EFFECT OF SOME GANGLION BLOCKING DRUGS ON THE RESPONSES OF THE RABBIT TRACHEAL CHAIN TO ADRENALINE, ISOPRENALINE AND AMINOPHYLLINE

By

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TEA, chlorisondamine, pempidine, pentolinium and mecamylamine potentiated the inhibitory effects of adrenaline, isoprenaline and aminophylline on the rabbit tracheal chain. Chlorisondamine and pempidine, in higher concentrations depressed the relaxant effect of adrenaline and isoprenaline. Hexamethonium had no effect either on adrenaline and isoprisenaline or on aminophylline induced relaxation of the rabbit tracheal chain.

Potentiation of the pressor effects of injected adrenaline and noradrenaline has been repeatedly demonstrated following ganglion blocking drugs, both in animals and in man (Page and Taylor, 1947; Corcoran and Page, 1947; Gefen and Ross, 1956). Enhanced responses to catechol amines after ganglion blocking drugs were formerly solely attributed to a blockade of compensatory cardiovascular reflexes (Moe, 1948; Page and Taylor, 1950; Bartorelli *et al.*, 1954). However, in recent years evidence has accumulated to show that at least part of the potentiating effect is due to a sensitization of the vascular smooth muscle to circulating catechol amines (St. Clair & Stone, 1951; Mantegazza *et al.*, 1958; Maengwyn-Davis *et al.*, 1958)

If ganglion blocking drugs sensitize the vascular smooth muscle with its preponderance of the excitatory or *alpha* drenergic receptors, then it is likely that they might also sensitize smooth muscle structures which have a preponderance of the inhibitory or *beta* adrenergic receptors. Studies on the modification of amine responses by ganglion blocking drugs, however, have been almost exclusively confined to the excitatory effects of catechol amines. The present paper describes the effects of certain monoquaternary, bisquaternary and nonquaternary ganglion blocking agents on the inhibitory effects of

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adrenaline and isoprenaline on the bronchial smooth muscle of the rabbit. Modification of responses to aminophylline, a non-adrenergic bronchodilator was also studied simultaneously.

METHODS

Albino rabbits of either sex weighing between 2 to 3 kg were killed by a blow on the head. Tracheal chains were prepared according to the method of Castillo and de Beer (1947). Preparations were suspended in a 30 ml. organ bath and connected to a balsa-wood frontal writing lever. The load on the tracheal chain was 1·5 to 2 g and the responses were magnified 8 times. Kreb's bicarbonate solution containing 0·01 M glucose and aerated with 95% oxygen and 5% carbon dioxide was used as the bathing medium. Pilocarpine nitrate was added in a concentration of 1 mg/100 ml. Inhibitory responses to adrenaline and isoprenaline were recorded on a smoked kymograph paper after the pilocarpine-induced spasm had reached a stable plateau. When the inhibition produced by a fixed dose of the amines was constant, the ganglion blocking agents were added to the bath and allowed to act for 3 to 4 min ; the inhibitory effect of the amines was again determined.

Drugs :—Tetraethylammonium bromide (TEA), hexamethonium chloride, pentolinium tartrate, chlorisondamine dimethochloride, mecamylamine hydrochloride, pempidine tartrate, and isoprenaline sulphate were used throughout the experiments and the concentrations refer to the salts. Adrenaline was used as the base dissolved in normal saline and the concentrations refer to the base.

RESULTS

The isolated rabbit tracheal chain was used to study the effect of ganglion blocking drugs on inhibitory responses to adrenaline, isoprenaline and aminophylline. Ordinarily the responses of the rabbit tracheal chain to adrenaline, isoprenaline and aminophylline varied with repeated doses, however, the addition of pilocarpine to the bathing fluid enabled a uniform inhibitory response to be obtained.

Effect on adrenaline and isoprenaline induced relaxation.

Tetraethylammoniam (TEA) :—TEA, in concentrations of 3×10^{-5} to 2×10^{-4} did not alter the pilocarpine induced spasm ; 3 to 5 min later the relaxing effect of adrenaline (1×10^{-6} to $3{\cdot}3\times10^{-6}$) or isoprenaline (1×10^{-6} to $3{\cdot}3\times10^{-6}$) was considerably enhanced. This potentiating effect persisted for 20 to 30 min despite repeated washing of the preparation. Fig. 1 shows the potentiation of the relaxant effect of adrenaline by increasing concentra-

tions of TEA. The potentiation was related to the dose; the magnitude of potentiation varied from 60 to 320 per cent of the control response.

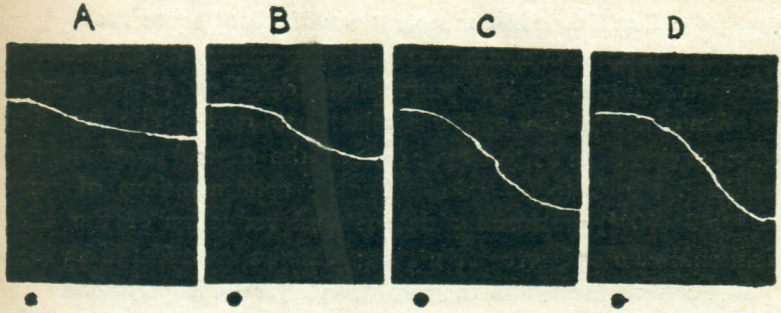

Fig. 1. Responses of the rabbit tracheal cheain to adrenaline 3.3×10^{-6} (at dots) alone (A) and in the presence of TEA, 3.3×10^{-5} (B), TEA, 6.6×10^{-5} (C), and TEA, 1.3×10^{-4} (D). Contact time for adrenaline 3 min.

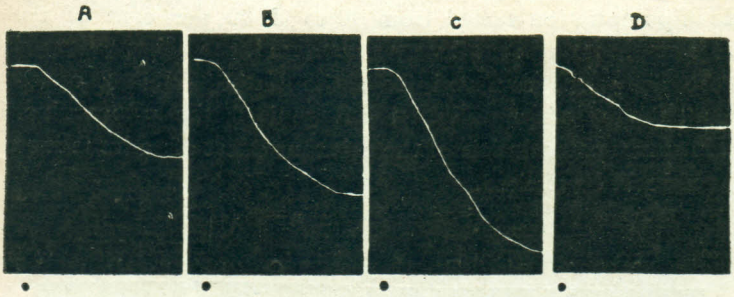

Fig. 2. Responses of the rabbit tracheal chain to isoprenaline 3.3×10^{-6} at (dots) alone (A) and in the presence of pempidine 0.5×10^{-6} (B), pempidine 1×10^{-6} (C), and pempidine 1×10^{-6} (D). Contact time for isoprenaline 3 min.

Chlorisondamine. —Chlorisondamine in concentrations of $0{\cdot}2 \times 10^{-6}$ to $2{\cdot}5 \times 10^{-6}$ had no effcct on the pilocarpine induced spasm of the tracheal chain; however, after exposure for 2 min the inhibitory responses to adrenaline and isoprenaline were greatly potentiated. The potentiating effect was related to dose, the inhibitory responses to the amines being progressively augmented with increasing concentrations of chlorisondamine. The magnitude of potentiaton varied from 155 to 400 per cent of the control response. Potentiation of amine response by chlorisondamine was of long duration, the effect persisting for $1\frac{1}{2}$ to 2 hr. despite repeated washing. Higher concentra-

tion (5×10^{-8} and above) of chlorisondamine reduced the inhibitory effect of the amines.

Pempidine. —Pempidine in concentrations of $0{\cdot}3 \times 10^{-6}$ to 1×10^{-6}, potentiated the relaxant effect of adrenaline and isoprenaline, without affecting the pilocarpine induced spasm. The potentiation developed at 3 to 5 min of the administration of pempidine and was related to dose. The magnitude of potentiation varied from 33 to 64 per cent of the control response and the effect persisted for 10 to 20 min. Higher concentrations of pempidine (1.5×10^{-6} to 3×10^{-5}) produced a dose-related reduction of the inhibitory effect of adrenaline and isoprenaline. Fig. 2 shows the effect of a wide range of pempidine concentrations on the inhibitory effect of isoprenaline.

Pentolinium. —Pentolinium in concentrations of 2.5×10^{-6} to 1.5×10^{-5} did not alter the pilocarpine induced spasm but after exposure for 1 min considerably enhanced the relaxant effect of adrenaline and isoprenaline. The potentiating effect was related to the dose of pentolinium Fig. 3) and the magnitude of potentiation varied from 40 to 1100 per cent of the control response. The potentiation was very short-lived, the effect disappearing as soon as the drug was removed from the bath. Higher concentrations (2×10^{-5} and above) of pentolinium antagonised the pilocarpine induced spasm. However, potentiation of the relaxant effect of adrenaline and isoprenaline could still be elicited.

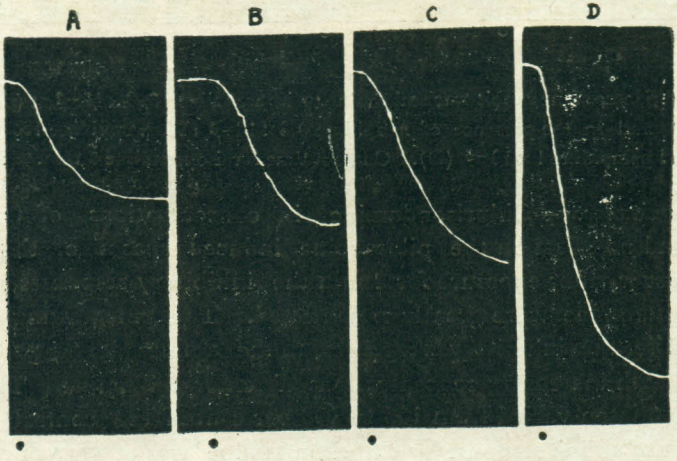

Fig. 3. Responses of the rabbit trachealchain to isoprenaline $3.3 \times 10{-}6$ (at dots) alone (A) and in the presence of pentolinium $2.5 \times 10{-}6$ (B), pentolinium $5 \times 10{-}6$ (C) and pentolinium $1 \times 10{-}5$ (D). Contact time for isoprenaline 3 min.

Mecamylamine.—Mecamylamine in concentrations of 3.3×10^{-6} to $1{\cdot}3 \times 10^{-4}$ had no effect on the pilocarpine induced spasm but after exposure for 1 min the relaxation caused by adrenaline and isoprenaline was enhanced. The potentiating effect of mecamylamine was related to dose and the magnitude of potentiation varied from 133 to 540 per cent of the control response. Augmentation of amine responses by mecamylamine was transient and disappeared soon after the removal of the drug from the bath. In higher doses (1.5×10^{-4}) and above mecamylamine antagonised the pilocarpine induced spasm; responses to adrenaline and isoprenaline were potentiated.

Hexamethonium.—Hexamethonium (0.2×10^{-6} to 1.5×10^{-4}) had no effect on the relaxation caused by adrenaline and isoprenaline.

Effect on Aminophylline induced relaxation.

TEA (3.3×10^{-5} and 6.6×10^{-5}); chlorisondamine (2×10^{-6}); pempidine (1×10^{-6}); pentolinium (0.5×10^{-5}) and mecamylamine (2×10^{-4}) all potentiated the relaxant effect of aminophylline (4.2×10^{-5}) on the tracheal chain (Fig. 4). Hexamethonium ($0{\cdot}2 \times 10^{-6}$ to 1.5×10^{-4}) had no effect.

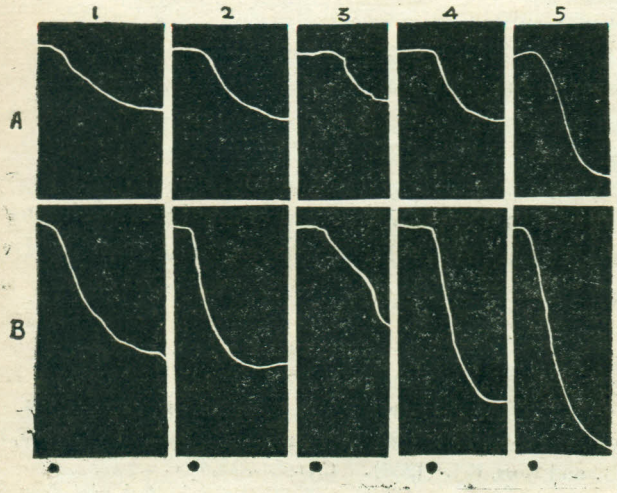

Fig. 4. Responses of the rabbit tracheal chain to aimnophylline $4.2 \times 10{-}5$ added at dots. Panel A shows the control responses; panel B shows the corresponding potentiated responses obtained after 4 min exposure to TEA, 3.3×10^{-5} in (1); to chlorisondamine, $2 \times 10{-}6$ in (2); to pempidine, $1 \times 10{-}6$ in (3); to pentolinium $0.5 \times 10{-}5$ in (4) and to mecamylamine, $2 \times 10{-}4$ in (5). Contact time for aminophylline 3 min.

DISCUSSION

The results of the present experiments utilizing the isolated rabbit tracheal chain have demonstrated that TEA, chlorisondamine, pempidine, pentolinium and mecamylamine act directly on effector cells in the bronchial smooth muscle to potentiate the inhibitory effects of adrenaline and isoprenaline. It is concluded that the sensitizing effect of ganglion blocking drugs is not limited to effector cells containing the excitatory or *alpha* adrenergic receptors, but also extends to those which have a preponderance of the *beta* adrenergic receptor and respond to catechol amines by relaxation. The potentiating effect of the ganglion blocking agents studied was not specific for adrenaline or isoprenaline as responses to aminophylline were also simultaneously potentiated. Though the exact mode of action of these drugs is not clear from our experiments it could be reasonably assumed that they act directly on effector cells in the bronchial smooth muscle to affect some fundamental biological function such as cell permeability to drugs and thereby sensitize them to bronchodilator drugs like adrenaline, isoprenaline and aminophylline.

Chlorisondamine and pempidine in higher concentrations produced a definite and dose-related depression of the inhibitory effects of adrenaline and isoprenaline. The nature of the depressant effect on amines responses is not clear. However, a depression of the contractile response of the aortic strip to adrenaline and noradrenaline by high concentrations of chlorisondamine has been reported (Kelkar *et al.*, 1964). Hexamethonium had no effect either on responses to adrenaline, isoprenaline or those to aminophylline. It is concluded that hexamethonium is devoid of any local sensitizing effect on the rabbit tracheal chain. A similar conclusion was drawn by Lum and Rashleigh (1961) and Kelkar *et al.* (1964) using the cat carotid strip and the rabbit aortic strip respectively.

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