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VASCULAR RESPONSES OF THE RAT TO BRADYKININ

BY

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The effects of oestrogens and of sympathetic blockade on the vascular response of rats to bradykinin were studied. No difference in response was found between males and oestrous or dioestrous females. The previous administration of an oestrogen did not affect the response. An augmentation of the depressor response to bradykinin was seen in both sexes after the intravenous administration of either dihydroergotamine or hexamethonium, but not after atropine. Pithing reduced the response to bradykinin. The differences between these results and those previously obtained with oxytocin are discussed.

Recent work has shown that the vasodilator action of oxytocin in the male or the dioestrous female rat may be converted to a constrictor and pressor action by previous treatment with an oestrogen, or by interruption of the sympathetic nervous system by surgical or chemical means, and that a pressor response to oxytocin is also seen during natural oestrus, and during the last half of pregnancy (Lloyd, 1959a, b ; Lloyd & Pickford, 1961). In view of this similarity between the effects of oestrogens and sympathetic denervation on the vascular responses, it was of interest to know whether this reversal in action was peculiar to oxytocin, or was shown by other agents which are normally vasodilator. Since bradykinin is a naturally occurring vasodilator, which also shares with oxytocin the property of stimulating the smooth muscle of the rat uterus (Rocha e Silva, Beraldo & Rosenfeld, 1949), it was decided to test the actions of oestrogens and sympathetic denervation on the response of the rat vascular system to this substance.

METHODS

Rats of 200 to 220 g body weight were used, anaesthetized with intraperitoneal sodium pentobarbitone (5 mg/100 g). The blood pressure was recorded from the cannulated carotid artery by means of a mercury manometer. All injections were made into a cannulated femoral vein in a total volume of 0.3 ml. of 0.9% sodium chloride solution. Intravenous infusions were made into a femoral vein at a rate of 0.05 ml./min. Where an oestrogen was given, this was injected subcutaneously in oil 24 hr before observations were begun. The phase of the reproductive cycle of all females was checked at the start of the experiment by taking vaginal smears, and staining with Leishmann stain. Where pithing was carried out, this was done by passing a steel rod (a no. 12 knitting needle) through the orbit and down the spinal canal.

The bradykinin used was the synthetic preparation, kindly supplied by Sandoz Products. The oestrogen preparation was stilboestrol dipropionate in oil (Organon), and the blocking agents used were dihydroergotamine methanesulphonate (Sandoz) and hexamethonium bromide (May & Baker). The oxytocin was synthetic (Syntocinon, Sandoz).

RESULTS

Control observations. Results were obtained from 4 male and 16 female rats, most of which were subsequently given sympathetic blocking agents, or pithed. Of the females, 9 were dioestrous, 4 in natural oestrus, and 3 in oestrus following the subcutaneous injection of stilboestrol (5 μg/100 g) on the previous day. All animals showed a prompt and transient depressor response to the intravenous injection of bradykinin (Fig. 1), though the dose required varied somewhat between different animals, 0.1 to 0.4 μg causing a fall of 10 mm Hg in the blood pressure. In any one animal the depressor response remained constant when intervals of at least 5 min were allowed between successive injections. There was no correlation between the dose of bradykinin required to produce a standard fall of 10 mm Hg in the blood pressure, and the sex of the animal or the stage of the reproductive cycle of the females (Fig. 1).

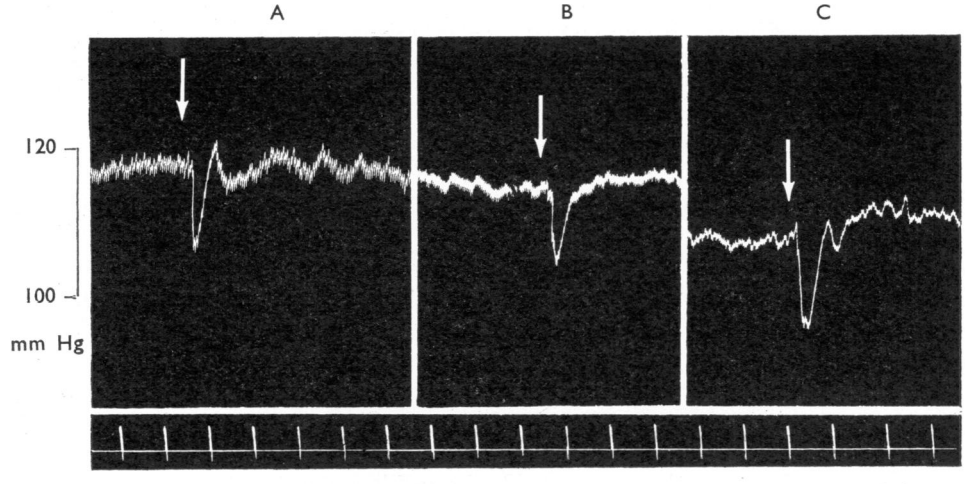

Fig. 1. The effect of 0.2 μg bradykinin, given intravenously, on the blood pressure of the rat. A, male rat; B, dioestrous female; C, oestrous female. Bradykinin injected at arrows. Time marker 30 sec.

Effect of autonomic blocking agents

Dihydroergotamine. During experiments on 7 rats, 0.1 to 0.15 mg dihydroergotamine methanesulphonate was given intravenously after the normal responses to bradykinin had been tested. Of these animals, 2 were male and 5 female. The dose of dihydroergotamine used was sufficient to abolish the normal pressor response to the intravenous injection of 0.1 μg noradrenaline. In all instances following the blocking agent, the blood pressure was 5 to 10 mm Hg below the previous level. In all animals the depressor response to intravenous bradykinin was greater after the adrenergic blockade than before (Fig. 2). For example, in one dioestrous female 0.2 μg bradykinin caused a fall in blood pressure of 10 mm Hg before dihydroergotamine was given, and a fall of 19 mm Hg after blockade. Similar increases in the depressor responses were seen in both males and females.

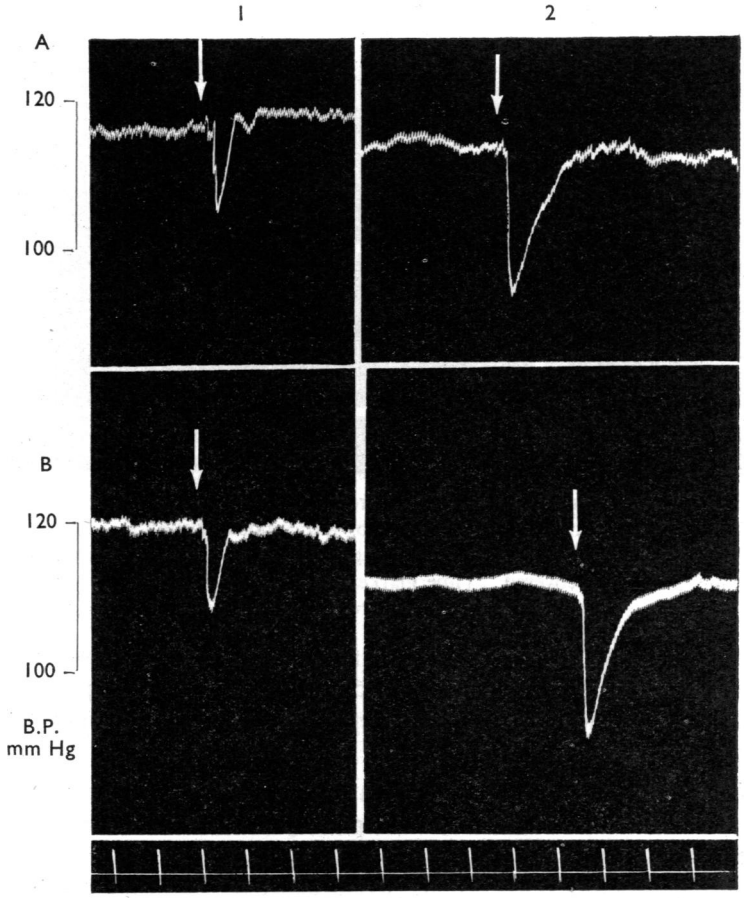

Fig. 2. The effect of sympathetic blockade on the response of the dioestrous female rat to 0.2 μg bradykinin, given intravenously. A, 0.1 mg dihydroergotamine intravenously between 1 and 2; B, 1 mg hexamethonium intravenously between 1 and 2. Bradykinin injected at arrows. Time marker 30 sec.

Hexamethonium. Hexamethonium (1 mg) was given intravenously to four rats (2 males and 2 females) during the course of observations, and the response to bradykinin again tested when the blood pressure had stabilized following the fall due to the blocking agent. In all animals the depressor response to bradykinin was increased by 60 to 100%.

That these increased responses were not due to the lower basal blood pressure seen after ganglionic or adrenergic blockade was shown in a further three females. In these animals intravenous infusions of isoprenaline (0.01 to 0.05 μg/min) were given to reduce the blood pressure by approximately 10 mm Hg. When bradykinin was given during these infusions, the response was no greater than that seen before the infusion, and in one case was reduced from 13 mm Hg to 6 mm Hg for a dose of 0.3 μg bradykinin (Fig. 3).

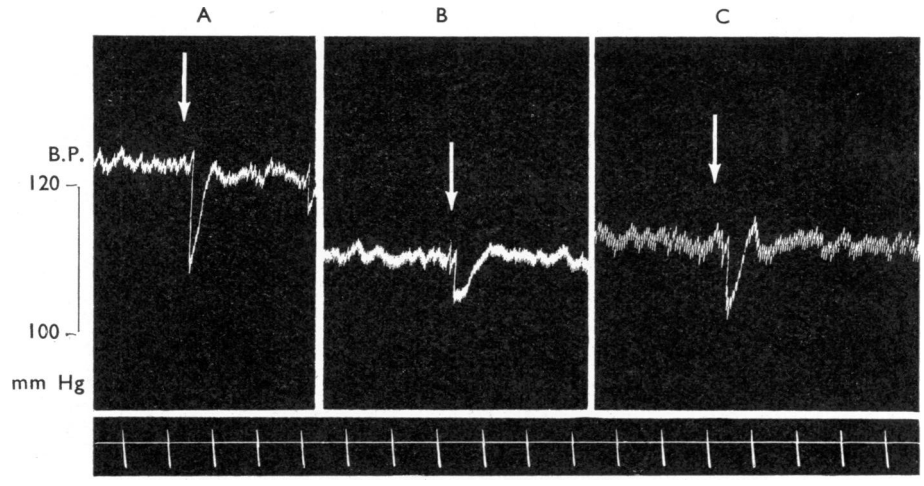

Fig. 3. The effect of isoprenaline infusion on the response of the dioestrous female rat to 0.3 μg bradykinin, given intravenously. Isoprenaline by intravenous infusion at 0.02 μg/min. Bradykinin injected at arrows. A, before, B, during the infusion; C, infusion ended, but blood pressure only partially recovered. Time marker 30 sec.

Atropine. Atropine (0.2 mg) was given intravenously during observations on 3 female rats. This dose was sufficient to abolish the depressor response to 0.1 μg acetylcholine, but in no case was the depressor response to bradykinin either increased or decreased.

Effect of pithing. A further two female rats were pithed after the normal response to bradykinin had been established. After pithing the animals were maintained on artificial respiration. In one animal the blood pressure was 55 mm Hg, and in the other 40 mm Hg. Before pithing both gave a depressor response of 10 mm Hg to a dose of 0.4 μg bradykinin. After pithing in one animal there was no response to doses of bradykinin ranging from 0.1 to 0.8 μg, while in the other 0.8 μg caused a fall in pressure of 7 mm Hg. No hint of a pressor response was seen in either animal.

DISCUSSION

The results of these experiments show that bradykinin still produces dilatation in the rat after pithing or sympathetic blockade, and also that oestrogens do not influence the response. This is in marked contrast with the results previously obtained with oxytocin, which though producing dilatation in the normal male and dioestrous female, causes constriction and a pressor response during oestrus or late pregnancy, after the administration of oestrogens, or after sympathetic nervous destruction or blockade (Lloyd, 1959a, b ; Lloyd & Pickford, 1961). In the present experiments the depressor response to bradykinin was seen to be increased after sympathetic blockade with either dihydroergotamine or hexamethonium. A similar potentiation was seen in the cat after sympatholytic agents (Rocha e Silva, Corrado & Ramos, 1960) using highly purified natural bradykinin, but these workers did not find an augmentation of response following hexamethonium. Whether the

difference between their results and those described here is due to species differences, or to differences between the highly purified natural bradykinin and the synthetic preparation, is not known. A further difference between the present results and those of previous workers is that in the former there was no hint of a pressor response to bradykinin even in the pithed animals, whereas Croxatto and Belmar (1961) described hypertensive actions of bradykinin in rats when the basal blood pressure was low, 8 to 24 hr after nephrectomy, or after pentolinium administration.

These results lend further support to the evidence that the conversion of the response to oxytocin by oestrogens or sympathetic blockade is not common to all vasodilator agents. The responses to isoprenaline and acetylcholine have previously been shown to be unaffected by ovarian hormone levels (Lloyd, 1959a, b). The contrast between oxytocin and bradykinin is, however, of particular interest, since both are naturally occurring small polypeptide vasodilators, and both are known to stimulate uterine contraction. This, perhaps, strengthens the possibility that the dilator effect of oxytocin may be of central origin, and dependent on the integrity of the sympathetic nervous system.

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