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THE POTENTIATION OF GANGLIONIC TRANSMISSION BY HISTAMINE AND PILOCARPINE

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Evidence has been obtained recently for the view that both histamine and pilocarpine are able to stimulate the superior cervical ganglion of the cat, if this ganglion is left with its normal circulation intact (Trendelenburg, 1954). Earlier work by Konzett (1952), who observed a potentiation by histamine of the action of nicotine-like substances on the perfused superior cervical ganglion, and by Marrazzi (1939), who obtained evidence for a potentiation of preganglionic impulses by pilocarpine, led to the investigation presented in the first part of this paper on the effect of histamine and pilocarpine on transmission through the superior cervical ganglion of the cat.

It has long been known that a secondary blood pressure rise may follow the initial fall after an intravenous injection of either histamine or pilocarpine into a spinal cat. The general assumption that this secondary rise is entirely due to release of sympathin from the adrenal medulla caused by these substances has recently been disproved by Slater & Dresel (1952) and by Root (1951). These authors observed that some secondary rise persisted after removal of the adrenal glands. They were, however, unable to present an explanation for this peculiar action of histamine and pilocarpine. In the light of the finding that these substances exert ganglionic actions, it seemed possible that they liberated sympathin not only from the adrenals but also from the post-ganglionic nerve endings. This hypothesis has been investigated and the results are presented in the second part of this paper.

METHODS

Cats of 2–4 kg of both sexes were used. After anaesthesia was induced with ether, 80 mg/kg chloralose was injected intravenously. Intra-arterial injections were made into the central end of the lingual artery, while the external and internal carotid arteries were occluded. The injected substance was thus diverted towards the superior cervical ganglion. The cervical sympathetic chain was cut and the peripheral end was placed on shielded electrodes and covered with warm liquid paraffin. Electrical stimuli of 0·7 msec duration were applied at a frequency of 15/sec.

Experiments on the blood pressure were performed either in cats under chloralose or in spinal preparations, set up as described by Burn & Trendelenburg (1954). When it was desired to work with adrenalectomized spinal cats, the right adrenal was removed under ether before making the spinal preparation and the left was removed afterwards. The blood pressure was recorded from the carotid artery; injections were made into the femoral vein.

The following substances were used: histamine dihydrochloride and pilocarpine nitrate (both dissolved in 0·9% NaCl solution (saline) and neutralized when to be injected intra-arterially), the doses being expressed in terms of the base; hexamethonium bromide, nicotine hydrogen tartrate, cocaine hydrochloride, atropine sulphate, mepyramine maleate, all expressed as salts; adrenaline hydrochloride and noradrenaline bitartrate, expressed as the free base of the L-form.

RESULTS

I. *The action of histamine and pilocarpine on the superior cervical ganglion*

Potentiation of the effect of preganglionic stimulation. When the preganglionic fibres to the superior cervical ganglion were stimulated submaximally for periods of 5 sec 2/min a series of contractions of the nictitating membrane was recorded as shown in Fig. 1*a*. The intra-arterial injection of 1 μg histamine increased the response of the nictitating membrane to the preganglionic stimulation. This small dose of 1 μg histamine did not itself stimulate the

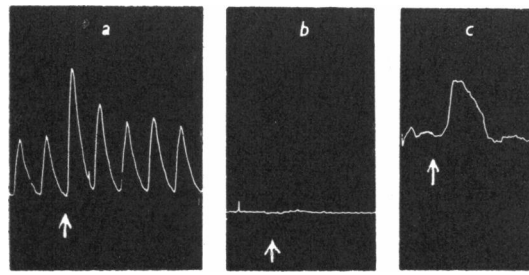

Fig. 1. Cat, chloralose, adrenals removed. Normal nictitating membrane. Arrow = intra-arteria injection of 1 μg histamine into lingual artery (*a*) during intermittent submaximal preganglionic stimulation (2/min for 5 sec each); (*b*) without stimulation; and (*c*) during continuous submaximal preganglionic stimulation. Observe the potentiation of preganglionic impulses by histamine.

ganglion and caused no contraction of the nictitating membrane in the absence of preganglionic stimulation (Fig. 1*b*). However, during a sustained contraction of the nictitating membrane due to continuous submaximal preganglionic stimulation 1 μg histamine caused a further increase in tone (Fig. 1*c*). As this potentiation of the response to preganglionic stimulation could have been caused by a lowering of the nerve threshold by histamine, the cervical sympathetic chain was split longitudinally and a portion of the preganglionic fibres was stimulated supramaximally. This arrangement excluded

any effect of histamine on the nerve, while providing a submaximal stimulus to the ganglion. A similar potentiation was obtained under these conditions. No potentiation was observed after intra-arterial injections of histamine when the external carotid artery was not occluded.

Similar results were obtained by intra-arterial injections of similar amounts of pilocarpine, the only difference being the longer duration of action observed after pilocarpine. This is in agreement with earlier observations that the stimulation of the ganglion by pilocarpine was of longer duration than that by histamine.

The response to increasing doses of histamine is shown in Fig. 2. In Fig. 2*a* it is shown that the injection of saline had no effect. The intra-arterial injections of 0·1, 1, 10 and 100 μg histamine then elicited potentiations of the responses of the nictitating membrane to preganglionic stimulation increasing the initial heights of contraction by 47, 78, 120 and 156% respectively. The duration of the potentiations increased from 2 min after 0·1 μg to 8½ min after

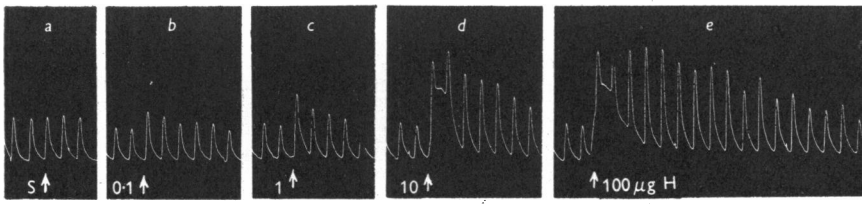

Fig. 2. Cat, chloralose, adrenals removed. Normal nictitating membrane. Submaximal stimulation of preganglionic fibres 2/min for 5 sec each. Injections of 0·2 ml. saline (S) in (*a*), and of 0·1 μg histamine in (*b*), 1 μg in (*c*), 10 μg in (*d*) and 100 μg histamine in (*e*).

100 μg histamine. After the injection of 10 and 100 μg histamine there appeared not only this potentiation of the response to preganglionic impulses but also stimulation of the superior cervical ganglion as shown by the contraction of the nictitating membrane. These findings confirm the earlier observation that the minimal dose of histamine which stimulated the ganglion was between 2 and 20 μg. The minimal dose for potentiation of preganglionic impulses was much lower, as Fig. 2 shows. It was found to lie between 0·01 and 0·1 μg histamine, being thus about $\frac{1}{200}$th of the minimal ganglion-stimulating dose.

Similar relations between dose, potentiation of response to preganglionic impulses and duration of response were observed after intra-arterial injections of pilocarpine.

Substances inhibiting the potentiation. Mepyramine, injected intravenously in a dose of 0·3–0·6 mg, abolished the effect of histamine without interfering with the response to pilocarpine or that to preganglionic stimulation. Atropine (200 μg injected intravenously) abolished the response to pilocarpine, without

affecting transmission or the action of histamine. Ganglion-blocking substances of both the depolarizing (nicotine) and competitive type (hexamethonium) abolished the response to preganglionic stimulation and thus prevented any potentiation of preganglionic impulses by histamine or pilocarpine.

Cocaine was recently found to inhibit the stimulation of the superior cervical ganglion by both histamine and pilocarpine, and it also abolished the effect of these substances on transmission through the ganglion. Fig. 3 shows that 10 μg histamine, when injected intra-arterially, both stimulated the ganglion (Fig. 3*a*) and potentiated the response to submaximal preganglionic stimulation (Fig. 3*b*). After the intravenous injection of 2 mg cocaine, however, the same dose of histamine failed to stimulate the ganglion (Fig. 3*c*), and also failed to potentiate the response to preganglionic impulses (Fig. 3*d*). This dose of cocaine did not interfere with transmission of nerve impulses through

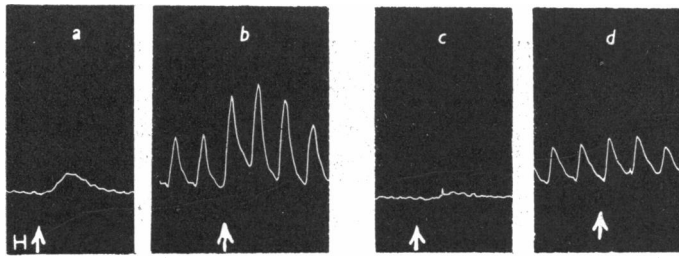

Fig. 3. Effect of cocaine on ganglionic actions of histamine. Cat, chloralose, adrenals removed. Normal nictitating membrane. Arrow = intra-arterial injection of 10 μg histamine without stimulation (*a* and *c*) and during submaximal stimulation of preganglionic fibres (*b* and *d*). Intravenous injection of 2 mg cocaine between (*b*) and (*c*). The strength of stimulation in (*d*) was less than in (*b*), because cocaine sensitized the membrane.

the ganglion. As this dose of cocaine sensitized the nictitating membrane, the strength of stimulation was reduced before recording Fig. 3*d*. Cocaine likewise abolished the ganglionic actions of pilocarpine.

The results of this series of experiments are summarized in the last columns of Tables 2 and 3.

II. *The secondary blood pressure rise after intravenous injections of histamine and pilocarpine*

Burn & Dale (1926), Root (1951) and Slater & Dresel (1952) observed that the secondary rise after histamine and pilocarpine was abolished by anti-adrenaline substances, and suggested that the secondary blood pressure rise was mediated by the liberation of sympathin. Experiments by Burn & Dale (1926) showed that the sympathin liberated by histamine came from the

adrenal medulla, whereas Root (1951) showed that the adrenal glands did not play an important part in the blood pressure response after injection of pilocarpine. Evidence is now presented that the pilocarpine effect is mainly, and the histamine effect partly, due to general stimulation of sympathetic ganglia and to potentiation by these substances of the tonic impulses passing through sympathetic ganglia.

Histamine. After the intravenous injection of 20 μg histamine into a spinal cat the fall of blood pressure was usually followed by a secondary rise. In cats under chloralose, however, a similar injection of histamine elicited a secondary rise only occasionally. Slater & Dresel (1952) observed that in cats under chloralose a secondary histamine rise was regularly obtained after a previous

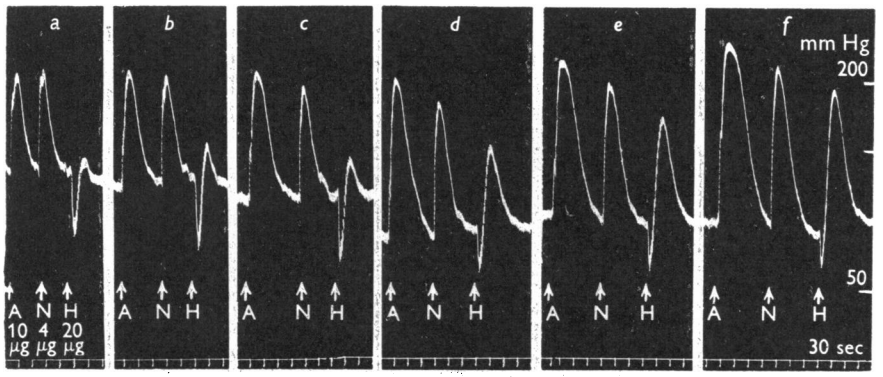

Fig. 4. Cat, chloralose, arterial blood pressure. A = intravenous injection of 10 μg adrenaline, N = that of 4 μg noradrenaline, H = that of 20 μg histamine. Responses of the blood pressure before (*a*) and after hexamethonium 2 mg (*b*), 6 mg (*c*), 18 mg (*d*), 54 mg (*e*) and 120 mg (*f*) injected intravenously.

injection of 2 mg hexamethonium. As it is well known that hexamethonium potentiates the pressor response to both adrenaline and noradrenaline, this increased sensitivity to the action of sympathin may account for the appearance of a secondary histamine rise after a previous injection of hexamethonium. The experiment recorded in Fig. 4 shows that the response of the blood pressure to equiactive amounts of adrenaline and noradrenaline was progressively increased by the injection of increasing amounts of hexamethonium. It shows, furthermore, that the very small secondary histamine rise observed before hexamethonium (Fig. 4*a*) was also increased and that its progressive increase was parallel to that of the response to both adrenaline and noradrenaline. The fall of blood pressure brought about by the injection of hexamethonium was not responsible for this action, since larger amounts failed to lower the blood pressure further (Fig. 4*e*, *f*), but they continued to

increase both the secondary histamine rise and the response to the pressor amines. Hexamethonium did not interfere with the liberation of pressor substances by histamine, which is in agreement with the earlier finding that the stimulation of both the adrenal medulla and of the superior cervical ganglion by histamine was not prevented by hexamethonium (Trendelenburg, 1954). By using hexamethonium it was thus possible to increase the response to sympathin in the cat under chloralose to that seen in the spinal cat which is much more sensitive to pressor effects. In some of the following experiments hexamethonium was therefore used to induce the appearance of a secondary histamine rise in cats under chloralose when it did not appear spontaneously, or to increase it, when the original secondary rise was too small for the purpose of the experiment.

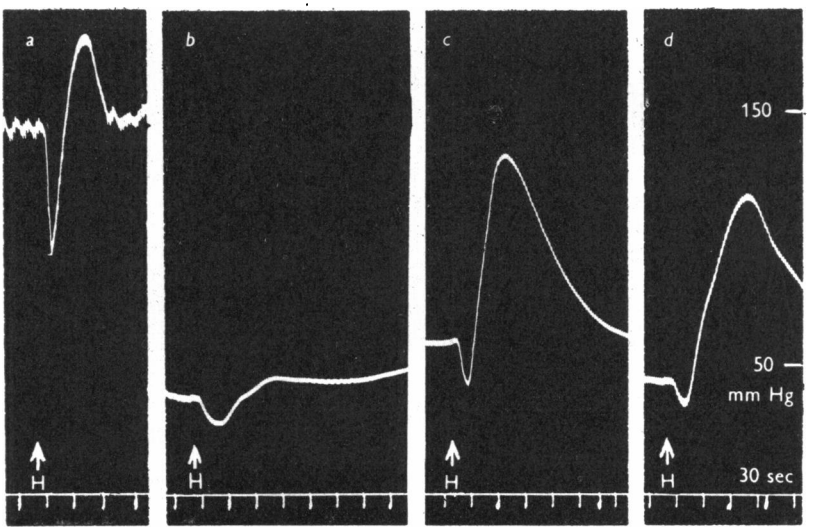

Fig. 5. Cat, chloralose. Arterial blood pressure. H = intravenous injection of 20 μg histamine. A series of nicotine injections (20 mg in all) was given between (*a*) and (*b*). (*c*) 10 min after (*b*). A second series of nicotine injections (56 mg in all) was given between (*c*) and (*d*). The failure to repeat the block is discussed in the text.

Cocaine also potentiates the response to sympathin, but it differed from hexamethonium in blocking the action of histamine on the superior cervical ganglion, whereas it did not interfere with the liberation of sympathin from the adrenal medulla by histamine (Trendelenburg, 1954). The repeated observation that cocaine increased the secondary histamine rise thus gave further evidence for the view that histamine liberated sympathin predominantly from the adrenal glands.

Nicotine was found earlier to abolish the stimulation of both the adrenal

medulla and of the superior cervical ganglion by histamine (Trendelenburg 1954) and was consequently expected to abolish the secondary histamine rise. Fig. 5 shows this action. After a series of injections of nicotine, the last of which failed to cause a pressor response, the injection of 20 μg histamine did not elicit a secondary rise (Fig. 5*b*). Recovery of the secondary rise was observed 10 min later (Fig. 5*c*). Abolition of the secondary histamine rise was, however, only obtained after the first series of nicotine injections. Fig. 5*d* shows that further injection of 56 mg nicotine failed to block the secondary

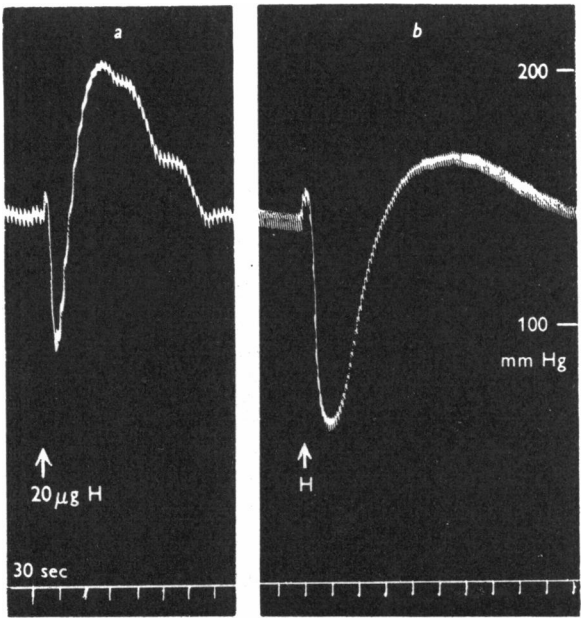

Fig. 6. Cat, chloralose. Arterial blood pressure. H = intravenous injection of 20 μg histamine 2 min after previous injection of 5 mg hexamethonium. Removal of adrenals, evisceration and ligation of kidney vessels between (*a*) and (*b*).

histamine rise. This failure will be discussed later. It was, furthermore, observed that nicotine also failed to block the secondary histamine rise when hexamethonium was injected previously in amounts sufficient to block any pressor response to the injection of nicotine.

The experiments described hitherto were all compatible with the assumption that histamine acted only on the adrenal medulla. Fig. 6 shows, however, that other factors contributed to the appearance of a secondary rise after injection of histamine. The large secondary rise elicited by the injection of 20 μg histamine after a previous injection of 5 mg hexamethonium was only reduced but not abolished by adrenalectomy. Evisceration and ligation of the vessels of

the kidneys also failed to abolish the persisting secondary rise. The persistence of this secondary rise after adrenalectomy demonstrated that histamine also liberated some sympathin from organs other than the adrenals. This sympathin may be liberated by the actions of histamine on sympathetic ganglia.

Evidence for this view has been obtained by determining the minimal time intervals required between histamine injections in order to obtain secondary blood pressure rises of similar magnitude. The minimal time interval before adrenalectomy was 5–10 min, whereas after adrenalectomy repeated injections of histamine elicited similar blood pressure responses only when given at intervals of 20–30 min. With shorter time intervals a second injection of histamine failed to elicit a comparable secondary rise. These observations were in close agreement with earlier findings that time intervals of 20–30 min were required between injections of histamine to obtain constant effects on the superior cervical ganglion, while constant responses were obtained with 5–10 min intervals on the adrenal glands (Trendelenburg, 1954).

Further support for the view that the action of histamine on sympathetic ganglia was responsible for the secondary blood pressure rise seen in the cat after adrenalectomy was provided by observations of Slater & Dresel (1952), which were confirmed in the present experiments. Cocaine always increased the secondary blood pressure rise after histamine before adrenalectomy; but after removal of the adrenals cocaine abolished the secondary rise. Since cocaine abolished the ganglionic actions of histamine this suggested that the sympathin responsible for the secondary rise after adrenalectomy was liberated by the action of histamine on sympathetic ganglia. Similarly, nicotine which has already been shown to block the ganglionic actions of histamine also abolished the secondary histamine rise after adrenalectomy.

The results of the experiments with histamine have been summarized in Tables 1 and 2.

Pilocarpine. Since Root (1951) found that the adrenal glands did not play an important part in the appearance of a secondary rise after injection of pilocarpine, the secondary blood pressure rise observed after injection of 100 μg pilocarpine may be chiefly due to the action of this substance on sympathetic ganglia. Evidence for this view is as follows:

(1) Hexamethonium which was found to potentiate the pressor response to sympathin, and which did not interfere with the action of pilocarpine either on the adrenal medulla or on the superior cervical ganglion, usually increased the secondary pilocarpine rise before adrenalectomy.

(2) Cocaine, on the other hand, reduced the rise of blood pressure after injection of 100 μg pilocarpine, as shown in Fig. 7. This observation, together with earlier findings that cocaine blocked the actions of pilocarpine on the superior cervical ganglion, suggested strongly that the secondary pilocarpine rise was mainly due to these ganglionic actions. The observation that cocaine

TABLE 1. Effects of various substances on the secondary blood pressure rise after 20 μg histamine and 100 μg pilocarpine

	Proportion of experiments in which histamine rise was			Proportion of experiments in which pilocarpine rise was		
	Increased	Unchanged	Decreased	Increased	Unchanged	Decreased
A. Intact cat						
Hexamethonium	10/11	1/11	—	4/7	2/7	1/7
Nicotine	—	—	5/5	—	—	1/1
Cocaine	2/4	1/4	1/4	—	—	3/3
B. Adrenalectomized cat						
Hexamethonium	2/6	1/6	3/6	1/6	3/6	2/6
Nicotine	—	—	1/1	—	—	2/2
Cocaine	—	—	6/6	—	—	6/6

TABLE 2. Action of substances on various effects of histamine

(Increase = +; no change = 0; decrease = −.)

	Liberation of sympathin from adrenals*	Secondary rise in intact cat	Secondary rise in adrenalectomized cat	Stimulation of sup. cerv. ganglion*	Potentiation of preganglionic impulses
Hexamethonium	0	+†	+, 0, or −†	0	−
Nicotine	−	−	−	−	−
Cocaine	0	+†	−†	−	−

* Trendelenburg (1954).

† Also observed by Slater & Dresel (1952).

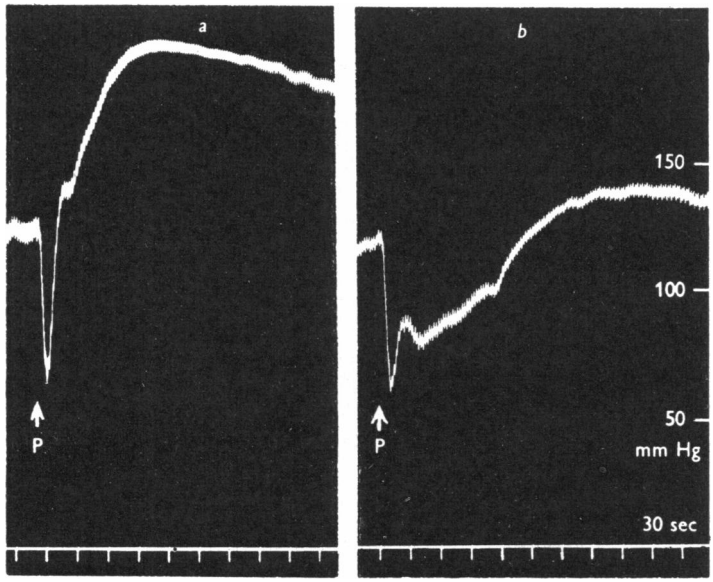

Fig. 7. Cat, chloralose. Arterial blood pressure. Arrow = intravenous injection of 100 μg pilocarpine 2 min after previous injection of 5 mg hexamethonium. Intravenous injection of 5 mg cocaine between (*a*) and (*b*).

did not completely abolish the secondary pilocarpine rise suggests, furthermore, that liberation of sympathin from the adrenal medulla contributed to a small extent to the appearance of a secondary rise of blood pressure. Further evidence for this conclusion was provided by the frequent observation that after adrenalectomy cocaine completely abolished the pilocarpine rise, as shown in Fig. 8*d*.

(3) The minimal time interval which was required to obtain identical responses to repeated injections of 100 μg pilocarpine was determined before and after adrenalectomy. In contrast to the findings with histamine the minimal time interval did not change and was always of about the same length as the time intervals which had to be kept when investigating the action of pilocarpine on the superior cervical ganglion (Trendelenburg, 1954).

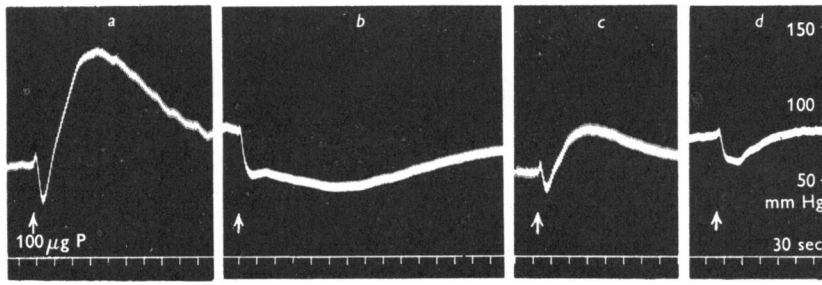

Fig. 8. Spinal cat, adrenals removed. Arterial blood pressure. P = intravenous injection of 100 μg pilocarpine, repeated at the arrows in *b*, *c* and *d*, at intervals of 40 min. A series of nicotine injections (23 mg in all) was given between (*a*) and (*b*). 5 mg cocaine was injected intravenously between (*c*) and (*d*).

TABLE 3. Action of substances on various effects of pilocarpine

(Increase = +; no change = 0; decrease = −.)

	Liberation of sympathin from adrenals*	Secondary rise in intact cat	Secondary rise in adrenalecto-mized cat	Stimulation of sup. cerv. ganglion*	Potentiation of preganglionic impulses
Hexamethonium	0	+, 0 or −†	+, 0 or −†	0	−
Nicotine	−	−‡	−	−	−
Cocaine	0	−§	−	−	−

* Trendelenburg (1954).

† Also observed by Root (1951).

‡ Also observed by Bacq & Simonart (1938).

§ Also observed by Koppanyi (1939).

(4) Nicotine, when injected in increasing amounts until a dose of 5–10 mg failed to elicit any pressor response, not only prevented the action of pilocarpine on the superior cervical ganglion but also abolished the secondary rise after 100 μg pilocarpine, as shown in Fig. 8*a*, *b*. In Fig. 8*c* a partial recovery of the secondary rise was seen after 40 min, and in Fig. 8*d* this rise was again abolished by cocaine. It was repeatedly observed that after cocaine the blood

pressure returned more quickly to its initial level than after nicotine, as comparison of Fig. 8, *b* and *d*, shows.

The results of the experiments with pilocarpine have been summarized in Tables 1 and 3. They show a close correlation with results obtained previously on the superior cervical ganglion, thus giving evidence that the main action of pilocarpine is exerted on the sympathetic ganglia.

III. *Is the secondary rise after adrenalectomy due to stimulation of ganglia or due to potentiation of preganglionic impulses?*

The question then arose whether the secondary rise of blood pressure due to the action on sympathetic ganglia was caused by stimulation of ganglion cells or by the potentiation of preganglionic impulses. Since hexamethonium abolished the latter action without interfering with the former, its action on the secondary blood pressure rise was investigated after removal of the adrenals.

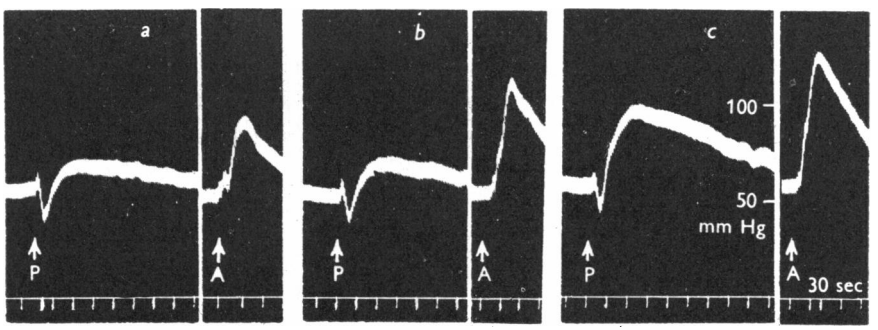

Fig. 9. Spinal cat, adrenals removed. Arterial blood pressure. Intravenous injections of 100 μg pilocarpine (P) and 1 μg adrenaline (A). 10 mg hexamethonium was injected between (*a*) and (*b*), 20 mg between (*b*) and (*c*).

The effect of hexamethonium on the secondary rise was variable after adrenalectomy (see Table 1). If a comparison was made between the changes produced by hexamethonium in the blood pressure rise caused by adrenaline and in the secondary rise after histamine or pilocarpine, no such parallelism was seen as was demonstrated in Fig. 4. Small doses of hexamethonium (5–10 mg) neither increased the rise of blood pressure due to adrenaline nor the secondary rise due to histamine or pilocarpine. This was indeed often reduced. Higher amounts of hexamethonium, however, increased both the response to adrenaline and the secondary rise. Fig. 9 shows that, in contrast to Fig. 4, the increase of the secondary pilocarpine rise was not parallel to the increase of the response to adrenaline. Whereas the response to adrenaline was

increased after the injection of 10 mg hexamethonium, the response to pilocarpine remained unchanged (Fig. 9*b*). After injection of 20 mg hexamethonium, however, both an increased secondary pilocarpine rise and a further increase of the response to adrenaline were observed (Fig. 9*c*). This suggested that hexamethonium without abolishing the liberation of sympathin reduced the amount liberated by the injection of pilocarpine. It can therefore be concluded that the stimulation of sympathetic ganglia plays a part as well as the potentiation of normally occurring vasomotor impulses on their way through sympathetic ganglia.

DISCUSSION

Recently it has been shown that both histamine and pilocarpine stimulated the superior cervical ganglion of the cat, when this ganglion was left with its normal circulation intact. The results obtained with various inhibiting substances suggested that the stimulation of the ganglion cells was brought about by an action of histamine and pilocarpine on receptors different from those affected by acetylcholine (Trendelenburg, 1954). The results presented in this paper demonstrate another ganglionic action of these two substances, namely that they potentiate the response to preganglionic stimulation. The potentiation was regularly observed after intra-arterial injections during occlusion of the external carotid artery, when the injected substance was diverted towards the ganglion; it was absent when the external carotid was not occluded. As it was possible that both histamine and pilocarpine caused potentiation of weak preganglionic impulses by changing the threshold of the nerve fibres, in some of the experiments the sympathetic cervical chain was split longitudinally and part of it was then stimulated supramaximally. Potentiation was observed under these conditions where a change of the threshold of the nerve could not have any effect. It was then concluded that these substances acted on the ganglion cells, probably by lowering their threshold.

Two different ganglionic actions of both histamine and pilocarpine have thus been found. After the intra-arterial injection of low doses (0·01–0·1 μg and more) potentiation of preganglionic impulses was observed, while the injection of 2–20 μg and more also caused a stimulation of the ganglion cells. It was found that both ganglionic actions were affected similarly by the inhibiting substances which were investigated, with the exception of hexamethonium. This typical 'competitive' ganglion-blocking substance did not interfere with the stimulation of the ganglion by either histamine or pilocarpine, but, of course, prevented their potentiating action on transmission.

Whereas it is uncertain whether amounts of histamine which are present under normal conditions are able to stimulate sympathetic ganglia, the probability that histamine plays a part in the regulation of the sympathetic system has now increased, since the amounts normally present may well influence the sensitivity of sympathetic ganglia by determining their threshold

of excitation. The action of histamine on ganglia may be as important as that of low amounts of adrenaline, which were also found to influence the sensitivity of ganglia (Bülbring & Burn, 1942; Bülbring, 1944). The actions of histamine and pilocarpine, however, differ from that of adrenaline in that no depression of sensitivity was observed after higher concentrations of histamine or pilocarpine.

The appearance of a secondary rise of blood pressure after injection of either histamine or pilocarpine has until recently been generally assumed to be due to the well-known liberation of sympathin from the adrenals by histamine (Burn & Dale, 1926) and by pilocarpine (Dale & Laidlaw, 1912). This does not fully account for the secondary rise, since Root (1951) found that the secondary pilocarpine rise was unaffected by adrenalectomy, whereas Slater & Dresel (1952) observed the persistence of a small secondary histamine rise after adrenalectomy. In the present paper the hypothesis has been put forward that the effects which cannot be explained by an action of histamine or pilocarpine on the adrenal medulla are due to an action of these substances on sympathetic ganglia.

Evidence for this view has been obtained by the investigation of the effects of hexamethonium, nicotine and cocaine on the secondary histamine and pilocarpine rise in cats before and after adrenalectomy. It was found that the results all agreed with the above-mentioned hypothesis, since the secondary rise observed after injection of histamine or pilocarpine into adrenalectomized cats was affected by hexamethonium, nicotine and cocaine in the same way as the actions of histamine and pilocarpine on the superior cervical ganglion.

It is thus concluded that histamine and pilocarpine elicit a secondary rise of blood pressure by the liberation of sympathin. Histamine was found to act predominantly on the adrenal medulla, and both the stimulation of sympathetic ganglia and the potentiation of vasomotor impulses on their way through sympathetic ganglia were of minor importance. The reverse was found to be true for pilocarpine, as this substance acted mainly on the ganglia and exhibited only a weak action on the adrenals. This peculiar difference between two substances which were found to have very similar actions, is explained by the observation that while they were equiactive on the superior cervical ganglion, histamine was fifty times more active on the adrenal glands (Trendelenburg, 1954). This discrepancy of the ratio of equiactive doses explains why pilocarpine, in contrast to histamine, had only a weak action on the adrenal glands.

The investigation of the effect of nicotine on the secondary rise after injection of histamine, threw new light on its mode of action. The fact that paralysing amounts of nicotine abolished the stimulation of the superior cervical ganglion by both histamine and pilocarpine has been interpreted as being due to the depolarization of the ganglion cells by nicotine. The abolition

of the secondary histamine and pilocarpine rise of blood pressure by paralysing amounts of nicotine gives further evidence for this view. The failure of a second and much higher dose of nicotine to abolish the histamine rise, and the similar failure of a second intravenous injection of paralysing amounts of nicotine to block the stimulation by histamine of the superior cervical ganglion (unpublished results), however, require explanation. This seems to be provided by the observation of Paton & Perry (1953) that the block of the superior cervical ganglion produced by the close-arterial injection of 200 μg nicotine was of longer duration than the depolarization of the ganglion cells. A second injection of the same amount of nicotine was found to block with hardly any depolarization. The authors concluded that nicotine first blocked transmission by depolarizing the ganglion cells and later by 'competition'. A second injection of nicotine thus resembled the action of the 'competitive' type of ganglion-blocking substances, such as hexamethonium which did not prevent the stimulation of the ganglion by histamine. This explains the failure of a second paralysing dose of nicotine to block the secondary rise after histamine or the stimulation of the ganglion by histamine.

SUMMARY

1. Evidence has been obtained for the potentiation of preganglionic impulses by histamine and pilocarpine. This effect has been observed after intra-arterial injections into the lingual artery of doses which were 0·5% of those necessary for stimulation of the superior cervical ganglion by these substances.

2. This potentiating action was abolished by cocaine, nicotine and hexamethonium. The action of histamine was specifically inhibited by mepyramine, that of pilocarpine by atropine.

3. The factors involved in the appearance of a secondary blood pressure rise after the intravenous injection of histamine or pilocarpine have been investigated by observing the effects of cocaine, nicotine and hexamethonium on this rise.

4. The histamine rise is mainly due to liberation of sympathin from the adrenal glands and only to a minor degree to general stimulation of sympathetic ganglia and to potentiation of tonic impulses travelling through sympathetic ganglia.

5. The pilocarpine rise, on the other hand, is mainly due to the ganglionic actions of this substance and is thus similar to the histamine rise in the adrenalectomized cat.

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