Brit. J. Pharmacol. (1965), **25**, 728–742.

THE RELEASE OF CATECHOL AMINES FROM THE ADRENAL MEDULLA BY HISTAMINE

BY

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(*Received May* 24, 1965)

The secondary rise of blood pressure produced by histamine has been attributed to the release of catechol amines from the adrenal medulla ever since Burn & Dale (1926) showed that, in cats, the response disappeared after bilateral adrenalectomy. Szcygielski (1932) injected small amounts of histamine into the arterial blood supply of the adrenal glands ; after denervation of the glands there was still a pressor effect which was decreased but not completely blocked by nicotine. Bein & Meier (1953) further showed that after bilateral adrenalectomy an infusion of small amounts of adrenaline or noradrenaline restored the biphasic action of histamine but not that of nicotine or coramine. Slater & Dresel (1952) suggested that histamine also caused a release of noradrenaline from sympathetic nerve endings and that this would contribute to the pressor action. They showed that the pressor phase produced by injection of histamine was potentiated by hexamethonium and blocked by dibenamine or by tripelennamine but not by atropine. In all these experiments on the cat the secondary rise in blood pressure or the contraction of the nictitating membrane was used as an indication of catechol amine release.

Comparatively few experiments have been published on the release of catechol amines by histamine in the dog. Slater & Dresel (1952) failed to find a secondary pressor effect and Woods & Richardson (1955) saw no cardiovascular actions attributable to catechol amine release after histamine. Woods, Richardson, Richardson & Bozeman (1956) found no change in the catechol amine concentration of arterial plasma after histamine. Robinson & Jochim (1960) detected increases in the concentrations of both noradrenaline and adrenaline in adrenal venous blood after massive doses of histamine, whereas Athos, McHugh, Fineberg & Hilton (1962) found mainly an increase in adrenaline secretion. They also showed that the denervated adrenal medulla perfused with blood did not respond to histamine. However, Feldberg (1941) and Vogt (1951) found that histamine released catechol amine from the Locke-perfused cat adrenal gland and from the blood perfused dog adrenal gland respectively.

We have injected histamine into cats and dogs and measured the changes in catechol amine concentrations of the circulating blood ; we have also studied the effects of blocking agents on these changes.

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METHODS

Cats of either sex weighing between 2 and 5 kg were anaesthetized with ethyl chloride and ether; anaesthesia was then maintained with chloralose (80 mg/kg, intravenously). Dogs of either sex weighing between 5 and 14 kg were anaesthetized with ether in a box; anaesthesia was then maintained with chloralose (100 mg/kg, intravenously).

A carotid artery was cannulated with polyethylene tubing to supply blood to an extracorporeal circulation for the blood-bathed organ technique (Vane, 1964) and to record the blood pressure on a mercury manometer. To detect the release of catechol amines into the blood, a continuous stream of arterial blood was superfused over the rat isolated stomach strip (Vane, 1957) and the chick isolated rectum (Mann & West, 1950); the blood was then returned to the animal through a cannula in a jugular vein. With these organs superfused in series, it was possible to distinguish between the release of adrenaline and noradrenaline (Armitage & Vane, 1964). In some experiments the series also included a rat colon to detect angiotensin or a guinea-pig ileum to detect histamine. Heparin (Pularin, Evans; 1,000 units/kg) was injected intravenously before the external circulation of blood was started. Artificial ventilation was maintained with a pump. To make intra-arterial injections to the adrenal glands, a fine polyethylene catheter was introduced into the aorta through a femoral artery so that the tip of the catheter lay above the origins of the adrenal arteries. In some experiments the animals were eviscerated and the catheter was inserted retrogradely into the aorta just below the adrenal glands so that the tip was above them.

The amounts of catechol amines released by intra-arterial or intravenous infusions or injections of histamine were determined by comparing the effects of the released catechol amines on the blood-bathed organs with the effects of intravenous injections or infusions of adrenaline and noradrenaline. When the actions of blocking agents were tested, the effects of a standard dose of histamine were determined immediately before and then several times during the 60 min after giving the blocking agent.

In some cats and dogs, after the chloralose had been given, the muscles of the neck were dissected to expose the atlanto-occipital membrane. Later in the experiment, in order to interrupt spinal cord transmission, either the spinal cord was cut (in cats) or 10 ml. of 1% lignocaine was injected through the membrane into the cord (in dogs). In other dogs, the spinal cord was cut at the beginning of the experiment through an incision in the atlanto-occipital membrane.

Drugs

The following drugs were used (doses of salts are expressed as base): (—)-adrenaline bitartrate (B.D.H.), synthetic angiotensin (Hypertensin, Ciba), synthetic bradykinin (Parke Davis), hexamethonium bromide (May & Baker), histamine acid phosphate (Burroughs Wellcome), lobeline hydrochloride (Sandoz), mecamylamine hydrochloride (Merk, Sharp & Dohme), mepyramine maleate (May & Baker), nicotine acid tartrate (B.D.H.), (−)-noradrenaline bitartrate, pentolinium tartrate (May & Baker), phentolamine (Ciba), promethazine hydrochloride (May & Baker), propranolol hydrochloride (I.C.I.), and tetramethylammonium bromide.

RESULTS

Cats

Histamine injections

In anaesthetized cats, injections of histamine intra-arterially regularly produced a release of catechol amines from the adrenal medulla. When the cat was eviscerated and the circulation to the hind-quarters of the animal was tied off, the same amounts were released by much smaller doses. Fig. 1 shows that the release was dose-dependent. Histamine (20 μg, intra-arterially) produced a release of catechol amine the effects of which were almost exactly matched on both the rat stomach and the chick rectum by adrenaline (1 μg, intravenously). This equivalence of effects on the two tissues showed that the catechol amine released was mainly, if not all, adrenaline. Histamine (20 μg, intravenously) produced a similar release of adrenaline. Histamine (10μg, intravenously)

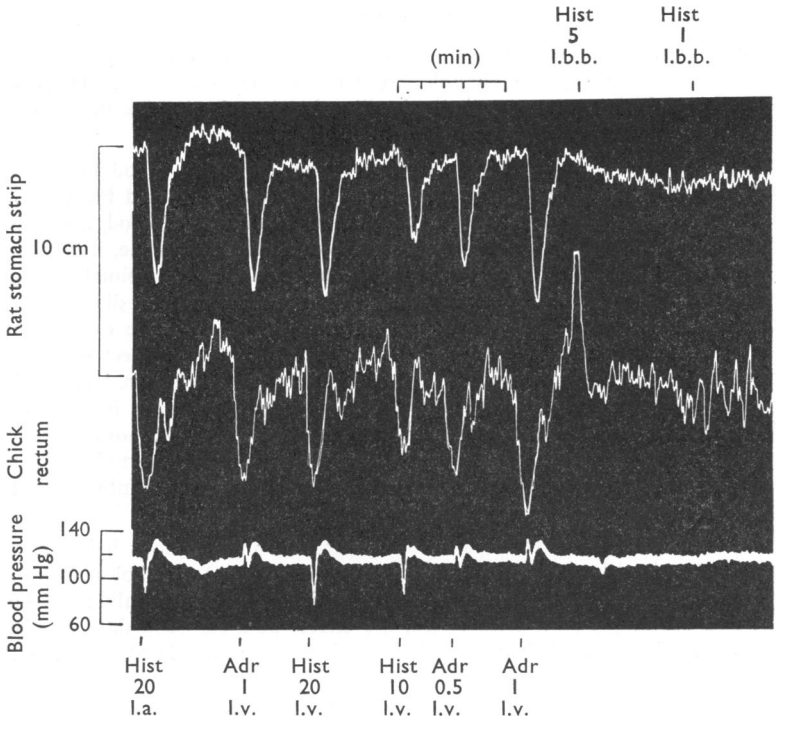

Fig. 1. Rat stomach strip (top) and chick rectum (middle) preparations superfused with carotid blood from a 2.8 kg cat anaesthetized with chloralose. The lowest record is blood pressure. The first part of the tracing illustrates that intra-arterial (I.a.) or intravenous (I.v.) histamine (Hist) releases adrenaline (Adr), as shown by the relaxation of both assay organs, an effect which can be matched by intravenous adrenaline. When injected directly into the bathing blood (I.b.b.) 5 μg of histamine contracts the chick rectum, but has no effect on the rat stomach strip; 1 μg of histamine, the maximum which could be expected to reach the assay organs after an intravenous or intra-arterial injection, had no direct effect on them. Time in minutes; vertical scales, 10 cm and mm Hg; all doses in μg.

released less than 0.5 μg of adrenaline. The rate of blood flow over the assay tissues was 15 ml./min, which represents only a small fraction (2 to 4%) of the total cardiac output. Thus, an injection of histamine (1 μg) directly into the bathing blood certainly exceeded the amount of histamine reaching the tissues after giving histamine (20 μg) intravenously. The last part of Fig. 1 shows that, whereas 1 μg histamine had no direct effect on the tissues, 5 μg caused contraction of the chick rectum but not of the rat stomach strip.

Doses of histamine were chosen to give a liberation of 0.5 to 1.5 μg of adrenaline; from these, the amount of histamine required to liberate 1 μg of adrenaline was calculated. This dose varied from 1 to 20 μg (twenty-six experiments); it was 1 to 5 μg in fourteen experiments, 5 to 10 μg in six experiments, and 10 to 20 μg in six experiments. The adrenal medulla usually became more sensitive to histamine as each experiment progressed; for instance, at the beginning of one experiment, 10 μg of histamine liberated 1.6 μg of adrenaline; 3 hr later, 2 μg of histamine liberated 1.7 μg of adrenaline.

In eight out of twenty experiments, intravenous histamine gave a greater release of adrenaline than the same dose intra-arterially. In the other twelve experiments the intravenous dose had to be one- to four-times greater than the intra-arterial to give the same release. Section of the spinal cord did not reduce the response to either intravenous or intra-arterial histamine. In eight experiments with eviscerated cats in which the circulation to the hind-quarters was cut off, 0.05 to 2.5 μg of histamine intra-arterially was required to release 1 μg of adrenaline. In one experiment in which the comparison was made, three-times more histamine had to be given intravenously than intra-arterially to produce the same release of catechol amine.

In several experiments the effects of histamine before and after adrenalectomy were compared. Fig. 2 shows a typical result. This tracing shows the effects of the adrenaline release by histamine on a rat stomach strip bathed in carotid arterial blood. Histamine,

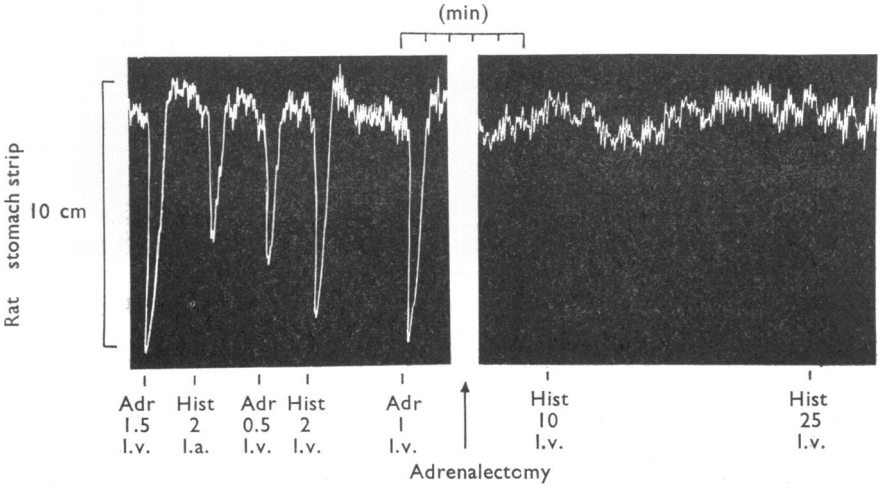

Fig. 2. Rat stomach strip superfused with carotid blood from a 2.4 kg cat anaesthetized with chloralose. In this experiment, intravenous (I.v.) histamine (Hist, 2 μg) was releasing more adrenaline (Adr) than intra-arterial (I.a.) histamine (2 μg). After adrenalectomy, no adrenaline release was detected, even with 25 μg of histamine intravenously. Time in minutes; vertical scale, 10 cm; all doses in μg.

2 μg, intra-arterially, released less than 0.5 μg of adrenaline whereas 2 μg of histamine intravenously released between 0.5 and 1 μg. After adrenalectomy, even 25 μg of histamine intravenously gave no release. In all, seven normal and four eviscerated cats were retested with histamine after adrenalectomy; in none was there any detectable release. Furthermore, after adrenalectomy there was no pressor response to histamine, although intra-arterial histamine almost always gave a pressor response when the adrenal glands were present.

Histamine infusions

Histamine was infused intra-arterially at rates of 1 to 50 μg/min. With the lower rates of infusion there was an initial burst of adrenaline secretion but this declined during the

next 2 or 3 min of infusion and there was no further secretion. With higher rates of infusion the initial burst was greater and, as this passed off, some maintenance of secretion was observed. In the experiment of Fig. 3, for instance, an infusion of histamine at a

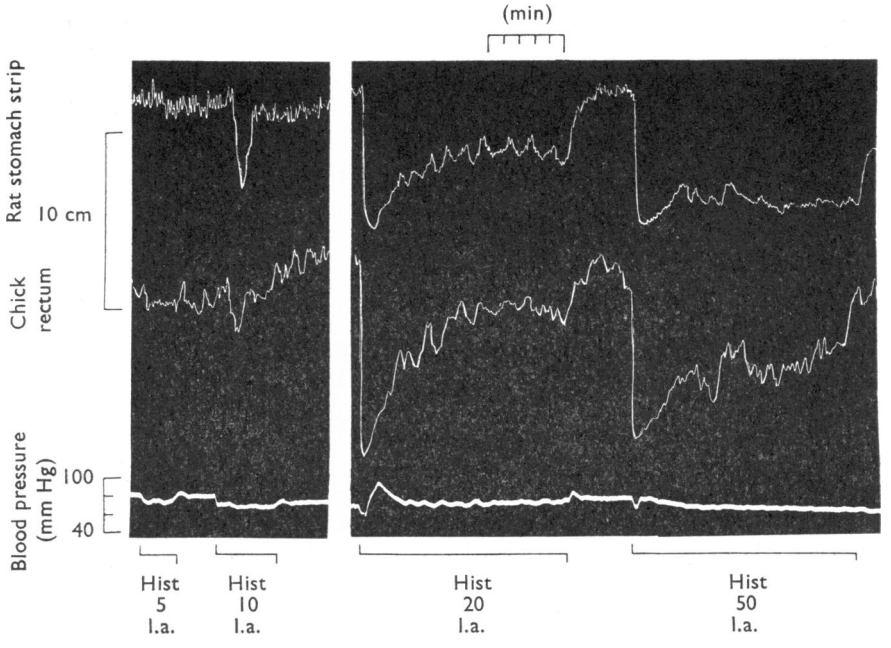

Fig. 3. Rat stomach strip (top) and chick rectum (middle) superfused with carotid blood from a 3.3 kg cat anaesthetized with chloralose. The bottom record is blood pressure. The tracing shows the effects of four infusions of histamine (Hist) intra-arterially (I.a.). A rate of 5 μg/min released little or no adrenaline; 10 μg/min gave an initial release; 20 μg/min gave a much bigger initial release, with some maintenance of adrenaline secretion and 50 μg/min gave a better maintained release. Note that the secondary pressor effect is seen only with an infusion rate of 20 μg/min. Time in minutes; vertical scales, 10 cm and mm Hg; doses in μg/min.

rate of 5 μg/min intra-arterially gave no detectable adrenaline release. With 10 μg/min there was a small release of adrenaline but this was not maintained. With 20 μg/min, however, there was a maintained secretion (corresponding to an output of 2 μg/min of adrenaline) and with 50 μg/min the secretion was maintained at an even higher rate. Intravenous infusions of histamine gave similar results.

Prolonged secretion of adrenaline after histamine

In some experiments on eviscerated cats, a single intra-arterial injection of histamine (0.2 to 1 μg) produced the usual transient secretion of adrenaline, but almost immediately the secretion increased again and was then maintained for the rest of the observation periods (30 to 150 min). Such an effect is seen in Fig. 4, in which persistence of adrenaline secretion is indicated also by a maintained elevation of the blood pressure. In some of the experiments with non-eviscerated cats a similar prolonged secretion followed the

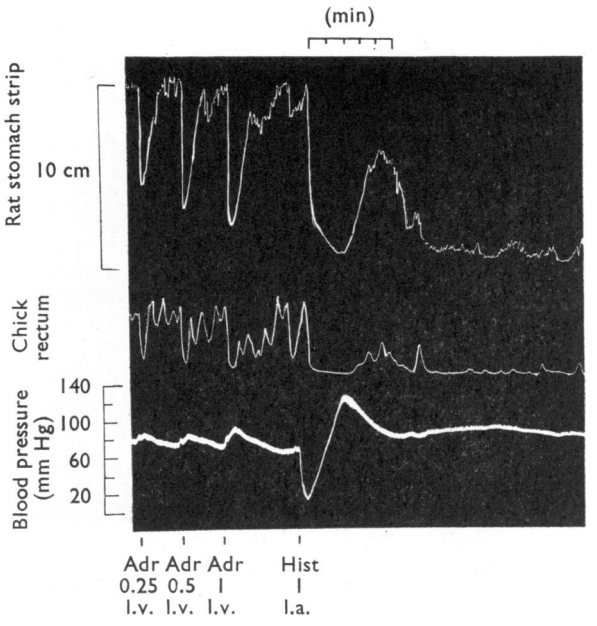

Fig. 4. Rat stomach strip (top) and chick rectum (middle) superfused with carotid blood from a 2.2 kg eviscerated cat anaesthetized with chloralose. The bottom record is blood pressure. The tracing shows first, a calibration of the assay organs with intravenous (I.v.) adrenaline (Adr) and then the effects of 1 μg of histamine (Hist) intra-arterially (I.a.). The large initial release of adrenaline began to decline but was then replaced by a continuous release which stopped only when the cat was adrenalectomized 150 min later. Time in minutes ; vertical scales, 10 cm and mm Hg ; all doses in μg.

end of an infusion of histamine. Once such a continuous secretion of adrenaline had been established, it was unaffected by antihistamine drugs. Whenever such a continuous secretion had been induced, small haemorrhages were seen on the surface of the glands.

Dogs

Histamine injections

In anaesthetized dogs, injections of histamine intra-arterially regularly released catechol amines into the circulation. As in the cat, the released amine was mainly if not entirely adrenaline and the glands gradually became more sensitive to histamine as the experiment progressed. Larger doses of histamine produced greater releases of adrenaline. In twenty-three experiments the amount of histamine required to release 1 μg adrenaline varied from 0.7 to 50 μg: in ten, 0.7 to 5 μg ; in six, 5 to 10 μg ; and in seven, 10 to 50 μg.

In six of nine dogs less histamine was needed intravenously than intra-arterially to give the same secretion of adrenaline ; in two, the same dose was needed ; and in one dog which had been eviscerated five-times more histamine was needed intravenously than intra-arterially. After removal of the adrenal glands (five experiments), there was no detectable catechol amine release when histamine (up to 1 mg) was injected intra-arterially or intravenously. A continuous release of adrenaline was sometimes seen in dogs which

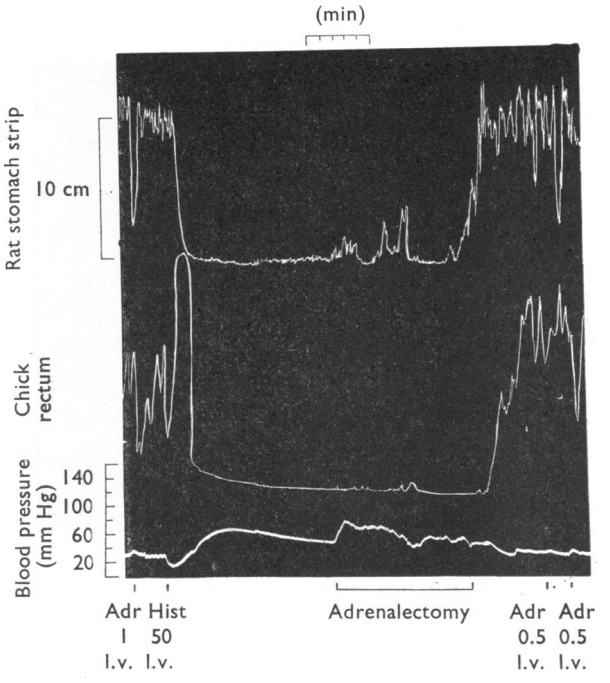

Fig. 5. Rat stomach strip (top) and chick rectum (middle) superfused with carotid blood from a 12.0 kg eviscerated dog anaesthetized with chloralose. The bottom record is blood pressure. The tracing shows persistent release of adrenaline (Adr) after 50 μg of histamine (Hist) intravenously (I.v.). Note also the prolonged rise in blood pressure. Adrenalectomy 15 min later completely stopped the release. Time in minutes; vertical scale, 10 cm and mm Hg; all doses in μg.

had been eviscerated. Fig. 5 illustrates an experiment in which a single intravenous dose of histamine (50 μg) led to a continuous secretion of adrenaline which stopped only when the adrenal glands were removed.

Histamine infusions

As in the cat, intra-arterial infusions of histamine (5 to 50 μg/min) caused a graded release of adrenaline. Lower rates of infusion did not produce maintained secretion, but with higher rates the output was maintained though at lower levels than the initial. Similar effects were seen with intravenous infusions of histamine.

Effects of antagonists on adrenaline release by histamine

Histamine antagonists

In confirmation of Emmelin & Muren (1949) and of Slater & Dresel (1952), antihistamine drugs antagonized the adrenaline-releasing effects of histamine.

In a typical experiment on a cat, 1.3 μg of histamine intra-arterially released 1 μg of adrenaline. Mepyramine (0.25 mg/kg) was then injected intravenously; 15 min later, 20 μg of histamine had to be injected to release 1 μg of adrenaline, giving a dose-ratio

of 15. A second intravenous injection of mepyramine (1 mg/kg) increased the dose-ratio to 30. In three other experiments similar effects were obtained. In another experiment, 6 μg of histamine released 1 μg of adrenaline. After promethazine (1 mg/kg), up to 300 μg of histamine did not release adrenaline. This antagonism by mepyramine or promethazine was specific for histamine because the adrenaline-releasing action of angiotensin or bradykinin was unchanged (Fig. 6).

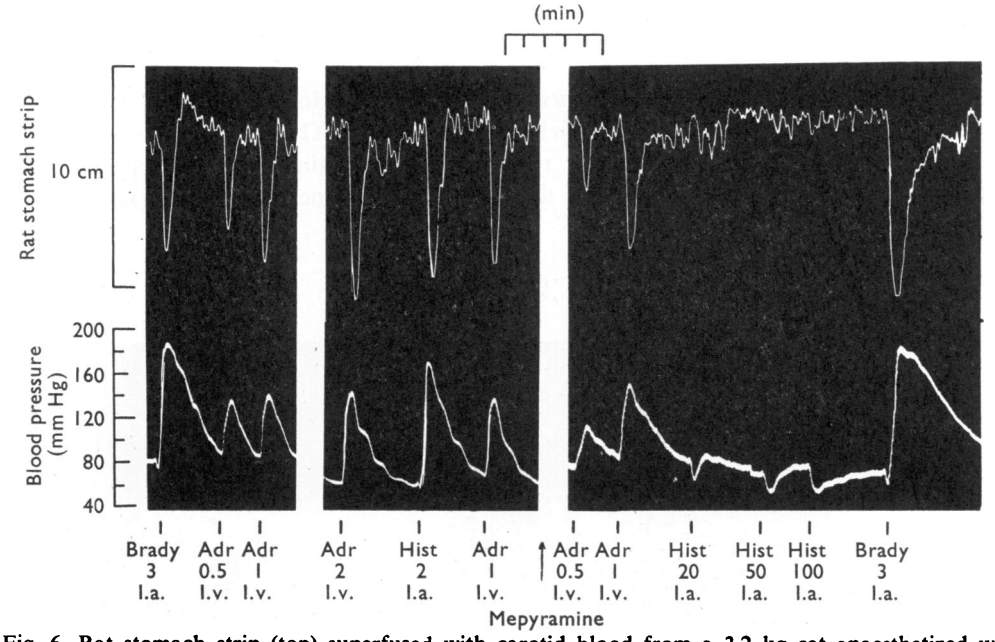

Fig. 6. Rat stomach strip (top) superfused with carotid blood from a 3.2 kg cat anaesthetized with chloralose. The lower tracing is blood pressure. The first two sections show the release of adrenaline by intra-arterial (I.a.) bradykinin (Brady, 3 μg) and histamine (Hist, 2 μg). Note that the rise in blood pressure produced by these injections is greater than that produced by intravenous (I.v.) adrenaline (Adr, 2 μg), even though the amount of circulating adrenaline is less. After intravenous mepyramine (5 mg/kg, 50 min before the right-hand record), the release of adrenaline by histamine is selectively abolished; even 100 μg gave no release. Bradykinin (3 μg) gave more release than before. Time in minutes; vertical scales, 10 cm and mm Hg; doses in μg.

Fig. 6 also shows an interesting lack of correspondence between effects on the blood pressure and the concentration of circulating adrenaline. A dose of bradykinin that released less than 1 μg of adrenaline produced a much bigger rise in blood pressure than 1 μg of adrenaline injected intravenously. Similarly histamine gave a larger blood pressure rise than 2 μg of adrenaline, even though the amount of adrenaline released was less. Lack of correspondence between concentrations of circulating adrenaline and the blood pressure responses after histamine or bradykinin was seen only occasionally in cats, and suggested that in these animals both bradykinin and histamine caused sufficient stimulation of sympathetic nerves to contribute to the rise of blood pressure. Since the blood pressure rise in response to histamine, as well as the release of adrenaline, was abolished by mepyramine (Fig. 6) stimulation of the sympathetic nerves by histamine was presumably also abolished.

In the dog mepyramine (up to 10 mg/kg) and promethazine (1 mg/kg) also antagonized the release of adrenaline by histamine: the dose-ratios were 30 to 100. In neither cat nor dog did mepyramine or promethazine themselves cause a release of catechol amine from the adrenal medulla. Although the antihistamines abolished the immediate effects of histamine on the adrenal medulla they had no effect on the continuous secretion already described.

Adrenaline antagonists

Sympathetic α-receptor blocking agents. In both cat and dog, the release of adrenaline by histamine was unchanged by sufficient phentolamine (1 mg/kg, intravenously or intra-arterially) to abolish the pressor responses to adrenaline. The responses of the assay tissues were unaffected by this dose of phentolamine. Such an experiment is illustrated in Fig. 7.

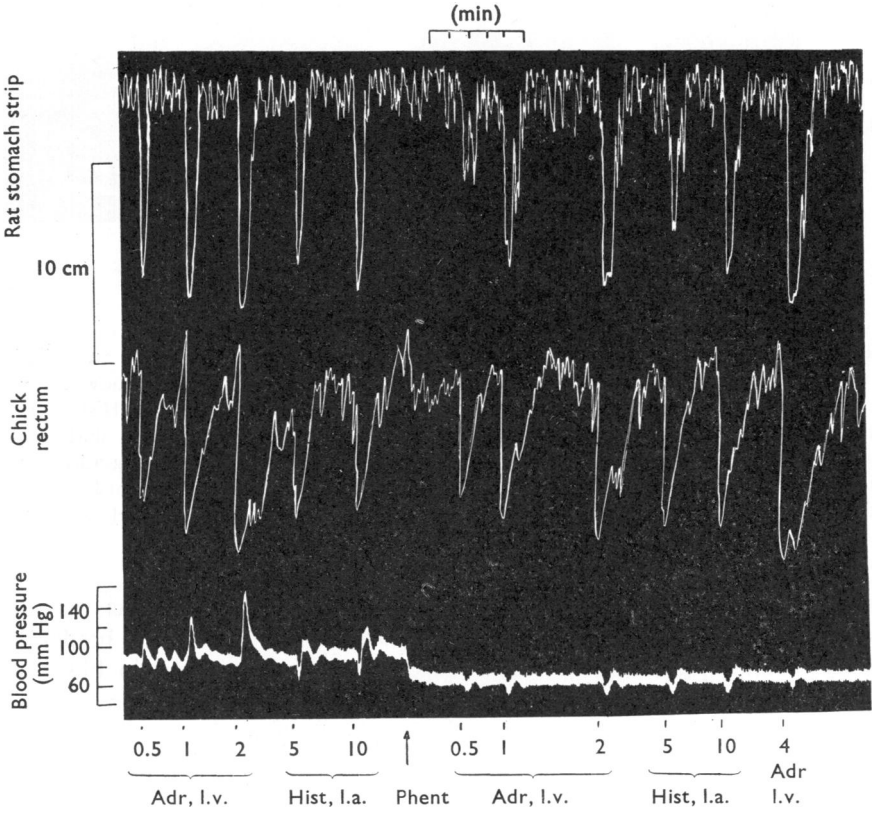

Fig. 7. Rat stomach strip (top) and chick rectum (middle) superfused with carotid blood from a 3.9 kg cat anaesthetized with chloralose. The bottom tracing is blood pressure. The tracing shows that intravenous (I.v.) phentolamine (Phent, 1.25 mg/kg) abolished the pressor effect of adrenaline (Adr) and histamine (Hist), but did not reduce the adrenaline release after histamine. Time in minutes; vertical scales, 10 cm and mm Hg; doses in μg. I.a.=intra-arterial.

Sympathetic β-receptor blocking agents. In both cat and dog, propranolol (3 mg/kg, intravenously) did not antagonize the release of adrenaline by histamine. The effect of adrenaline on the rat stomach strip was unaffected by propranolol but the relaxation of the chick rectum was greatly diminished.

Ganglion-blocking agents

In the cat, the concentration of adrenaline in the carotid arterial blood after intravenous or intra-arterial histamine was always increased by intravenous hexamethonium (10 mg/kg), pentolinium (2 mg/kg) or mecamylamine (2 mg/kg). The secondary rise in blood pressure was also greater.

Trendelenburg (1961) showed that, in the cat, the secondary pressor response to histamine was abolished by a depolarizing ganglion-blocking agent. In one experiment, we infused tetramethylammonium bromide intra-arterially. The resulting secretion of adrenaline from the adrenal medulla gradually waned and eventually stopped; immediately thereafter, histamine no longer released adrenaline.

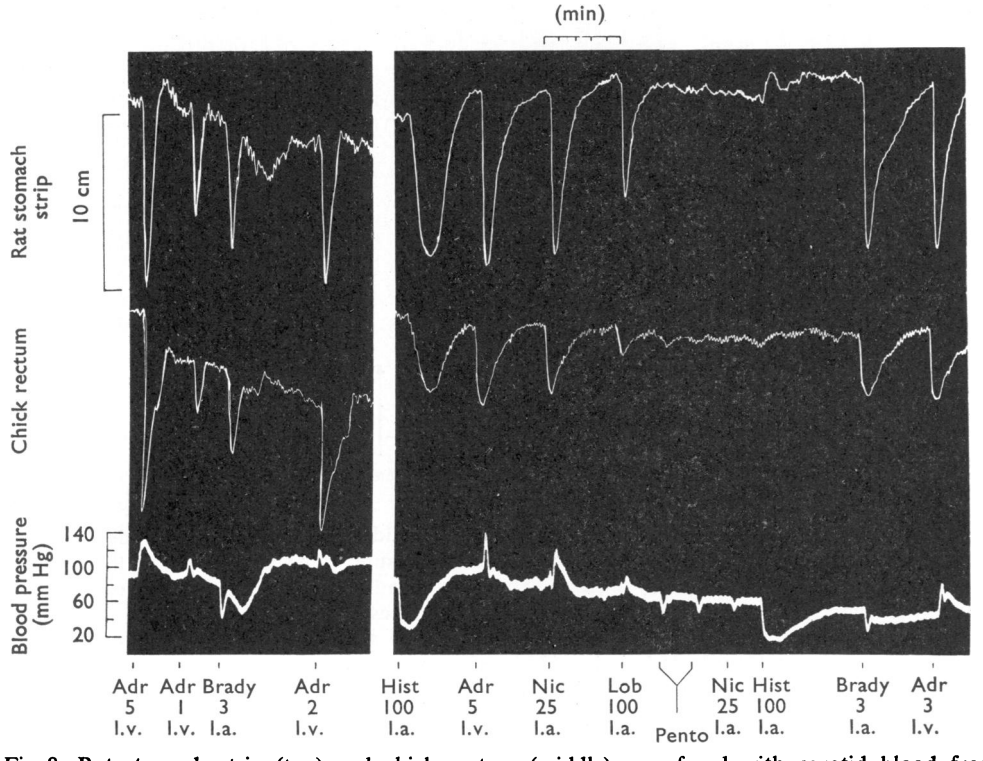

Fig. 8. Rat stomach strip (top) and chick rectum (middle) superfused with carotid blood from a 9.7 kg dog anaesthetized with chloralose. The bottom tracing is blood pressure. Intra-arterial (I.a.) bradykinin (Brady, 3 μg), histamine (Hist 100 μg), nicotine (Nic, 25 μg) and lobeline (Lob, 100 μg,) all released adrenaline (Adr). After intra-arterial pentolinium (Pento, 4 mg/kg), nicotine and histamine were ineffective, whereas bradykinin gave a bigger release than before. Time in minutes; vertical scales, 10 cm and mm Hg; doses in μg. I.v.=intravenous.

In the dog, ganglion-blocking agents reduced or abolished the release of adrenaline by histamine but not that by bradykinin or angiotensin. An example is seen in Fig. 8. Bradykinin (3 μg, intra-arterially) released between 1 and 2 μg of adrenaline, and histamine (100 μg, intra-arterially) about 5 μg as did nicotine (25 μg, intra-arterially). Lobeline (100 μg, intra-arterially) released much less. After two injections of pentolinium (2 mg/kg, intra-arterially) neither nicotine nor histamine released adrenaline but bradykinin released more than before.

To elucidate further this unexpected result, the following experiments were performed. Three dogs were anaesthetized with chloralose and their spinal cords cut. Adrenaline was still released by histamine but only by larger doses; this release was, however, susceptible to ganglion-block. The experiment in Fig. 9 shows the effects of spinal

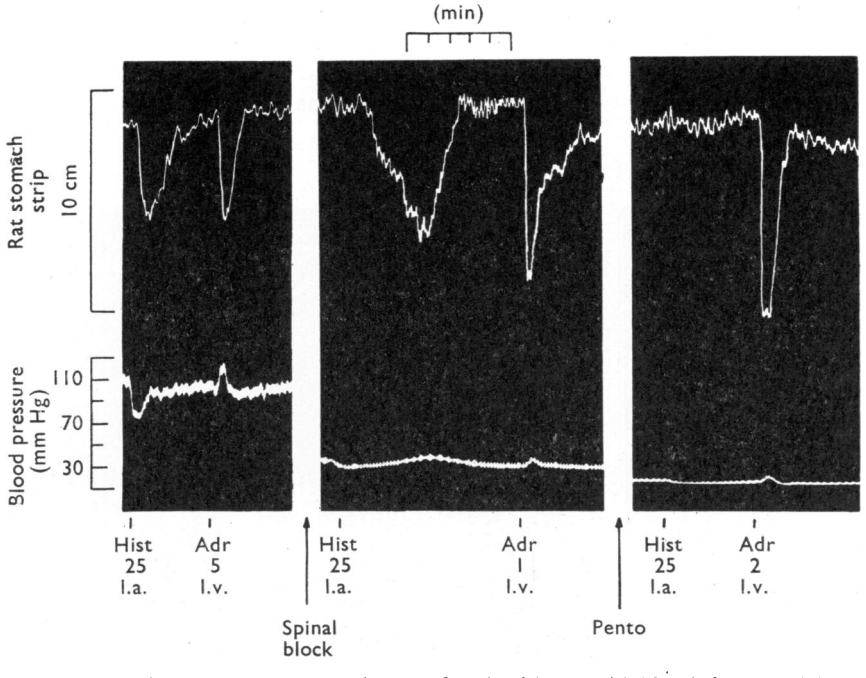

Fig. 9. Rat stomach strip (upper record) superfused with carotid blood from a 5.5 kg dog anaesthetized with chloralose. The lower tracing is blood pressure. The tracing shows that intra-arterial (I.a.) histamine (Hist, 25 μg) released about 5 μg of adrenaline (Adr). After blocking the spinal cord, the same dose of histamine gave much less release of adrenaline and this was completely blocked by intravenous (I.v.) pentolinium (Pento, 2 mg/kg). Time in minutes; vertical scales, 10 cm and mm Hg; doses in μg.

block followed by pentolinium. Histamine (25 μg, intra-arterially) released approximately 5 μg of adrenaline. Lignocaine was then injected into the spinal cord. Histamine (25 μg, intra-arterially) now released rather less than 1 μg of adrenaline. After pentolinium (2 mg/kg, intravenously) the release of adrenaline by histamine (25 μg, intra-arterially) was completely abolished, but much higher doses of histamine (200 to 300 μg, intra-arterially) still released some adrenaline.

DISCUSSION

There are certain disadvantages in using either the response of the blood pressure or that of the nictitating membrane as an indication of catechol amine release by histamine. First, the concentration of catechol amine in the arterial blood is maximal at the time when the fall in blood pressure produced by the injected histamine is still present; therefore, the secondary pressor response is the resultant of two opposing actions. Indeed, although histamine causes substantial release of catechol amine in the dog, there is usually no secondary pressor effect. Secondly, stimulation by histamine of ganglia or of chemoreceptors may contribute to the responses of the blood pressure and nictitating membrane. Although in cats such stimulation may only be a minor effect (Trendelenburg, 1961), we occasionally saw rises in blood pressure which were too great to be explained by catechol amine release alone (see Fig. 6).

We have used the blood-bathed organ technique to measure directly catechol amines released into the circulation. This method distinguishes between a change in release of catechol amine and a change in effect of the released amine. Thus, although Trendelenburg (1961) and Slater & Dresel (1952) showed that antagonists of catechol amines block the secondary pressor effects of histamine, we have demonstrated that antagonists of the effects of adrenaline at α- or β-receptors do not reduce the release of catechol amine but prevent the actions of the released amine. Indeed, the only substances which reduced the release of catechol amines by histamine were the antihistamine compounds, and these did so selectively and specifically, as had previously been shown by Emmelin & Muren (1949) and by Slater & Dresel (1952). The antihistamine drugs failed to stop the continuous prolonged release of adrenaline which we sometimes observed after histammine suggesting that this release was caused by a prolonged indirect effect of histamine, possibly involving damage to the adrenal glands or to the nerve terminals in them.

The blood-bathed organ technique distinguishes between adrenaline and noradrenaline by their differential activities on the rat stomach strip and the chick rectum (Vane, 1964). The technique is unlikely to detect less than 10% of noradrenaline in a mixture with adrenaline but would certainly detect more than 15%. In cats, 13 to 91% of the total catechol amine of the adrenal medulla is noradrenaline, with a mean value of about 45% (West, 1955; Butterworth & Mann, 1957). The secretion of the resting or denervated medulla or that induced by splanchnic nerve stimulation has a considerable proportion of noradrenaline (Vogt, 1952; Marley & Paton, 1961) although fast rates of stimulation lead to higher proportions of adrenaline (Rapela, 1956; Marley & Paton, 1961). In our experiments, there was no detectable noradrenaline in the circulation after stimulation of the adrenal medulla by histamine, suggesting either that histamine stimulates only cells which secrete adrenaline or that the stimulation mimics a fast rate of nerve stimulation. Similarly, although the dog adrenal medulla contains an average of 30% of noradrenaline (West, 1955) histamine caused a secretion only of adrenaline. Athos, McHugh, Fineberg & Hilton (1962), using a chemical method of estimation (Weil-Malherbe & Bone, 1952), also found predominantly adrenaline in the adrenal venous blood after giving massive doses of histamine (2.5 mg, intravenously) to dogs.

In adrenalectomized cats or dogs, even large doses of histamine brought about no detectable release of catechol amine into the bloodstream. Thus, if ganglia or nerve

endings are stimulated by histamine, the amount of catechol amine diffusing into the circulation is negligible.

In the animals most sensitive to histamine, 1 μg intra-arterially released about 1 μg of adrenaline. Since the blood flow to the adrenal glands represents a small fraction of the aortic blood flow, one molecule of histamine evidently releases several hundred molecules of adrenaline. Intravenous injection of histamine sometimes produced more adrenaline than intra-arterial injection of the same amount. This result is difficult to explain although it might be due to the streamline nature of flow down the aorta, leading to insufficient mixing of the histamine injected intra-arterially with the blood reaching the adrenal glands. The result is also reminiscent of the fact that infusions of histamine intra-arterially gave much less secretion of gastric juice in the cat than an equivalent dose intravenously (Born & Vane, 1953; Sewing, Born & Vane, 1965).

In the dog, disparity between the effects of intravenous and intra-arterial histamine might be explained by baro- or chemoreceptor activation by intravenous histamine but, in the cat, activation of baroreceptor reflexes releases very little catechol amine into the blood stream (Vane, 1964). Furthermore, in the cat, neither cutting the spinal cord nor administration of ganglion-blocking agents decreased adrenaline liberation. Indeed, like Slater & Dresel (1952) we found that the secondary rise in blood pressure was increased by ganglion-blocking agents. This increase was partly due to an increased release of adrenaline from the medulla and partly to increased sensitivity of the vessels. Both phenomena may be related to the decrease in uptake of adrenaline into storage sites caused by ganglion-blocking agents (see Vane, 1962). If this explanation is correct, some of the adrenaline released by histamine is normally reabsorbed into the adrenal gland before reaching the blood stream and a ganglion-blocking agent diminishes this reabsorption.

The most surprising result was that the release of adrenaline by small doses of histamine in the dog was completely prevented by ganglion-blocking agents suggesting that the release was induced either reflexly or through direct stimulation of nerve endings in the adrenal medulla. Athos *et al.* (1962) found that histamine released catechol amine from dog adrenals *in situ* but not from adrenals isolated and perfused with blood. This suggests that reflex activity plays a part in the release. Our experiments demonstrate that, in the dog, at least three mechanisms are involved in the released adrenaline by histamine:

(1) excitation of chemo- or baroreceptor reflexes shown by the reduction of release after cutting or blocking the spinal cord;

(2) stimulation of nerve endings in the adrenal medulla, because the release persisting after spinal section was reduced further by ganglion-blocking agents. Stimulation of preganglionic nerve endings by histamine, susceptible to ganglion-block, has been demonstrated in guinea-pig stomach by Paton & Vane (1963); and

(3) a direct effect on the medulla, produced only by large doses and observed when the other two actions have been eliminated.

The relative importance of the first two mechanisms is uncertain but, individually or in combination, they account for most of the release of adrenaline which occurs after intravenous or intra-arterial injections of histamine into anaesthetized dogs. In cats,

by contrast, the effects of histamine on the adrenal medulla are wholly direct with no contribution from nerve stimulation.

SUMMARY

1. The blood-bathed organ technique was used to measure the release of catechol amines into the bloodstream of cats and dogs after intra-arterial and intravenous injection of histamine.

2. The catechol amine released was mainly, if not all, adrenaline. The release of adrenaline was dependent on the dose of histamine and no release could be detected after adrenalectomy. Histamine intravenously was sometimes as potent, or more potent, than histamine intra-arterially.

3. Infusions of histamine gave an initial burst of adrenaline secretion. With low rates of infusion the secretion then stopped; with higher rates it was maintained, but never at the initial rate of secretion.

4. Antihistaminic drugs prevented the release of adrenaline by histamine, whereas antagonists of catechol amines did not.

5. In the cat, the release of adrenaline was not reduced by cutting the spinal cord; ganglion-blocking agents increased the release. The effects of histamine were therefore directly upon the adrenal medullary cells.

6. In the dog, cutting the spinal cord decreased the secretion of adrenaline induced by histamine and ganglion-blocking agents decreased it further. The effects of histamine on the adrenal medullary cells were therefore mainly indirect, acting through reflex pathways and nerve endings.

One of us (J. S.-B.) would like to thank the Squibb Foundation and the Wellcome Trust for personal grants, and Professor G. V. R. Born for hospitality and kindness in his department. We would like to thank Mr Rodney Ginn for his excellent technical assistance.

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