two such experiments in which the potentiating effect was obtained with doses of hexamethonium or pentolinium which produced 50% or less ganglionic blockade. Larger doses did not alter the magnitude of the potentiating effect.

In a second series of experiments, contractions of the nictitating membrane were elicited by the intra-arterial administration of adrenaline in doses which produced submaximal responses. The intravenous administration of either hexamethonium or pentolinium was followed by an increased response (Fig. 5). This potentiation was produced by doses of hexamethonium and pentolinium comparable to those necessary to affect contractions elicited by postganglionic stimulation. The time course of the effect was also similar.

Discussion

Hexamethonium and pentolinium are powerful ganglionic blocking substances, and in order to detect peripheral action only tests which avoid ganglionic interference can be used. Such conditions are offered by the response of the blood vessels of a limb to adrenaline and noradrenaline, or the response of the nictitating membrane to postganglionic stimulation or to injected adrenaline.

The results reported above demonstrate that hexamethonium and pentolinium sensitized the

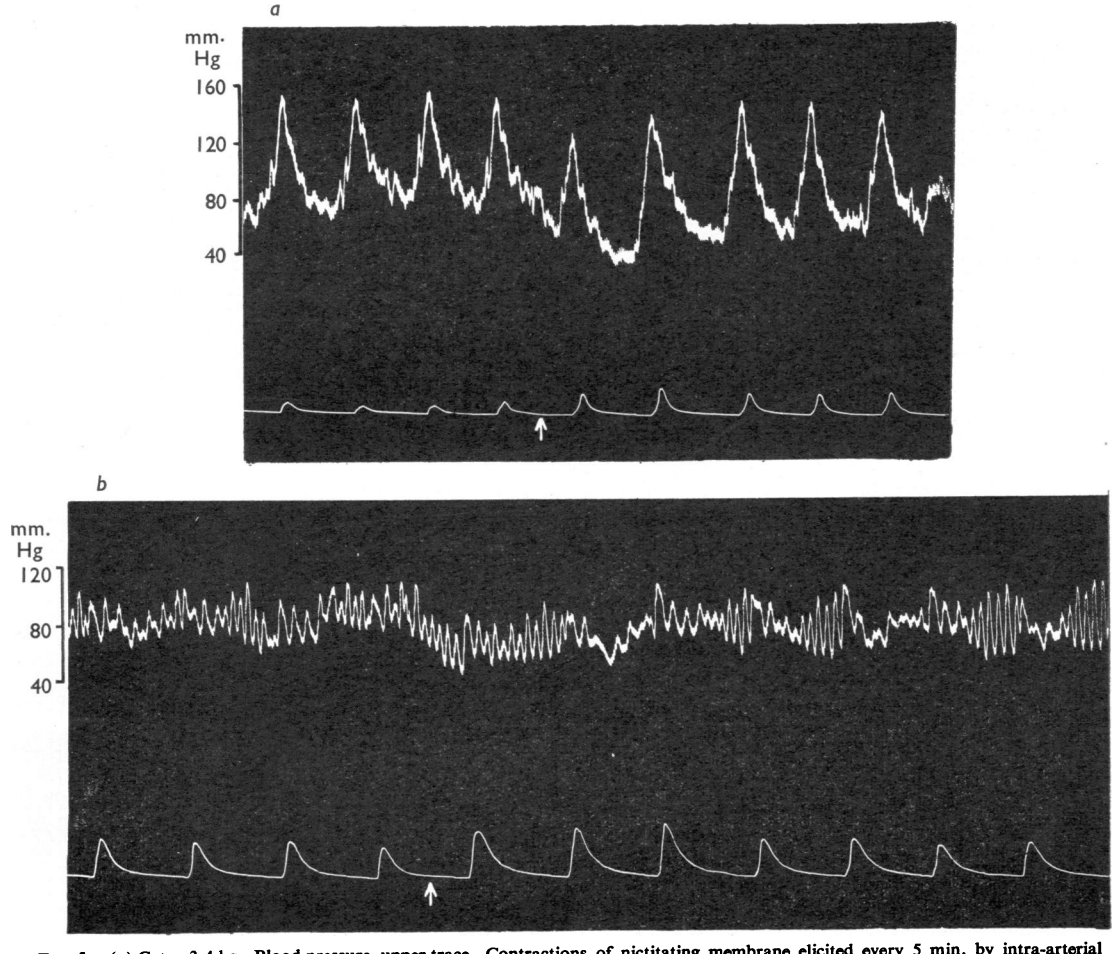

FIG. 5.—(a) Cat : 3·4 kg. Blood pressure, upper trace. Contractions of nictitating membrane elicited every 5 min. by intra-arterial injection of 2 μg. of adrenaline, lower trace. At arrow, intravenous injection of 2 mg. of hexamethonium. (b) Cat: 2·4 kg. Similar experiment but with intra-arterial injection of 1 μg. of adrenaline. At arrow, intravenous injection of 580 μg. of pentolinium.

effector cells to adrenaline, noradrenaline, and to sympathetic stimulation. This sensitization, although usually small, could always be detected, and it was independent of the route of administration of either the sympathomimetic amines or the ganglionic blocking drugs. The effect appeared with doses of hexamethonium or pentolinium smaller than those producing a complete ganglionic blockade. With repeated or larger doses the potentiating effect remained the same.

Evidence that quaternary ammonium compounds with powerful ganglionic blocking activity can increase the response of effector cells to chemical and mechanical stimuli can be found in several reports. Very often, however, such evidence has been misinterpreted or has passed unnoticed.

Shimamoto, Kanauchi, and Uchizumi (1955), in experiments on the nictitating membrane of the cat, found that both tetraethylammonium and hexamethonium potentiate the action of adrenaline, noradrenaline, and postganglionic sympathetic stimulation. This effect was present in normal as well as in denervated preparations and also after adrenalectomy. The same investigators reported that, under the influence of the two quaternary ammonium compounds, the relaxation of the isolated uterus of the cat and of the isolated sphincter pupillae muscle of cats and rabbits produced by adrenaline and noradrenaline was inhibited or even reversed. Discussing their results, Shimamoto *et al.* (1955) reached a conclusion which is rather difficult to understand. According to them, all these effects were produced because tetraethylammonium and hexamethonium " abolish the inhibitory action of adrenaline, noradrenaline, and postganglionic sympathetic stimulation." Perry and Wilson (1956), when studying the relative effects of ganglion blocking drugs on the sympathetic and parasympathetic supply to the heart in cats, found that pentamethonium was more active on parasympathetic ganglia and that the rapid onset of parasympathetic block which the drug produced was accompanied by a potentiation of the effect of sympathetic stimulation. They made the further observation that the potentiation of the sympathetic response was also present when the sympathetic stimulation was postsynaptic, indicating that this effect was a peripheral and not a ganglionic one. Bülbring (1955), using the isolated taenia coli of the guinea-pig, demonstrated that hexamethonium had a stimulant action and sensitized the muscle to different forms of stimulation.

Zauder (1954) found that hexamethonium potentiated the responses of the isolated intestine of the cat to both acetylcholine and histamine, an action which he considered was independent of innervation and probably due to " an increase in the excitability of the muscle in a manner as yet unexplained." Meier, Tripod, and Wirz (1957), using the perfused rabbit hind limb preparation, found that hexamethonium markedly increased the vasoconstrictor action of 5-hydroxytryptamine.

Thus it appears that hexamethonium and pentolinium can potentiate smooth muscle responses to different stimuli. It is difficult to say how this sensitization is brought about. Possibly these quaternary ammonium compounds produce permeability changes which in turn alter the behaviour of excitable cells in response to physiological and pharmacological stimuli.

From the results reported in this paper and from the evidence produced by other investigators, the conclusion may be drawn that subsequent doses of hexamethonium or pentolinium produce decreasing blood pressure effects, not because the magnitude of the ganglionic blockade is diminished, but because this is partially masked by the peripheral sensitization of the blood vessels to adrenaline and noradrenaline. Considering the extent of the vascular tree it is obvious that even a small increase in the response of the blood vessels to adrenaline and noradrenaline will produce pronounced haemodynamic consequences (Folkow, 1956). Sensitization of the blood vessels may well account for the increase in the responses produced by adrenaline and noradrenaline in the presence of hexamethonium or pentolinium, and for the development of " tolerance " which appears during the treatment of hypertensive patients.

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