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A COMPARATIVE STUDY OF THE EFFECTS OF MORPHINE IN UNANAESTHETIZED AND ANAESTHETIZED CATS

BY

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It is well established that morphine and other narcotic analgesics produce a mania-like behavioural condition in the cat accompanied by some signs reminiscent of sympathetic stimulation such as pupil dilatation and pilo-erection (Sollmann, 1957). Morphine given intravenously or intraventricularly into unanaesthetized cats also induces a remarkable hyperglycaemia. This effect is due to the stimulation of certain receptors in the central nervous system and is mediated through the peripheral sympathetic nervous system (Borison, Fishburn, Bhide & McCarthy, 1962).

In spite of the foregoing findings regarding the sympathetic-like actions of morphine at certain sites in the body, this drug was claimed to cause a sustained fall in blood pressure and to have a "shock-like" effect in unaesthetized cats (Schmidt & Livingstone, 1933). No other reference has been found as to the effect of morphine on the blood pressure of such cats to elucidate this discrepancy. Therefore it seemed to be of interest to compare the changes in blood pressure of unanaesthetized cats with those of anaesthetized ones under uniform experimental conditions to get insight into the extent to which the blood pressure response to a centrally acting agent was modified by anaesthesia. (Since it is fairly common to make deductions about the action of a drug in the intact conscious animal on the basis of results obtained in the anaesthetized animal, this attempt is concerned with one of the current problems of pharmacology.)

Morphine has been shown to cause a precipitous and sustained fall in the blood pressure of chloralose-anaesthetized cats when given intravenously (Evans, Nasmyth & Stewart, 1952). Although we obtained a similar result, a different view of its mechanism of action will be presented here.

METHODS

Cats of either sex, weighing between 2 and 4 kg, were used. Surgery was carried out during ether anaesthesia. The trachea was cannulated for artificial respiration. In cats in which the carotid occlusion response was to be tested both common carotid arteries were dissected from the surrounding tissues. All cats were vagotomized. A femoral vein was cannulated for injection of drugs. Coagulation of blood was prevented by injecting 5 mg/kg of heparin sodium intravenously. Blood pressure was recorded from the femoral artery on the same side as the cannulated femoral vein by a mercury manometer writing on smoked paper. The femoral nerve was cut as proximal as possible on this side.

After surgery the wounds in the neck and thigh were painted thoroughly with a 1% solution of amethocaine hydrochloride. In order to avoid local anaesthesia of the carotid sinus region by diffusion the incision in the neck was done as far caudally as possible. Ether anaesthesia was stopped and artificial respiration was established, using an Ideal Respiration Pump (Palmer). Cats were paralysed by gallamine triethiodide given at an initial dose of 2 mg/kg intravenously. Half of this dose was repeated every 15 to 20 min to maintain the immobilization of the animal. The experiment was started 1 hr after the end of anaesthesia, in order to allow for excretion of the ether.

In some cats experiments were carried out during pentobarbitone anaesthesia. These cats were given 25 to 30 mg/kg of pentobarbitone sodium intravenously. After the blood pressure had recovered from the initial fall caused by pentobarbitone the experiment was started. The artificial respiration and the administration of gallamine were continued in these cats throughout the experiment for the sake of uniformity of method and to rule out any effect on blood pressure secondary to the respiratory depression by morphine.

The carotid occlusion response was elicited by clamping the common carotid arteries bilaterally for 30 sec. Care was taken to avoid stretching the arteries and irritating the neighbouring tissue.

Spinal-cord section was performed at the level of the first cervical segment. These cats were allowed to recover from the initial effects of the section for 8 hr before starting the experiment. Gallamine triethiodide was given as in the intact animals for the sake of uniformity of method.

Drugs used were morphine hydrochloride (Sandoz), diamorphine hydrochloride (Boehringer Sohn), nalorphine hydrochloride (Nalline, Merck Sharp & Dohme), mepyramine maleate (Neo-antergan, Specia) tripelennamine hydrochloride (Pyribenzamine, Ciba), phenoxybenzamine hydrochloride (Dibenzyline, Smith Kline & French), hexamethonium chloride (Squibb), 1,1-dimethyl-4-phenylpiperazinium iodide (Parke Davis) and (—)-noradrenaline bitartrate (Hoechst). All drugs were given intravenously. The doses are expressed in terms of the salts except for (—)-noradrenaline, the dose of which is expressed as the base.

RESULTS

Unanaesthetized cats

Effect of morphine on blood pressure. Morphine given in a dose of 1 to 4 mg/kg usually elicited a transient rise in blood pressure. It occasionally caused a transient fall. Spontaneous successive transient increases in blood pressure appeared after a delay of 10 to 25 min depending on the dose. They were variable in size. Since they occurred frequently, sometimes superposed one upon the other, the course of the blood pressure appeared quite unsteady. In about half of the experiments the blood pressure showed a slowly developing prolonged rise almost simultaneously with the appearance of the spontaneous changes. In some experiments the blood pressure was so unsteady that the changes appeared to be rhythmic.

After administration of larger doses of morphine ranging from 5 to 10 mg/kg the blood pressure fell 3 to 10 min before the spontaneous fluctuations started.

Since the background blood pressure was very unsteady, the changes in the responses to carotid occlusion and the administration of dimethylphenylpiperazinium and noradrenaline were not easy to assess properly unless they were of greater magnitude. In some experiments changes in the response to carotid occlusion were tested before spontaneous fluctuations in blood pressure began. The results were variable. In some cats 3 mg/kg of morphine reduced the response to half the control value, while in the others there was no obvious change even after the administration of 10 mg/kg of morphine.

In three cats attempts were made to reduce the carotid occlusion response by increasing the dose of morphine. The result in one of them is shown in Fig. 1. In that cat there was

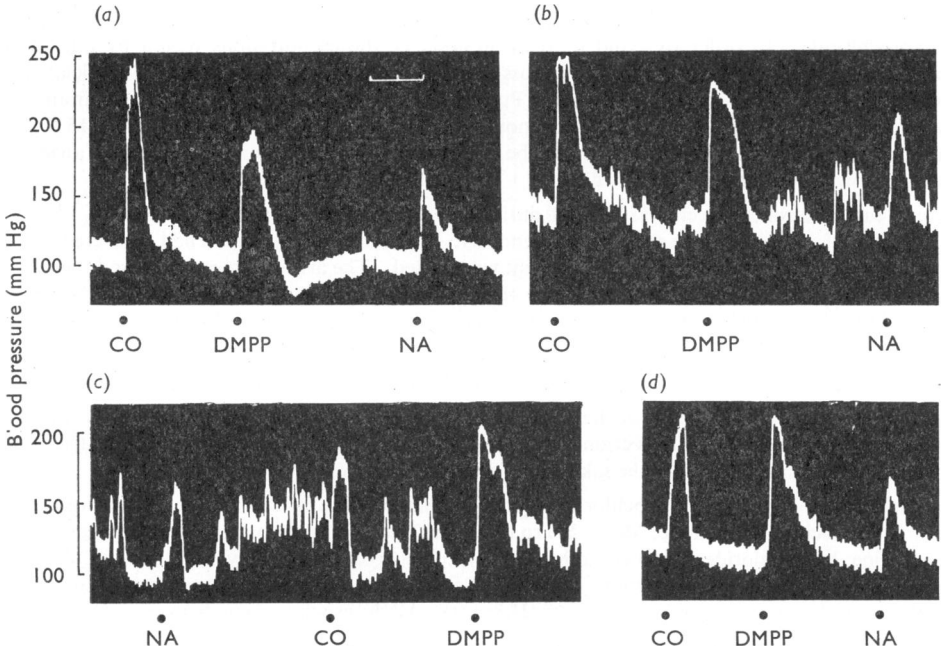

Fig. 1. Cat paralysed with gallamine and artificially ventilated. Recording of blood pressure from a femoral artery. The effect of morphine on blood pressure and the responses to carotid occlusion (for 30 sec at CO), dimethylphenylpiperazinium (40 μg/kg intravenously at DMPP) and noradrenaline (4 μg/kg intravenously at NA). (*a*) Control responses; (*b*) after the administration of 10 mg/kg of morphine; (*c*) after the administration of another 10 mg/kg of morphine; (*d*) after the administration of 4 mg/kg of nalorphine. Note the appearance of spontaneous fluctuations in blood pressure in (*b*) and (*c*). Time marks, 1 min.

a slight decrease in the carotid occlusion response after administration of 10 mg/kg morphine. When a further 10 mg/kg of morphine was given, the hypertensive response to carotid occlusion was abolished almost completely and it was followed by a fall in blood-pressure. The responses to dimethylphenylpiperazinium and noradrenaline were not much reduced. After the administration of 4 mg/kg of nalorphine the carotid occlusion response was partly restored and the spontaneous fluctuations disappeared.

In all experiments nalorphine (1 to 4 mg/kg) restored blood pressure to a stable control value within less than 10 min. Nalorphine (5 mg/kg) itself did not alter the pressor response to carotid occlusion in two cats. If a prolonged rise of blood pressure occurred after the administration of morphine, it was reduced to the initial blood pressure level by nalorphine.

Effect of diamorphine on the blood pressure. In order to compare the effect of morphine with that of another narcotic analgesic, diamorphine was given in a dose of 1 to 4 mg/kg in five cats. Fig. 2 shows the effect of diamorphine on the blood pressure in one of the cats. The differences observed were that the spontaneous fluctuations and the prolonged rise in blood pressure started earlier, and that the slowly developing rise in blood pressure was produced more frequently (in four out of five cats). Nalorphine abolished the effect of diamorphine on blood pressure (Fig. 2).

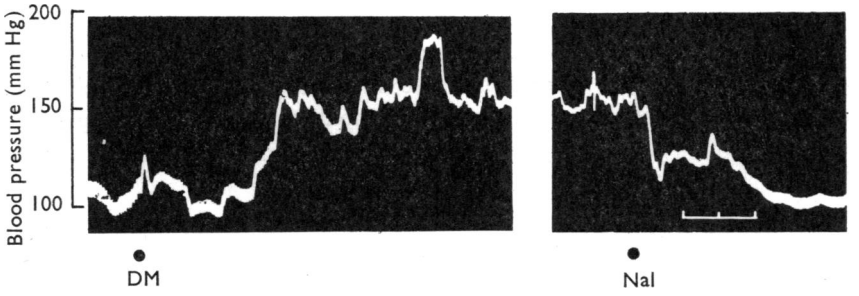

Fig. 2. Cat paralysed with gallamine and artificially ventilated. Recording of blood pressure from a femora artery. The effect of diamorphine (2 mg/kg intravenously at DM) on the blood pressure and abolition of this effect by nalorphine (1 mg/kg intravenously at Nal). The interval between the two records is 10 min. Time marks, 1 min.

Effect of morphine on the blood pressure of spinal cats. Morphine (1 to 5 mg/kg) given to five spinal cats caused a transient rise in blood pressure starting 15 to 20 sec after its administration. The magnitude of the rise ranged between 35 to 90 mm Hg. In two of the cats a sustained fall of smaller magnitude occurred after the initial rise when 5 mg/kg of morphine was given. The blood pressure recovered in 10 to 15 min. Morphine in this dose also depressed the pressor response to dimethylphenylpiperazinium (10 μg/kg) without causing any change in the pressor response to 1 μg/kg of noradrenaline. The latter effect of morphine, which lasted only 15 to 25 min, appeared to be abolished by nalorphine. No fluctuations in blood pressure were observed in spinal cats after the administration of morphine.

Effect of antihistaminic agents on the action of morphine on the blood pressure. Mepyramine or tripelannamine was given in a dose of 10 mg/kg to four cats. In all of the cats thus treated morphine (1 to 5 mg/kg) induced a transient rise in blood pressure, followed by a sustained rise in three of them (Fig. 3). Morphine in doses smaller than 5 mg/kg did not produce any initial fall in blood pressure in the treated cats. Fluctuations in blood pressure appeared as in cats not treated with antihistamines.

Effect of certain blocking agents on the action of morphine on the blood pressure. When phenoxybenzamine (5 mg/kg) was given during the phase of fluctuating blood pressure it

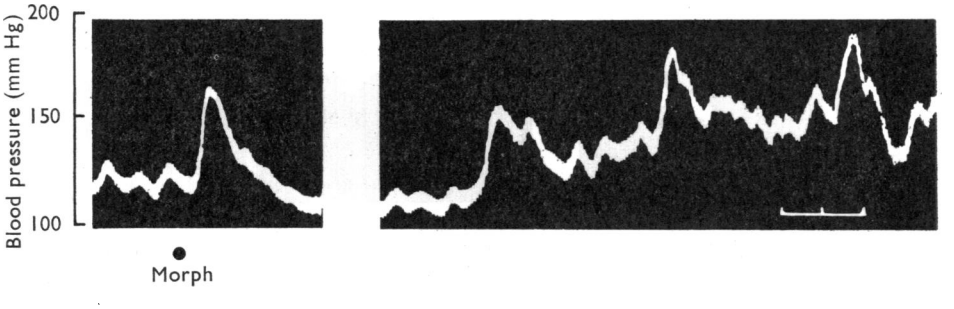

Fig. 3. Cat paralysed with gallamine and artificially ventilated and treated with 10 mg/kg of mepyramine. Recording of blood pressure from a femoral artery. The effect of morphine (3 mg/kg intravenously at Morph) on the blood pressure. The interval between the two records is 5 min. The right-hand record shows the delayed spontaneous sustained rise and fluctuations of blood pressure. Time marks, 1 min.

depressed the blood pressure and made it steady. A similar result was obtained after the administration of 10 mg/kg of hexamethonium. In cats treated with 15 mg/kg of hexamethonium, morphine did not produce any rise in blood pressure but doses of morphine larger than 3 mg/kg induced a fall of pressure of smaller magnitude lasting for less than 15 min.

Anaesthetized cats

The effect of morphine was studied in six cats anaesthetized with 25 to 30 mg/kg of pentobarbitone sodium and given gallamine and artificial respiration. Morphine in doses of more than 2 mg/kg now caused a precipitous fall in the blood pressure, usually preceded by a small initial rise (Fig. 4). The blood pressure remained low and did not recover during the observation period of 45 min. Nalorphine (1 to 4 mg/kg) restored the blood pressure within a few minutes.

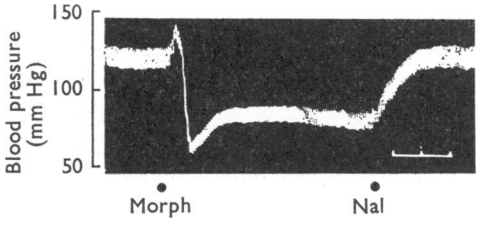

Fig. 4. Cat anaesthetized with pentobarbitone and given gallamine and artificial respiration. Recording of blood pressure from a femoral artery. The effect of morphine (3 mg/kg intravenously at Morph) on blood pressure and the action of nalorphine (1 mg/kg intravenously at Nal) on this effect. Time marks, 1 min.

In anaesthetized cats treated with nalorphine, smaller doses (2 to 4 mg/kg) of morphine induced a short-lasting fall in blood pressure and this effect was not observed after the administration of 10 mg/kg of mepyramine. Fig. 5 shows the blocking action of mepyramine on the transient depressor response to 3 mg/kg of morphine in a nalorphine-treated cat. However, a larger dose of morphine (6 mg/kg) still caused a short-lasting fall in blood pressure.

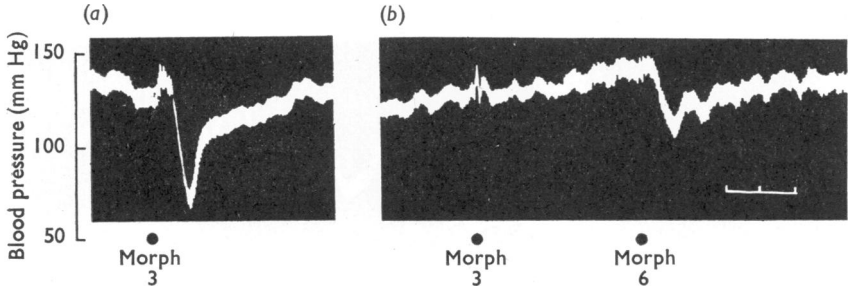

Fig. 5. Cat anaesthetized with pentobarbitone and treated with 2 mg/kg of nalorphine. Recording of blood pressure from a femoral artery. The response to morphine (doses in mg/kg intravenously at Morph) and the effect of mepyramine on this response. (*a*) Control response; (*b*) after the administration of 10 mg/kg of mepyramine intravenously. Time marks, 1 min.

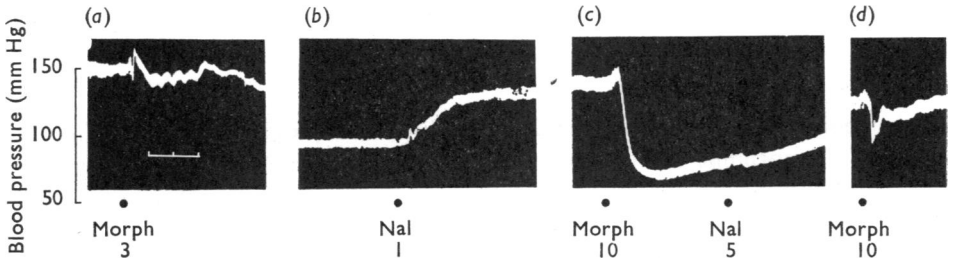

Fig. 6. Cat anaesthetized with pentobarbitone and treated with 10 mg/kg of mepyramine, and given gallamine and artificial respiration. Recording of blood pressure from a femoral artery. The effect of morphine (Morph) at two different doses (in mg/kg, intravenously) and the action of nalorphine (in mg/kg intravenously at Nal) on this effect. (*a*) Effect of morphine (3 mg/kg); (*b*) abolition of this effect by nalorphine; the interval between (*a*) and (*b*) is 10 min; (*c*) effect of morphine (10 mg/kg) and the failure of nalorphine to abolish this effect; between (*b*) and (*c*) 3 mg/kg of nalorphine was injected intravenously; (*d*) response to the third dose of 10 mg/kg of morphine. Time marks, 1 min.

In cats treated with 10 mg/kg of mepyramine, morphine (2 to 4 mg/kg) caused a slowly developing fall in blood pressure (Fig. 6). No precipitous initial fall was observed in these cats. After the blood pressure had reached its lowest level 1 mg/kg of nalorphine was given and this restored the blood pressure to the initial level within a few minutes.

In nalorphine-treated cats morphine (10 mg/kg) caused a sustained fall in blood pressure. This response was also observed in cats treated with 10 mg/kg of mepyramine in addition to nalorphine (Fig. 6) and was not abolished by administration of a larger dose of nalorphine. The effect of morphine was diminished by repeated administration.

DISCUSSION

The characteristic feature of the action of morphine on the blood pressure of unanaesthetized cats was the occurrence of spontaneous successive transient increases. They were variable in size and consistent in occurrence. There was a latent period of moderate duration between the administration of morphine and the appearance of the fluctuations. A similar latent period has been observed in the behavioural excitatory action of morphine in the unrestrained cat (Tavat & Akçasu, 1956). On the other hand, diamorphine produced fluctuations in blood pressure earlier than did morphine. This latent period may be due to the time taken by morphine and diamorphine to penetrate into their site of action in the central nervous system. Starting from this assumption the difference between the latent periods of these agents may perhaps be explained on the basis suggested by Martin (1963) as due to a greater ease of entry into the brain by diamorphine because of its greater solubility in lipids.

It seems likely that the fluctuations in blood pressure arise from stimulation of a centre or centres located in the brain as evidenced by their absence in spinal cats. The present work gives no information of the location of these centres in the brain. Both the behavioural excitation and the blood pressure changes due to morphine occur in an intermittent burst pattern after a latent period. In view of these similarities it may be that these two effects of morphine are induced by its firing a common trigger mechanism which interacts with the vasomotor centres.

It is interesting to note that in three unanaesthetized cats given altogether 20 mg/kg of morphine the fluctuations in blood pressure persisted despite the almost complete abolition of the carotid occlusion response.

Another point of interest is the sustained rise in blood pressure, which was more commonly with diamorphine than with morphine in unanaesthetized cats and was usually simultaneous with the appearance of the fluctuations. It occurred neither in the spinal cat nor after the blockade of the sympathetic nervous system by hexamethonium or phenoxybenzamine. It seems that diamorphine and, to a lesser extent, morphine may induce a tonic excitatory influence upon the vasomotor centres in addition to the intermittent or phasic one mentioned above.

The effect of morphine was quite different in the anaesthetized cats, in which it invariably produced a fall in blood pressure. This fall appeared to be made up of at least two different components, an initial short-lasting fall and a slowly developing sustained fall. Only the first component was produced in cats treated with nalorphine. It was blocked by mepyramine. This suggests that it might be due to the liberation of histamine from the tissues by morphine and that the histamine releasing action of morphine was not blocked by nalorphine. Indeed, morphine has been shown to release histamine from the isolated perfused gastrocnemius muscle and skin of the cat, as well as to increase the plasma histamine level when given intravenously (Feldberg & Paton, 1951). Only the second component resulted when the cat had been previously treated with mepyramine. It may be due to an inhibitory action of morphine on the vasomotor centres. Such an action of morphine in anaesthetized cats has been suggested by Evans *et al.* (1952). Trendelenburg (1957) has produced evidence that morphine inhibits the release of the sympathetic transmitter from postganglionic nerve endings in the nictitating membrane of the cat without affecting transmission through the sympathetic ganglion. This suggestion was confirmed by Cairnie, Kosterlitz & Taylor (1961). This mechanism which may affect cardiovascular sympathetic tone might be also involved in the sustained component of the depressor action of morphine. The selective depression of the pressor response to dimethylphenylpiperazonium, a nicotine-like compound, observed after the administration of 5 mg/kg of morphine in the spinal cats may be related to the inhibition of sympathetic transmitter release from postganglionic nerve endings. The slow development of the sustained component observed in the present work may be explained on the basis of the slow penetration of morphine to its site of action in the brain as discussed above.

Morphine given in larger dose (10 mg/kg) produced a fairly sustained and profound fall in blood pressure, which was not abolished by nalorphine. Treatment of the cats with mepyramine was not sufficient to block the depressor response to the larger amount of histamine released by morphine at this dose. The fall in blood pressure lasting 10 to 15 min observed in spinal cats might also be due to the release of histamine. However, the fall in blood pressure in these cats was small, when it occurred at all, possibly because of the lower tone of the blood vessels. The release of histamine may be responsible for the initial transient fall in blood pressure occasionally observed after the administration of morphine in unanaesthetized cats. It did not occur in the cats treated with an antihistaminic agent.

Our results do not agree with those obtained by Evans *et al.* (1952) in one important respect. These authors did not observe any alteration in the fall of blood pressure caused

by 4 mg/kg of morphine given intravenously after treatment of the anaesthetized cats with 5 mg/kg of mepyramine. It seems possible that their failure may be due to an inadequate dose of the antihistamine.

The initial transient rise of varying magnitude which was observed after the administration of morphine in anaesthetized, unanaesthetized or spinal cats may be due to the release of catechol amines from the adrenal medulla by morphine, though no attempt was made to obtain direct evidence confirming this. Morphine releases catechol amines from the adrenal medulla in the dog (Wada, Tanaka, Hirano & Taneiti, 1938) and the cat (Outschoorn, 1952).

It is obvious that the action of morphine on blood pressure is quite different in unanaesthetized and anaesthetized cats. In view of the results in the two groups of cats, we believe that the excitatory action of morphine on the vasomotor centres, regardless of whether it is tonic or phasic, was completely abolished by the pentobarbitone anaesthesia, which may also have potentiated the depressor action of morphine at this site. In keeping with these results pentobarbitone anaesthesia has been shown to abolish the sympathetically mediated central hyperglycaemic effect of morphine (Borison *et al.*, 1962).

SUMMARY

1. In unanaesthetized cats the effect of morphine on the blood pressure is predominantly pressor. Spontaneous fluctuations and sometimes a sustained rise in blood pressure occurred after a latent period. These pressor responses were abolished by ganglion-blocking and sympathetic α-receptor blocking agents. They were not observed in spinal cats.

2. In cats anaesthetized with pentobarbitone the response to morphine is depressor and characterized by a precipitous sustained fall. The response can be shown to have two components.

3. Nalorphine antagonized both central vasomotor stimulatory and inhibitory effects of morphine. But it did not seem to abolish the histamine-releasing action of morphine.

4. Five distinct mechanisms are suggested to take part in the effect of morphine on the blood pressure in the cat: indirect stimulation of the vasomotor centres, abolished by anaesthesia; depression of the vasomotor centres by a direct action which is predominant in anaesthetized cats; inhibition of the postganglionic sympathetic transmitter release; liberation of histamine from tissues; and liberation of catechol amines from the adrenal medulla.

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