PRESSOR EFFECTS OF ADRENALINE, NORADRENALINE AND REFLEX VASOCONSTRICTION SENSITISED BY LOW CONCENTRATIONS OF GANGLION BLOCKING DRUGS

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In cats, rats and pigeons, concentrations of hexamethonium, tetraethylammonium and pentolinium ions too low to influence transmission in autonomic ganglia potentiate the pressor effects of adrenaline, noradrenaline and of reflex vasoconstriction. These effects of the ganglion blocking drugs are not modified by spinalization or by acute adrenalectomy but are absent after pretreatment of an animal with reserpine or of a tissue by postganglionic sympathetic denervation. These concentrations of ganglion blocking drug increase the uptake of noradrenaline by the adrenal medulla, increase the total amine and the proportion of it present as adrenaline in this gland, fail to antagonise adrenal medullary depletion of catecholamine by reserpine and can reverse a pre-existing potentiation of the pressor effects of adrenaline and noradrenaline induced by cocaine.

PAGE and Taylor (1947) first drew attention to potentiation of the pressor actions of adrenaline and noradrenaline by ganglion blocking drugs, an observation confirmed by others (St. Clair and Stone, 1951; Bartorelli, Carpi and Cavalca, 1954). In general, the concentration of ganglion blocking drugs has been sufficient to prevent transmission in autonomic ganglia. Indeed, Bartorelli and others (1954) found no evidence of potentiation in dogs until blocking concentrations of tetraethylammonium were used.

Our interest in this phenomenon was aroused by a chance observation made in the cat. A single intravenous dose of tetraethylammonium ions, sufficient to produce no more than a 50 per cent reduction in the submaximal response of a nictitating membrane to preganglionic stimulation of the ipselateral ascending cervical sympathetic chain potentiated the pressor actions of adrenaline or noradrenaline. Moreover, this potentiation persisted for more than an hour after all trace of the ganglion blocking action of the tetraethylammonium ions had disappeared.

METHODS

The male or female wistar rats weighed 300 to 450 g. unless otherwise stated and were killed either by a blow on the head or were anaesthetised by the intraperitoneal injection of 1 ml. 10 per cent urethane in 0·9 per cent sodium chloride per 100 g. body weight, or were made spinal under ether anaesthesia. Records of arterial pressure were taken from a carotid artery and intravenous injections were made through a polythene cannula inserted into an external jugular vein. Cats varied in weight

from 0·75 to 3·2 kg.; anaesthesia was induced with ether and was maintained by the intravenous injection of 8·0 ml. 1·0 per cent chloralose in 0·9 per cent sodium chloride per kg. body weight. Records of arterial pressure were taken either from a carotid or from a femoral artery; intravenous injections were made through cannulae inserted into femoral veins. Heparin was used as anticoagulant. Cocaine hydrochloride, dissolved in 0·9 per cent sodium chloride, was either injected intravenously, 1 mg./kg. or subcutaneously 5 mg./kg. Reserpine, dissolved in 20 per cent aqueous ascorbic acid, was injected intramuscularly, 5 mg./kg., 48 and 24 hr. before experiments. Postganglionic denervation of nictitating membranes was effected by aseptic removal of the corresponding superior cervical ganglia under pentobarbitone anaesthesia 8 to 10 days before experimental use.

Measurement of the effect of blocking agents on pressor responses to adrenaline and noradrenaline. Three, occasionally two, different doses either of (—)-adrenaline or of (—)-noradrenaline, submaximal in effect, were administered to rats in the order of Latin Squares until the resting blood pressure and responses to individual doses were uniform and had remained so for more than 30 min. Intravenous injection of a small quantity of a ganglion blocking drug was then made; the doses selected were too small to depress the resting arterial pressure and failed to reduce submaximal effects of injections of nicotine acid tartrate introduced intravenously. When absence of ganglionic effect had been demonstrated, the dose effect curve for the catecholamine was redetermined. The procedure was repeated with increase in the dose of the ganglion blocking agent until potentiation of the pressor effects of the catecholamine was well developed. Potentiation was then shown; it was reversible with time. The procedure in experiments made on cats differed in that the effects of ganglion blocking agents were examined simultaneously on the pressor actions of adrenaline and noradrenaline. Absence of ganglion block was evidenced by failure to reduce the submaximal effects of preganglionic stimulation of a vagus nerve on the mean arterial pressure and of stimulation of an ascending cervical sympathetic chain on a nictitating membrane.

Measurement of the effect of small repeated doses of ganglion blocking agents on adrenal medullary amines in rats. Litter mates of both sexes, weighing 180–205 g., were evenly distributed, and one animal from each group began a 10-day period of treatment on each successive day. All animals were killed on the eleventh day for the preparation of extracts of adrenal glands from which the amines were separated chromatographically, eluted and assayed biologically. No significant differences were detected in the adrenal medullary amines of the two sexes.

Measurement of the effect of low concentrations of ganglion blocking agents on the uptake of noradrenaline by the adrenal glands and aortae of rats. Litter mates of both sexes were divided evenly between groups to which separate treatments were assigned for use in subsequent acute

experiments. Thereafter one animal from each group was used daily in a series of experiments made according to a standardised procedure. First, an intramuscular injection was made of a ganglion blocking agent or of saline alone. Immediately afterwards, anaesthesia was induced with urethane, and a polythene cannula was inserted into an external jugular vein. Through this, intravenous injection was made either of saline or of saline containing a blocking agent. This was at once followed by the continuous infusion of 80 μg. noradrenaline in 2 ml. 0·9 per cent NaCl at constant rate over 40 min. The adrenals were removed for the preparation of extracts 5 min. after the infusion ended. Amines were separated chromatographically from these extracts and were assayed biologically.

Extracts of adrenal glands. Adrenal glands were carefully cleaned of fatty tissue immediately after removal and were stored in the refrigerator at 0° C. for 2 hr. before weighing and grinding in 0·1N HCl with silver sand. The extract and the mortar washings were combined, heated in a boiling water bath for 2 min., cooled and centrifuged. Thereafter the chromatographic separation of adrenaline and noradrenaline was effected, and the amines were eluted and prepared for biological assay as described by Lockett (1954). Assays of adrenaline were made on the rat uterus or colon (Gaddum, Peart and Vogt, 1949) and of noradrenaline on the rat colon or on the mean arterial pressure of pithed rats.

RESULTS

Potentiation of the pressor effects of adrenaline or noradrenaline and of reflex activity in the sympathetic nervous system. Experiments on rats, pigeons and cats have shown that concentrations of three different ganglion blocking agents, too small to influence transmission in autonomic ganglia, increase the pressor effects of intravenous adrenaline and noradrenaline and of reflex activity in vasoconstrictor fibres of the sympathetic nervous system. The ganglion blocking agents studied were tetraethylammonium, hexamethonium and pentolinium ions. The criteria accepted as evidence of absence of ganglion action were unchanged submaximal vascular responses to nicotine in the rat and the pigeon and unchanged submaximal effects of preganglionic stimulation of the peripheral end of a divided vagus on arterial pressure and of the ascending cervical sympathetic on the nictitating membrane in the cat. The increased pressor effects of fixed doses of adrenaline and of noradrenaline induced by a concentration of tetraethylammonium ions too small to influence transmission in autonomic ganglia (Fig. 1) are of variable duration; in general, it may be expected to last from 40 min. up to several hours in cats, from 20 to 60 min. in rats and from 10 to 25 min. in pigeons: it was always reversible. The increase in the pressor effects of intravenous adrenaline and noradrenaline was accompanied by increase in the pressor component of the carotid mechanoreceptor reflex (Fig. 2). The sensitisation was induced with equal ease in anaesthetised animals

(Figs. 1 and 2) and in those made spinal, vagotomised and acutely adrenalectomised (Fig. 3). An analysis of the changes occurring in the log dose effect curves for the pressor actions of adrenaline and noradrenaline under the influence of sub-blocking doses of tetraethylammonium and of hexamethonium ions was made in rats under urethane

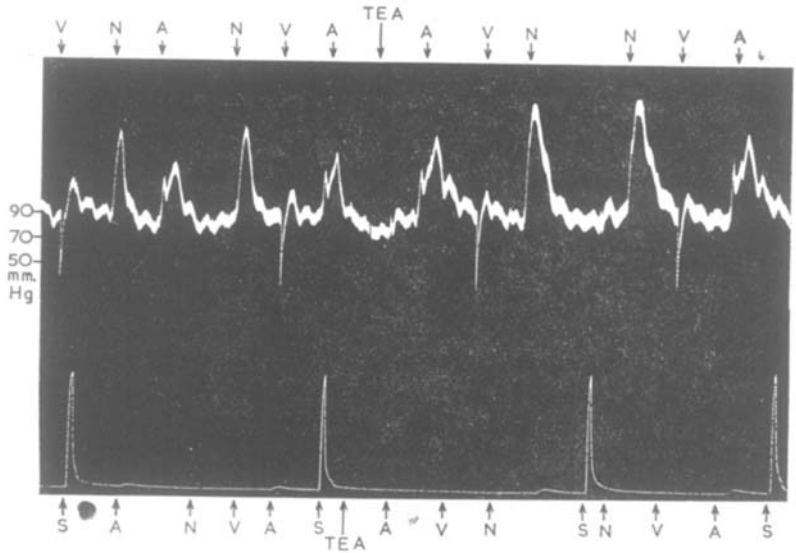

FIG. 1. Low concentrations of a ganglion blocking drug potentiate pressor effects of adrenaline and noradrenaline. Records of mean arterial pressure (above) and the contractions of a nictitating membrane (below), taken from a cat 2·2 kg. under chloralose anaesthesia. Intravenous injections: A, 3 μg. (−)-adrenaline; N, 1 μg. (−)-noradrenaline; TEA, tetraethylammonium chloride, 1 mg./kg. V signifies rectangular pulses to R. peripheral vagus, 250 μsec., 20/sec. 4 V. S, rectangular pulses to ascending cervical sympathetic, 250 μsec., 5/sec. 2 V. for 30 sec. in each case.

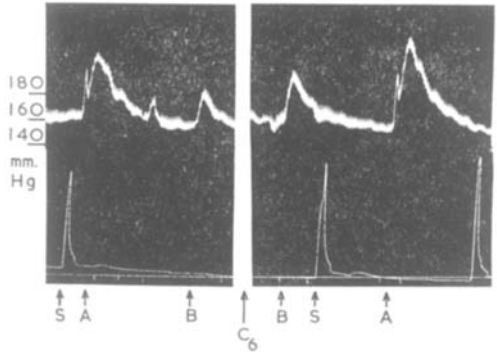

FIG. 2. Low concentrations of a ganglion blocking drug potentiate reflex vasoconstriction. Records of mean arterial pressure and of contractions of a nictitating membrane from a cat, 2·3 kg. under chloralose anaesthesia. Intravenous injections: A, 2·5 μg. (−)-adrenaline; C_6, hexamethonium bromide, 1 mg./kg. Other procedures: B, occlusion of the L. carotid for 30 sec., S as in Fig. 1.

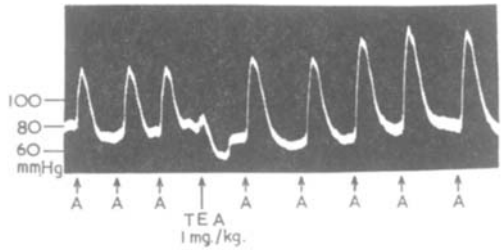

FIG. 3. Low concentrations of a ganglion drug potentiate the pressor effects of adrenaline in a spinal, vagotomized and acutely adrenalectomised cat, 1·9 kg., responding to i.v. injection of 4 μg. (−)-adrenaline at intervals of 4 min. TEA as in Fig. 1.

anaesthesia. The results of these experiments are summarised in Table I. In every experiment the dose-effect curve for the catecholamine shifted to the left without change in its slope.

TABLE I

CONCENTRATIONS OF HEXAMETHONIUM AND TETRAETHYLAMMONIUM IONS TOO LOW TO DEPRESS ACTIVITY IN AUTONOMIC GANGLIA, SHIFT THE LOG-DOSE EFFECT CURVES FOR THE PRESSOR ACTIONS OF ADRENALINE AND NORADRENALINE IN RATS UNDER URETHANE ANAESTHESIA TO THE LEFT, BUT DO NOT INFLUENCE THEIR SLOPE

	Log-dose effect curves			
	Adrenaline		Noradrenaline	
Ganglion blocking drug	Value of b	mm.Hg rise, 0·4 μg.	Value of b	mm.Hg rise, 0·4 μg.
Tetraethylammonium μg./kg. i.v.				
0	35·7 ± 1·08	28·7 ± 1·65	37·7 ± 2·77	29·0 ± 1·53
125	37·0 ± 1·41	34·0 ± 1·00*	36·3 ± 3·37	34·3 ± 1·54*
250	41·0 ± 3·22	39·3 ± 2·01**	41·0 ± 2·18	38·7 ± 1·83**
500	37·0 ± 2·52	44·3 ± 0·91**	41·0 ± 2·05	43·3 ± 2·83**
Hexamethonium μg./kg. i.v.				
0	36·5 ± 3·48	13·0 ± 1·23		
200	36·0 ± 4·01	20·2 ± 2·24**		
400	37·5 ± 5·49	25·4 ± 20**		

Three rats per group. Significance of effective alteration in a mean as a result of the blocking agent was tested by '*t*' test, and is shown by asterisk; one, P = <0·05, two, P = <0·01.

How do low concentrations of ganglion blocking drugs increase the pressor effects of intravenous adrenaline and noradrenaline? Sensitisation to the pressor effects of adrenaline and of noradrenaline may follow from changes in the tissue chromaffin stores, from inhibition of enzyme systems capable of metabolising these catecholamines or from an increase in the efficiency of the response mechanisms. Fig. 4 shows that whereas a partially blocking concentration of tetraethylammonium caused an increase in the effects of adrenaline on mean arterial pressure almost immediately, sensitisation of the normal nictitating membrane was more gradual; there was no sensitisation in the denervated membrane. Whereas tetraethylammonium, in low concentration, readily potentiates the pressor effects of adrenaline and noradrenaline in spinal rats, it fails to do so if the tissue chromaffin stores have been depleted by pretreatment with reserpine (Fig. 5).

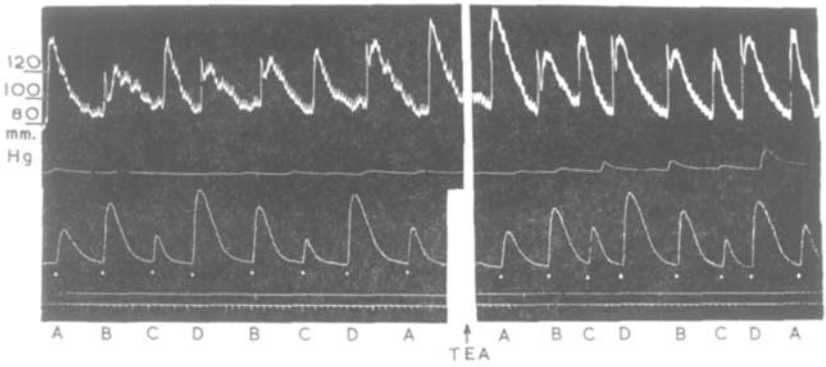

FIG. 4. Low concentrations of a ganglion blocking drug potentiate the effects of adrenaline on a normal but not a denervated nictitating membrane. Spinal cat, 3·2 kg. Records, from above, downward: mean arterial pressure, normal nictitating membrane, membrane 10 days after postganglionic denervation. Intravenous injections: A, 2 μg. and C, 1 μg. (−)-noradrenaline; B, 2 μg. and D, 4 μg. (−)-adrenaline. TEA as in Fig. 1 between the two sets of tracings, in 3 min. interval.

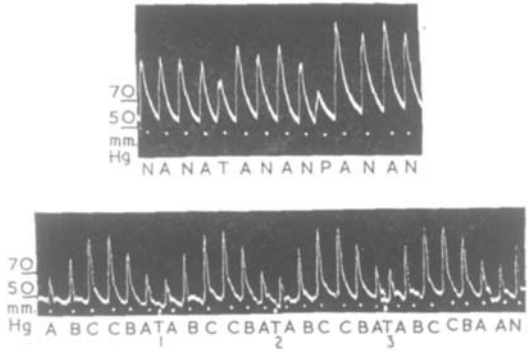

FIG. 5. Absence of potentiation in reserpine-treated animals. Record of mean arterial pressure from a spinal rat, 450 g. above, and a spinal reserpine-treated rat 490 g., below. Injections, i.v. (above), N, 50 ng. (−)-noradrenaline; A, 200 ng. (−)-adrenaline; T, TEA 100 μg./kg.; P, pyrogallol, 25 mg./kg. (below), A, B and C, 40, 80 and 160 ng. (−)-noradrenaline respectively. T_1, T_2 and T_3, 50, 100 and 200 μg. TEA respectively.

Potentiation of the pressor effects of adrenaline and noradrenaline by cocaine, 1 mg./kg., i.v., or 5 mg./kg. subcut., lasts for more than an hour in spinal rats; it is, however, rapidly reversed shortly after its onset by concentrations of these ganglion blocking drugs too small to influence transmission in autonomic ganglia (Fig. 6). Whereas pyrogallol, 25 mg./kg. given intravenously further increases sensitisation to the pressor effects of adrenaline and noradrenaline when this has been caused by low concentrations of ganglion blocking drug, these same concentrations of the blocking drugs fail to augment the pressor effects of the catecholamines in the presence of a pre-existing submaximal potentiation produced by pyrogallol (Fig. 7).

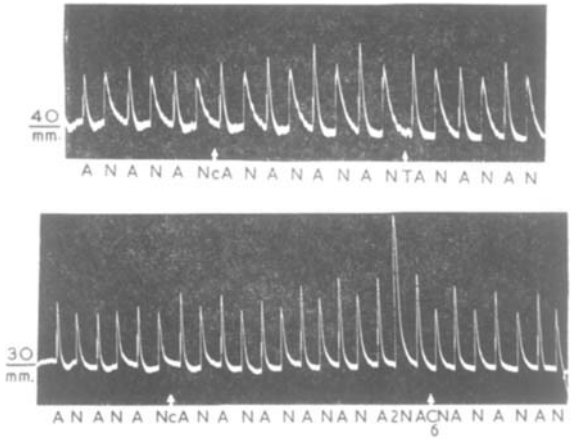

FIG. 6. Reversal of cocaine potentiation of pressor responses to adrenaline and noradrenaline by low concentrations of ganglion blocking drugs. Records of mean arterial pressure from two spinal rats, 400 and 350 g. responding to the following intravenous injections: A, (−)-adrenaline, 100 ng. N, (−)-noradrenaline, 50 ng. Cocaine administered subcutaneously 5 mg./kg. TEA and C_6 as in Figs. 1 and 2 respectively.

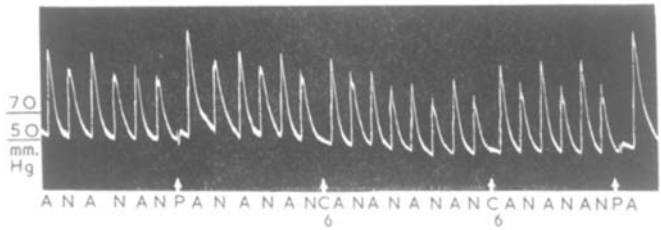

FIG. 7. Interactions between potentiations caused by pyrogallol and low concentrations of ganglion drugs in pressor responses to adrenaline and noradrenaline. Record of the mean arterial pressure of a spinal rat 450 g. responding to the following intravenous injections: A, 0·1 μg. (−)-adrenaline, N, 0·05 μg. (−)-noradrenaline; P, pyrogallol, 25 mg./kg. C_6 as in Fig. 2.

Concentrations of these ganglion blocking drugs too small to influence transmission in autonomic ganglia, which increased pressor responses to adrenaline and noradrenaline, failed to alter pressor responses to tyramine (Fig. 8).

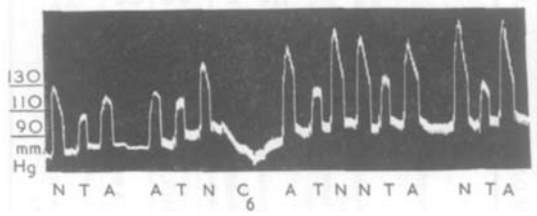

FIG. 8. Low concentrations of a ganglion blocking drug fail to potentiate the pressor effects of tyramine. Record of the mean arterial pressure of a cat, 1·5 kg., under chloralose anaesthesia. Intravenous injections: A, 3 μg. (−)-noradrenaline; T, 100 μg. tyramine hydrochloride. C_6 as in Fig. 2.

TABLE II

THE EFFECT OF TETRAETHYLAMMONIUM IONS, 1 OR 10 MG./KG. AND OF ATROPINE SULPHATE 5 MG./KG. GIVEN SUBCUTANEOUSLY TWICE DAILY FOR 10 DAYS, AND OF COCAINE HYDROCHLORIDE 1 MG./KG. FOR 2 DAYS, ON THE ADRENAL MEDULLARY HORMONES OF RATS AND CATS

Treatment	Weights		μg. Amine per mg. adrenal gland				Number of animals
	Body, g.	Adrenal, mg.	Noradrenaline	Adrenaline	Total pressor amine	Adrenaline / noradrenaline	
Rats							
None	203 ± 4·5	45 ± 3·4	0·15 ± 0·020	0·65 ± 0·065	0·80 ± 0·671	4·4 ± 0·64	8
Hexamethonium, 1 mg./kg.	186 ± 6·6	44 ± 2·1	0·07 ± 0·008*	1·16 ± 0·106*	1·25 ± 0·081*	17·7 · 0·04**	8
Tetraethylammonium, 1 mg./kg.	200 ± 5·0	43 ± 3·0	0·09 ± 0·011*	1·28 ± 0·141*	1·36 ± 0·143*	16·8 ± 0·31**	8
None	188 ± 2·1	45 ± 3·0	0·14 ± 0·015	0·56 ± 0·061	0·70 ± 0·063	4·3 ± 0·87	8
Hexamethonium, 10 mg./kg.	196 ± 4·6	49 ± 3·7	0·09 ± 0·019*	1·03 ± 0·130*	1·12 ± 0·122*	14·8 ± 0·33**	8
Tetraethylammonium, 10 mg./kg.	197 ± 1·7	49 ± 4·4	0·08 ± 0·013*	0·085 ± 0·118	0·95 ± 0·105	16·0 ± 0·40**	8
None	273 ± 4·5	53 ± 6·4	0·13 ± 0·015	0·67 ± 0·339	0·80 ± 0·040	7·2 ± 4·4	4
Cocaine-HCl, 1 mg./kg.	273 ± 4·2	48 ± 5·1	0·20 ± 0·010*	1·21 ± 0·108**	1·41 ± 0·061*	8·1 ± 3·7	4
None	284 ± 6·5	43 ± 4·4	0·07 ± 0·093	0·34 ± 0·049	0·41 ± 0·047	4·9 ± 1·18	8
Atropine, 5 mg./kg.	296 ± 6·1	47 ± 2·1	0·07 ± 0·007	0·30 ± 0·033	0·37 ± 0·033	4·3 ± 0·85	8
Cats	kg.						
None	1·3 ± 0·16		0·15 ± 0·03	0·32 ± 0·09	0·47 ± 0·08	2·6 ± 0·01	4
Hexamethonium, 1 mg./kg.	1·2 ± 0·02		0·07 ± 0·02*	0·62 ± 0·18	0·69 ± 0·02*	10·4 ± 3·14**	4

Significance of differences between means was examined by '*t*' test and is indicated by asterisks: one, P = <0·05; two, P = <0·01.

TABLE III

THE EFFECT OF GANGLION BLOCKING DRUGS AND COCAINE ON THE DEPLETION OF STORES OF ADRENALINE AND NORADRENALINE IN THE RAT ADRENAL MEDULLA BY RESERPINE 5 MG. PER KG. DAILY FOR 2 DAYS

Ganglion blocking agent		μg. Catecholamine per mg. adrenal gland				Rats		
Drug	mg./kg. 12 hrly subcut. for 2 days	Noradrenaline	Adrenaline	Total	Adrenaline / noradrenaline	Body wt. g.	Adrenal wt. mg.	No.
None		0·02 ± 0·003	0·09 ± 0·008	0·12 ± 0·012	6·2 ± 1·24	390 ± 5·8	45 ± 2·8	16
Tetraethylammonium	1·0	0·05 ± 0·006*	0·10 ± 0·025	0·13 ± 0·025	2·6 ± 0·28*	420 ± 7·9	45 ± 1·8	8
,, ,,	5·0	0·04 ± 0·012*	0·11 ± 0·013	0·15 ± 0·010	4·5 ± 0·14	421 ± 9·0	54 ± 4·7	6
Hexamethonium	1·0	0·03 ± 0·005	0·10 ± 0·009	0·19 ± 0·047	4·1 ± 0·64	399 ± 4·5	43 ± 2·6	8
,,	5·0	0·04 ± 0·012*	0·13 ± 0·020	0·17 ± 0·020	6·3 ± 0·51	397 ± 7·8	52 ± 5·2	6
None		0·008 ± 0·001	0·08 ± 0·005	0·09 ± 0·018	7·2 ± 4·4	274 ± 5·2	53 ± 5·5	4
Cocaine hydrochloride	1·25	0·095 ± 0·014*	0·325 ± 0·078*	0·42 ± 0·087*	8·1 ± 3·7	273 ± 4·7	53 ± 4·6	4

The significance of differences in the action of reserpine caused by the presence of a second drug is indicated by an asterisk where $P = <0.05$.

TABLE IV

THE EFFECT OF TETRAETHYLAMMONIUM AND HEXAMETHONIUM IONS ON THE UPTAKE OF NORADRENALINE BY THE ADRENAL GLANDS OF NORMAL AND RESERPINISED RATS

Pretreatment			Weight		μg. Amine per mg. adrenal gland				
Drug	mg./kg. both i.m. and i.v.	Infusion	Body g.	Adrenals mg.	Noradrenaline	Adrenaline	Total	Adrenaline / noradrenaline	No. of rats
Normal rats									
None	nil	noradrenaline	295 ± 5·6	58 ± 3·7	0·14 ± 0·023††	0·52 ± 0·045	0·67 ± 0·054††	4·8 ± 1·23	8
None	nil	0·9% NaCl	297 ± 11·6	62 ± 5·1	0·06 ± 0·006	0·51 ± 0·044	0·57 ± 0·043	5·0 ± 1·11	8
Tetraethylammonium	1·0	noradrenaline	297 ± 5·4	63 ± 5·2	0·74 ± 0·052*	1·45 ± 0·413*	1·91 ± 0·039*	6·3 ± 1·18	8
,,	10·0	noradrenaline	259 ± 5·0	66 ± 4·5	0·36 ± 0·081*	2·00 ± 0·473**	2·25 ± 0·501	6·5 ± 2·89	8
,,	10·0	0·9% NaCl	282 ± 7·4	68 ± 4·8	0·07 ± 0·004	0·47 ± 0·044	0·58 ± 0·040	8·3 ± 2·23	8
Hexamethonium	1·0	noradrenaline	263 ± 6·7	64 ± 4·2	0·35 ± 0·056*	1·61 ± 0·438*	1·98 ± 0·375*	3·6 ± 0·51	8
,,	10·0	0·9% NaCl	259 ± 5·0	68 ± 3·1	0·24 ± 0·036*	1·38 ± 0·262**	1·62 ± 0·258**	3·8 ± 0·85	8
Reserpinised rats									
None	nil	noradrenaline	273 ± 3·7	72 ± 4·7	0·047 ± 0·018†	0·05 ± 0·005	0·10 ± 0·011†	1·0 ± 0·06††	6
None	nil	0·9% NaCl	270 ± 3·9	71 ± 3·5	0·019 ± 0·008	0·06 ± 0·011	0·07 ± 0·017	3·5 ± 0·17	6
Tetraethylammonium	1·0	noradrenaline	273 ± 3·5	73 ± 5·6	0·061 ± 0·023*	0·08 ± 0·033	0·14 ± 0·010*	1·4 ± 0·28*	6
Hexamethonium	1·0	noradrenaline	272 ± 2·3	68 ± 2·7	0·063 ± 0·021*	0·08 ± 0·081	0·14 ± 0·013*	1·4 ± 0·22*	6

Significance of differences between means was examined by '*t*' test and is shown by crosses for the effect of infusions of noradrenaline alone, and by asterisks for the effect of a ganglion blocking drug:—one, $P = <0.05$; two, $P = <0.01$.

The influence of ganglion blocking agents on the adrenal medullary amines of rats and cats. Subcutaneous injections of as little as 1 mg. per kg. of either hexamethonium or tetraethylammonium ions, given twelve hourly for 10 days, increase the total stores of pressor amine and the proportion present as adrenaline and decrease of noradrenaline in the adrenal medullae of rats and cats (Table II). These same subcutaneous doses of the ganglion blocking drugs fail effectively to antagonise depletion of the chromaffin stores in the adrenal medulla by reserpine, as, by contrast, cocaine does (Table III). Given intramuscularly these small amounts of blocking drug augment the rate of uptake of noradrenaline and its conversion to adrenaline by the adrenals of normal and reserpine treated animals (Table IV).

Discussion

Bartorelli, Carpi and Cavalca (1954) were unable to demonstrate potentiation of the pressor effects of adrenaline and noradrenaline by concentrations of tetraethylammonium ions that failed to block transmission in autonomic ganglia. Their work was done in dogs. By contrast, in rats, cats and pigeons (Figs. 1 to 8) concentrations of hexamethonium, tetraethylammonium and pentolinium ions too low to influence transmission in autonomic ganglia, increased the pressor effects of intravenous adrenaline and noradrenaline and of reflex vasoconstriction. It is probable that changes in the chromaffin stores in tissues are concerned with this sensitisation since low concentrations of ganglion blocking drugs do not increase the pressor effects of adrenaline and noradrenaline when the chromaffin stores have degenerated after postganglionic sympathectomy (Fig. 4 and Schmitterlow, 1948) or have been depleted by reserpine (Fig. 5 and Burn and Rand, 1957). Burn and Rand have suggested that cocaine potentiates the responses to adrenaline and noradrenaline by "sealing" the chromaffin stores and that the effect of the "sealed stores" is equivalent to the disappearance of chromaffin tissue after postganglionic denervation: cocaine certainly makes tissue stores more resistant to depletion by reserpine (Table III), and probably hinders the rate of release of catecholamine from the adrenal gland (Table II). But, the ganglion blocking drugs studied also sensitise to the pressor effects of adrenaline and noradrenaline by an action on the tissue stores but they do not "seal" these stores. Indeed, they increase the rate of uptake of noradrenaline by the adrenal gland and accelerate the conversion of noradrenaline to adrenaline in some cells (Tables IV and II, and Eränkö, 1955). Since low concentrations of these ganglion blocking drugs also antagonise a pre-existing sensitisation by cocaine (Fig. 6) to the pressor affects of adrenaline and noradrenaline, both drugs may share a common site of action, not necessarily in the tissue stores. One possibility is that both cocaine and the ganglion blocking drugs inhibit the *o*-methyl transferase (Fig. 7). The resulting potentiation of the pressor effects of adrenaline and noradrenaline would then sum with the action of cocaine on tissue stores and mask the opposing action of

the ganglion blocking drugs at the same site, if the hypothesis concerning the "sealing of stores," advanced by Burn and Rand, holds.

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