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THE ACTION OF POSTERIOR PITUITARY HORMONES AND OESTROGENS ON THE VASCULAR SYSTEM OF THE RAT

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In two recent papers (Lloyd, 1959*a*, *b*) it was shown that the vascular responses of the rat to oxytocin and vasopressin varied with the concentration of ovarian hormones in the body. For example, oxytocin was dilator in the dioestrous rat, though without effect on the blood pressure, while in the oestrous animal, during late pregnancy, or after ovarian hormone administration, oxytocin was pressor and constrictor. It was not known how far this reversal of effect was due to an altered state of the peripheral vasculature, or how far central mechanisms were involved. Since peripheral vasodilatation is one of the consequences of the administration of oestrogen, it was of interest to test the effect of other dilator substances on the response to oxytocin and vasopressin in the rat, and for this purpose infusions of histamine, acetylcholine, isoprenaline and 5-hydroxytryptamine (5-HT) were used. In addition, procedures such as pithing, decerebration, and the administration of autonomic blocking agents were used to determine whether reduction of vasomotor tone would affect the responses to posterior pituitary hormones, and to discover if any part was played by the central and peripheral nervous systems.

METHODS

All experiments were made on rats of approximately 200 g body weight. Anaesthesia, injection of drugs, and recording of blood pressure were effected by the methods previously described (Lloyd, 1959*a*, *b*). The stage of the reproductive cycle was checked in all females by vaginal smears stained with Leishmann stain. All drugs were dissolved in NaCl solution 0·9 g/100 ml. Single intravenous injections were made up to a volume of 0·3 ml.; intravenous infusions were made into a cannulated femoral vein, at a rate of 0·05 ml./min. Autonomic blocking agents were either given intravenously during the experiments, or subcutaneously 2–3 hr before observations were begun. In experiments in which rats were pre-treated with an oestrogen, stilboestrol dipropionate was used, given in a dose of 3·5 μg/100 g 24 hr before observations were made.

The oxytocin used was the synthetic brand Syntocinon (Sandoz). Previous experience showed that the actions of Syntocinon were identical with those of purified oxytocic extracts of the posterior pituitary (Brooks & Pickford, 1958; Nixon & Smyth, 1957). The vasopressin was either Parke Davis's Pitressin or du Vigneaud's highly purified arginine vasopressin. The bretylium tosylate (Darenthin) was supplied by the Wellcome Research Laboratories,

and the 5-hydroxytryptamine (as Serotonin creatinine sulphate) by Abbott Laboratories. The reserpine was the Ciba product Serpasil, and the ergot preparation Dihydroergotamine (Sandoz). Histamine was used in the form of the acid phosphate (British Drug House). The dibenamine solution was prepared by the method of Dekanski (1952).

RESULTS

The effect of infusion of dilator substances

The vasodilator substances used were acetylcholine, isoprenaline, histamine and 5-hydroxytryptamine. The doses and results are summarized in Table 1. All dilator drugs were administered by slow intravenous infusion lasting approximately 30 min, and the responses to oxytocin and vasopressin were tested before, during and after the infusions. The general blood pressure was lowered by as much as 20 mm Hg by infusion at the higher concentrations, though with the smaller doses any depressor action was temporary. In eleven experiments on dioestrous females up to

TABLE 1. The effect of intravenous infusions of vasodilators on the response to oxytocin

Substance infused (μg/min)	Total no. of rats	Effect of oxytocin on blood pressure	
		Pressor before, during and after infusions	No effect before, during or after infusions
Acetylcholine 0·05–1·0	6	2 (*F*, oestrous)	4 (3*F*, dioestrous, 1*M*)
Isoprenaline 0·02–1·0	7	2 (*F*, oestrous)	5 (2*F*, dioestrous, 3*M*)
5-HT 0·5–1·0	5	1 (*F*, oestrous)	4 (4*F*, dioestrous)
Histamine 2·5–5·0	4	1 (*F*, oestrous)	3 (2*F*, dioestrous, 1*M*)

F = female; *M* = male.

100 m-u. oxytocin had, as expected, no effect on the blood pressure before infusion of a dilator substance, and it was found that no pressor response to oxytocin appeared either during or for 2 hr after infusion of any of the dilator agents (Fig. 1*A*). In five experiments on normal males similar results were obtained; that is, no pressor response to oxytocin was observed before, during or after infusions of any of the vasodilator substances. The effect of the infusions on the response to vasopressin was also tested in most of these animals, and in no instance was the magnitude of the pressor response altered.

In six oestrous rats, in which a pressor response to oxytocin was present before infusion, the size and duration of this effect were unaltered by any of the dilator drugs (Fig. 1*B*). For example, 50 m-u. oxytocin raised the blood pressure by 10 mm Hg before, during and after the infusion of isoprenaline. Similarly, though the pressor effect of vasopressin was greater in this group of animals than in the dioestrous females or males, the size

of the response was unchanged by the infusions. Thus, if 0·2–0·3 m-u. vasopressin increased the blood pressure by 10 mm Hg before infusion, it raised it to the same extent during and after the infusion.

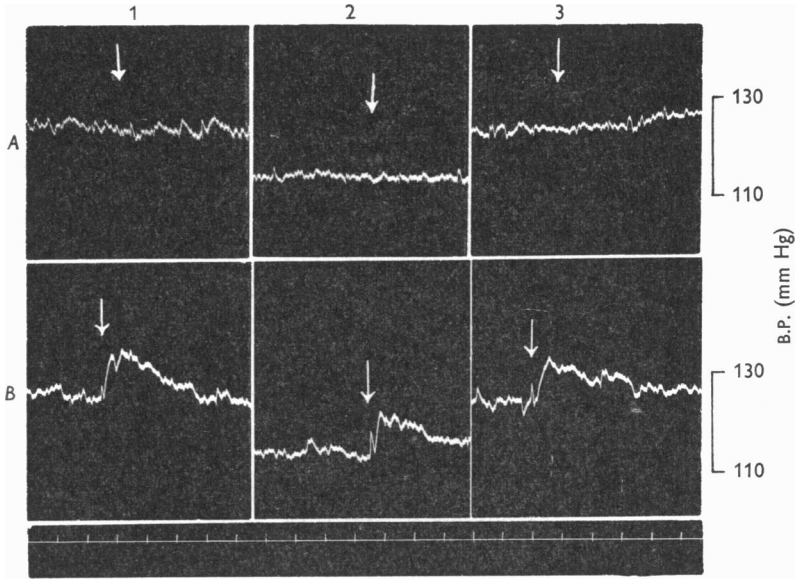

Fig. 1. The effect of 50 m-u. oxytocin on the blood pressure of (*A*) the dioestrous and (*B*) the oestrous rat, (1) before, (2) during, and (3) after the intravenous infusion of isoprenaline, 0·05 μg/min for 30 min. Time marker, 30 sec.

The effect of surgical interference with the nervous system

Pithing. Twenty-three rats were pithed after the normal responses to oxytocin and vasopressin had been established. The animals were maintained on artificial respiration. The results are summarized in Table 2. In eight dioestrous females and four males oxytocin initially had no effect on the blood pressure, but after pithing all save two (both dioestrous females) showed a pressor response (Fig. 2*A*). The magnitude of the pressor response was variable, but it was usually of the order of a 10–20 mm Hg rise for a dose of 50 m-u. oxytocin, and in most cases the response lasted for 4 min or more. The reason for the lack of response after pithing in the two females was not apparent. Of the eleven rats initially showing a pressor response to oxytocin, either because they were in oestrus or had been treated with stilboestrol, seven gave an exactly equal pressor response after pithing. The remaining four showed an enhanced rise in blood pressure to similar doses of oxytocin (Fig. 2*B*). The action of vasopressin was also tested in twenty of the animals. In all but five (three oestrous and two dioestrous females) the pressor response to vasopressin

was increased. In the five exceptions the magnitude of the pressor response was similar to that seen before pithing.

In all the pithed rats the general blood pressure was between 40 and 60 mm Hg. That the appearance of the pressor response to oxytocin was not due solely to this low level was shown in two males and four dioestrous

TABLE 2. The effect of pithing on the response to oxytocin

Effect of oxytocin on blood pressure before pithing	No. of rats	Effect of oxytocin after pithing	
		Pressor	No effect
Pressor			
Oestrous females	6	6	—
Stilboestrol-treated males	5	5	—
No effect			
Dioestrous females	8	6	2
Normal males	4	4	—

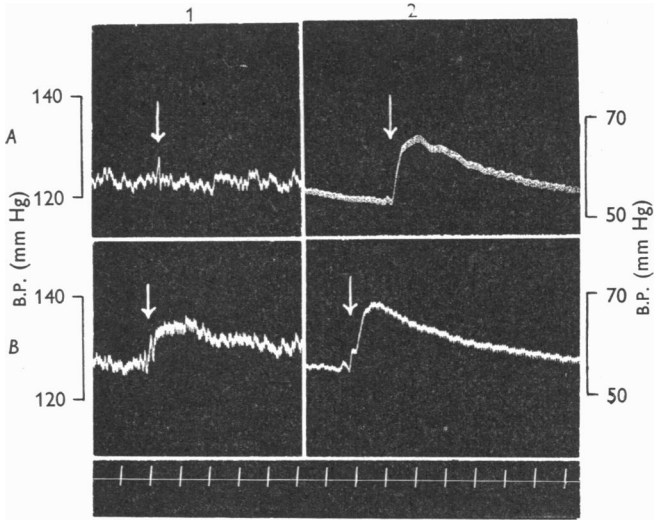

Fig. 2. The effect of 50 m-u. oxytocin on the blood pressure of (*A*) the dioestrous and (*B*) the oestrous rat, (1) before and (2) after pithing. Time marker, 30 sec.

females, to which intravenous infusions of either vasopressin or noradrenaline were given to restore the blood pressure to the levels which had been observed before pithing. In all cases oxytocin was still pressor both during and after the infusions, though no pressor effect had been present before the animals were pithed (Fig. 3).

Vagotomy. Bilateral cervical vagotomy was carried out during observations on a total of thirty-one rats. The results are given in Table 3. Of thirteen dioestrous females, normally showing no pressor response to

oxytocin, a pressor response appeared in six after bilateral vagotomy, the remaining seven still showing no increase in blood pressure. Of two normal males, a pressor response to oxytocin occurred in one after vagotomy. In all cases where a pressor response to oxytocin developed after section of the vagi, this was of the order of a 10–20 mm Hg rise for a dose of 50 m-u. oxytocin. In the twelve females normally showing a pressor response to

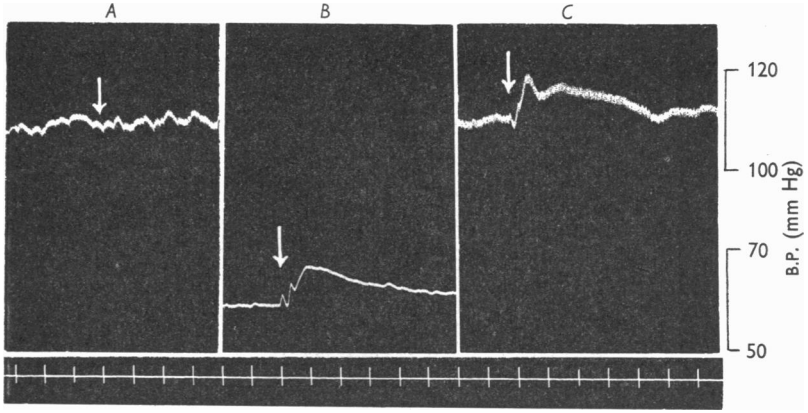

Fig. 3. The effect of 50 m-u. oxytocin on the blood pressure of the dioestrous rat, (*A*) before and (*B*) after pithing, and (*C*) during the infusion of Pitressin 0·5 m-u./min after pithing. Time marker, 30 sec.

TABLE 3. The effect of bilateral cervical vagotomy on the response of the rat to oxytocin

Before section of vagi	Total no. of rats	Response to oxytocin after section		
		Unchanged	Increased	Decreased
Oxytocin pressor				
Female oestrous or pregnant	12	9	2	1
Stilboestrol-treated male	4	3	1	—
Oxytocin no effect		Pressor	No effect	
Female dioestrous	13	6	7	
Normal male	2	1	1	

oxytocin (in oestrus or late pregnancy) this pressor response was unaltered by nerve section in nine, increased in two, and reduced in one. In four males pre-treated with stilboestrol the pressor response was unaltered in three after vagotomy, and increased in the fourth.

Decerebration was carried out on four female rats. Of these two were in oestrus and showed the typical pressor response to oxytocin, while the other two were dioestrous and their blood pressure was unaffected by 50 m-u. oxytocin. After decerebration the two oestrous rats continued to give an unchanged pressor response to oxytocin. The two dioestrous rats

developed a pressor response of 10–20 mm Hg following a dose of 50 m-u. oxytocin. In all four rats the response to vasopressin was increased by 50–60 %.

The effects of autonomic blocking agents

Since crude surgical procedures such as decerebration, pithing, and vagotomy could alter the response to oxytocin, it was decided to use a variety of autonomic blocking drugs in the hope of determining which part of the autonomic nervous system was of particular importance in this effect. Both ganglionic and peripheral blocking agents were used, and were usually administered intravenously during the course of an experiment, after the normal response to posterior-lobe hormones had been determined. In some cases the blocking agents were given subcutaneously several hours before the observations were begun. The results of this series of experiments are summarized in Table 4.

TABLE 4. The effect of autonomic blocking agents on the response to oxytocin

Blocking agent given during experiment	No. of rats		Effect before block		Effect after block	
	F	*M*	Pressor	No effect	Pressor	No effect
Dihydroergotamine	6	1	2	5	7	0
Bretylium	4	1	1	4	4	1
Dibenamine	6	0	2	4	5	1
TEA	7	2	5	4	9	0
Atropine	10	3	4	9	4	9
Blocking agent given before experiment						
Dihydroergotamine	4	0	—	—	4	0
Bretylium	4	0	—	—	4	0
Reserpine	6	2	—	—	8	0

F = female; *M* = male.

Dihydroergotamine. Dihydroergotamine, 0·05–0·1 mg, was injected intravenously into seven rats. After an initial abrupt fall the blood pressure always returned to slightly below the original level. That the dose given was adequate in all cases was shown by the reversal of the pressor response to injected adrenaline, and the abolition of the pressor response to tyramine.

In four dioestrous and one male rat, in which 50 m-u. oxytocin had initially no effect on the blood pressure, this dose produced a rise in blood pressure of 5–14 mm Hg in all animals after intravenous dihydroergotamine. In all cases the pressor response to vasopressin was increased by 30–50 % over that previously seen (Fig. 4). For example, in one animal 0·8 m-u. vasopressin raised the blood pressure by 10 mm Hg before the block, and by 15 mm Hg after blocking. The change in the responses was apparent as soon as the general blood pressure had become steady after the administration of the blocking agent (5–15 min), and the magnitude of the responses did not vary over the period of 2–2½ hr during which they

were observed. In two other dioestrous females the effect of oxytocin on the mesenteric vessels was observed before and after dihydroergotamine. In both animals a dose of 50 m-u. oxytocin, given intravenously, was dilator to the small mesenteric vessels before blocking, and constrictor after blocking.

In two oestrous rats the pressor response to oxytocin was unaffected by the blocking agent. In both these animals the pressor response to vasopressin was somewhat increased, 0·4 m-u. giving a rise of 10 mm Hg in both animals before dihydroergotamine, and 14 and 15 mm Hg respectively after blocking. These effects persisted for at least 2 hr after the development of the block.

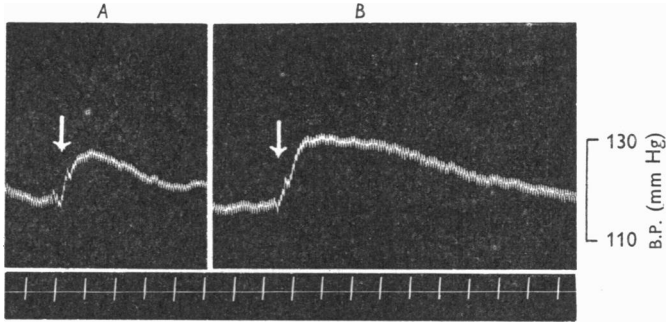

Fig. 4. The effect of 0·8 m-u. Pitressin on the blood pressure of the dioestrous rat, (*A*) before and (*B*) after 0·1 mg dihydroergotamine intravenously. Time marker, 30 sec.

In four females 0·2 mg dihydroergotamine was injected subcutaneously 2–3 hr before the start of the experiment. Of these four three were dioestrous and would not normally have been expected to give a pressor response to oxytocin, while the fourth was in an advanced stage of pregnancy, when a pressor response would normally have been obtained. In all four animals a pressor response to oxytocin was present at the time of observation, 50 m-u. raising the blood pressure by 10–15 mm Hg, and there was a depressor response to injected adrenaline, showing that the dose of dihydroergotamine had been sufficient.

Bretylium tosylate. Bretylium tosylate, 1–2 mg, was injected intravenously into each of five rats in which the normal responses to vasopressin and oxytocin had been established. The blood pressure responses were tested at intervals for 2–2½ hr after the administration of the blocking agent.

In three dioestrous females and one normal male oxytocin was, as expected, without effect on the blood pressure before blocking. After

bretylium the blood pressure rose 10–15 mm Hg following a dose of 50 m-u. oxytocin in two of the females and the male (Fig. 5*A*). The interval between the time of administration of the blocking agent and the appearance of the pressor response was variable, lying within the range of 5–60 min. The other female was exceptional in that no pressor response to oxytocin had developed when the experiment was concluded 2 hr after the bretylium administration. In only one animal was the magnitude of the pressor response to vasopressin increased, and in that animal the increase

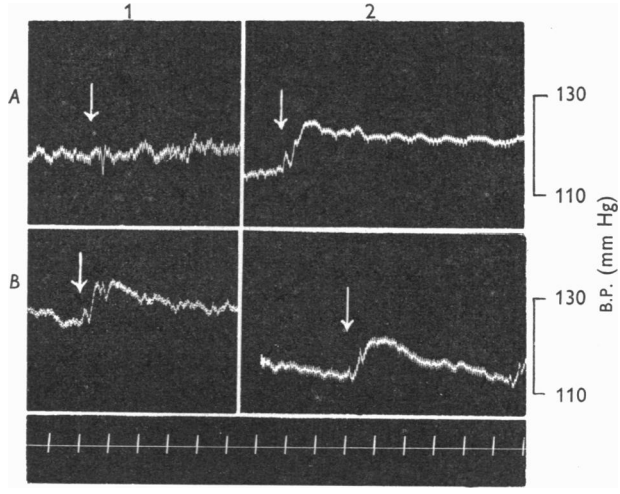

Fig. 5. The effect of 50 m-u. oxytocin on the blood pressure of (*A*) the dioestrous and (*B*) the oestrous rat, (1) before and (2) after 1 mg bretylium tosylate intravenously. Time marker, 30 sec.

was of questionable significance, since 0·8 m-u. vasopressin raised the blood pressure by 10 mm Hg before bretylium was given, and by 13 mm Hg afterwards. In the one oestrous female tested the pressor responses to both oxytocin and vasopressin were unaltered for 2 hr after bretylium was given (Fig. 5*B*), 30 m-u. oxytocin or 0·4 m-u. vasopressin raising the blood pressure by 10 mm Hg throughout the experiment.

Of four rats in which bretylium (2 mg) was injected subcutaneously 2½ hr before the start of observations, all gave pressor responses to oxytocin. Of these four, two were in the dioestrous state, one in oestrus, and one in late pregnancy. In two of these animals (one oestrous and one dioestrous) a marked response to the injection of 0·9 % NaCl solution was noticed; in the former a rise in blood pressure occurred and in the latter a fall in pressure. These volume responses interfered with the assessment of the results of injection of test drugs. A similar difficulty was not

encountered in those experiments in which bretylium was given intravenously during the course of the experiments.

Dibenamine. Dibenamine was administered intravenously during observations on six rats, in 2 or 3 doses of 200 μg at 10 min intervals (Dekanski, 1952). In all but one animal the response to intravenous adrenaline was abolished for the remainder of the experiment.

In four dioestrous rats 50 m-u. oxytocin had, as usual, initially no pressor action. In three of these animals the administration of dibenamine caused the appearance of a pressor response to the same dose of oxytocin. In the fourth this dose was still without effect. This was the rat in which the response to adrenaline was not abolished by dibenamine; presumably the block was ineffective, though the dose was the same as that which proved adequate in the other animals. In the three rats in which a pressor response to oxytocin appeared after blocking, the pressor response to vasopressin was increased. For example, in one animal 0·6 m-u. vasopressin raised the blood pressure by 10 mm Hg before blocking, and this same degree of elevation was regularly produced by only 0·3 m-u. after blocking. In two oestrous females the rise in blood pressure of 10 mm Hg following 50 m-u. oxytocin or 0·4 m-u. vasopressin was unaltered by the administration of dibenamine.

Tetraethylammonium iodide (TEA) (4–8 mg) was administered intravenously to each of nine rats while the blood pressure was recorded. The immediate response to the drug was variable; a rise in blood pressure, a fall, or no change being recorded, probably depending on the size of dose and speed of injection. In four rats in which there was initially no pressor response to oxytocin (two males and two dioestrous females) the administration of TEA resulted in the appearance of a pressor response to oxytocin, though in two cases (one male and one female) this was small, 50 m-u. giving a rise of only 6 mm Hg. In all four the pressor response to vasopressin was increased. In five oestrous or stilboestrol-treated rats oxytocin was pressor both before and after TEA administration; in two out of the five the size of the pressor response to both oxytocin and vasopressin was increased, and in three out of the five the pressor responses to both hormones were unchanged in either magnitude or duration.

Atropine. Atropine was injected intravenously into each of thirteen rats, the dose used (1–2 mg) being sufficient to block all depressor responses to injected acetylcholine. In six dioestrous females and three normal males oxytocin had no effect on the blood pressure either before or after atropine administration, while the pressor response to vasopressin remained unchanged. In four oestrous females the pressor response to both oxytocin and vasopresin was unaltered by atropine. It was also noted that such treatment with atropine did not prevent the development of a pressor

response to oxytocin if sympathetic blocking agents were later administered (five rats).

Reserpine. Since Burn & Rand (1958) have shown that in certain circumstances blood vessels which have lost their stores of noradrenaline are unable to contract normally, it was decided to see whether pre-treatment with reserpine would prevent the development of a pressor response to oxytocin. Eight rats (six female and two male) were treated with 0·5 mg reserpine subcutaneously daily for 2–4 days. On the day following cessation of treatment the response to oxytocin was tested. In all the animals oxytocin had a pressor action, 50 m-u. raising the blood pressure by 10–25 mm Hg, though all females showed dioestrous vaginal smears

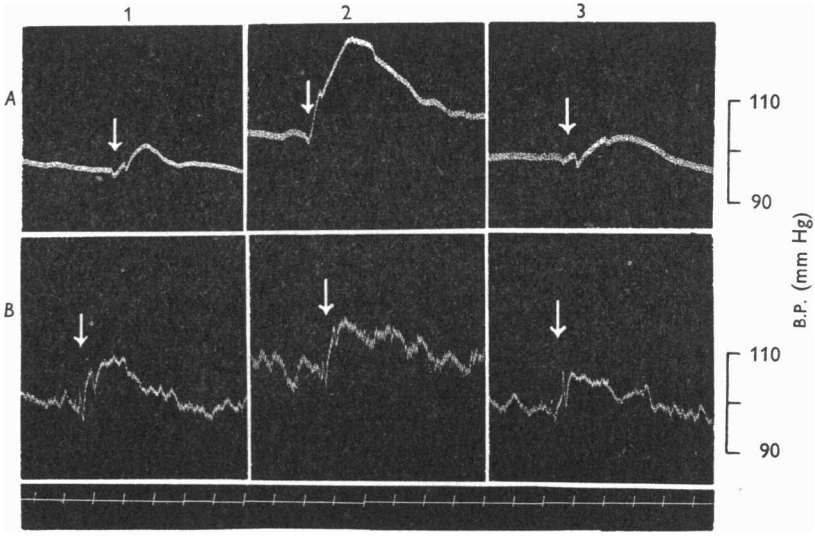

Fig. 6. The effect of (*A*) 0·02 mg tyramine, and (*B*) 50 m-u. oxytocin on the blood pressure of the reserpine-treated rat. (1) Before infusion of noradrenaline, (2) during infusion of noradrenaline 0·05 μg/min, (3) 30 min after end of infusion. Rats treated with two consecutive daily doses of 0·5 mg reserpine subcutaneously. Time marker, 30 sec.

during administration of reserpine and on the day on which the blood pressure was observed. The intravenous infusion of noradrenaline at rates of 0·05–2·0 μg/min for 30–40 min did not alter the pressor response to oxytocin (Fig. 6*B*), though it did increase the pressor response to tyramine (Fig. 6*A*). In all the animals the pressor response to vasopressin tended to be greater than in normal dioestrous animals, e.g. 0·4–0·5 m-u. raised the blood pressure by 10 mm Hg, as compared with an average of 0·6–0·8 m-u. necessary for inducing the same degree of raise in the normal dioestrous rat. Two female rats were treated with reserpine for two days, and

stilboestrol (3·5 μg/100 g) given subcutaneously on the second day. On the following day, when observations were made, it was found that oxytocin was pressor in both, 50 m-u. raising the blood pressure by 10 and 13 mm Hg respectively; that is, stilboestrol and reserpine showed no mutual interference.

Infusion of dilator agents during sympathetic blockade

Since it was found, as described above, that the infusion of vasodilator substances to dioestrous rats did not cause the appearance of a pressor response to oxytocin, though dilatation and fall in blood pressure induced by sympathetic blocking agents did so, it was of interest to determine whether the infusion of dilators after sympathetic blockade would affect

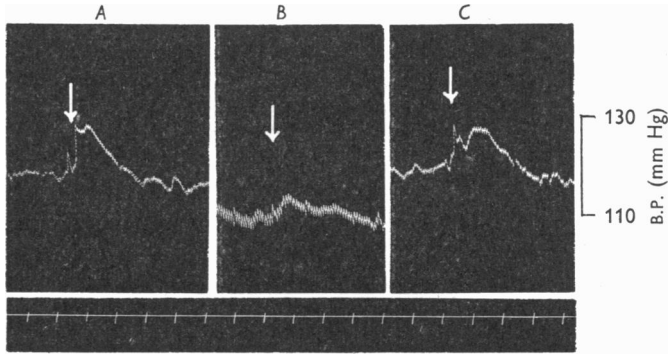

Fig. 7. The effect of 50 m-u. oxytocin on the blood pressure of the dioestrous rat after 0·1 mg dihydroergotamine intravenously. (*A*) Before infusion of isoprenaline, (*B*) during infusion of isoprenaline 0·02 μg/min, and (*C*) after infusion of isoprenaline. Time marker, 30 sec.

the pressor action of oxytocin. Six rats were given infusions of isoprenaline or acetylcholine after sympathetic blockade with bretylium or dihydroergotamine, and the effects of oxytocin and vasopressin tested before, during and after the infusions. In five animals the pressor response to oxytocin was reduced during the infusions, with recovery of the normal pressor response after the infusion had ended and the blood pressure had returned to its previous level (Fig. 7). In one animal the response to oxytocin was completely abolished during the infusion of isoprenaline after the administration of dihydroergotamine, but was again present after the infusion ended. The pressor response to vasopressin was similarly reduced during the infusions in all these experiments.

DISCUSSION

Previous results have been regularly confirmed, that oxytocin is a vasodilator without effect on blood pressure in dioestrous female and in male rats, whereas it is constrictor and pressor in oestrogen-treated dioestrous females, oestrous females, in late pregnancy, and in males treated with oestrogen with or without the addition of progesterone (Lloyd, 1959*a*, *b*). The present experiments have further shown two things. First, that a low blood pressure and dilated peripheral vasculature do not of themselves cause small doses of oxytocin to become pressor and constrictor, since without exception oxytocin did not raise the blood pressure of dioestrous or male rats during the infusion of a variety of vasodilator agents. Nor when the low blood pressure of pithed rats was raised with vasoconstrictors did oxytocin act as a vasodilator. It is, however, possible to reduce or abolish the constrictor response to both oxytocin and vasopressin by extreme vasodilatation, such as can be produced by the infusion of a vasodilator after the administration of a sympathetic blocking agent. Secondly, it has been shown that the nervous system plays an important role in the maintenance of the dilator response to oxytocin. Since atropine did not alter the existing response to oxytocin, whatever that response might be, and did not prevent a change in response induced by other means, it is concluded that cholinergic nerves are not involved. On the other hand, interference with other parts of the autonomic nervous system always converted a dilator action of oxytocin to a pressor one, whilst leaving untouched an already developed pressor response. Thus, surgical methods (pithing and decerebration) which left the post-ganglionic neurones intact caused oxytocin to become a pressor substance. That decerebration as well as pithing was effective suggests the importance of higher centres in the nervous system. Bilateral cervical vagotomy was sometimes effective, probably because in the rat it is difficult to divide the vagus nerves without damage to cervical sympathetic fibres. Drugs were used to block different parts of the peripheral autonomic nervous system in an attempt to determine the pathways of the central control. Again, oxytocin became constrictor following the administration of any sympathetic blocking agent, whether the block lay in ganglia or in a part or the whole of the sympathetic nervous system. It was interesting that reserpine caused oxytocin to become a pressor substance and vasopressin to be somewhat more active than in normal dioestrous rats. Thus, even this type of interference with the sympathetic nervous system brought out the constrictor property of oxytocin. That these varied peripherally-acting drugs, with presumably little or no central action, convert the dilator action of oxytocin to a constrictor one suggests that whatever influence the central

nervous system exerts is transmitted directly through the peripheral nerves, and is not dependent on any unknown indirect neurohumoral path. For the present, the following suggestion is put forward to account for the facts; that oxytocin, though feeble in its action, like vasopressin contracts the smooth muscle of blood vessels, but that with an intact sympathetic nervous system a diminution of constrictor tone more than compensates for the direct vasoconstriction, unless large doses of oxytocin are used (van Dyke, Adamsons & Engel, 1955). This means one of two things: that intravenously administered oxytocin has a central indirect as well as a peripheral direct action on the vascular system, or that oxytocin given intravenously allows time for centrally initiated homoeostasis. Little information is at present available to permit a choice between these possibilities, except that after oxytocin homoeostasis is curiously and imperfectly achieved in that small blood vessels can be shown to dilate in both rat and man, and in man blood pressure is maintained by an increase in cardiac output (Kitchin, Lloyd & Pickford, 1959). This perhaps points to a central action of oxytocin.

Another interesting fact is the similarity found between the results of administration of oestrogens and of denervation, whether surgical or chemical. Probably the peripheral vasodilator action of oestrogens is not the cause of the change in response to oxytocin following ovarian hormone treatment, since other dilator agents do not induce the appearance of such a change. The possibility must therefore be considered that oestrogens can depress sympathetic nervous activity or block the hypothetical central dilator action of oxytocin, thus unmasking the peripheral constrictor effect. Further experiments are needed to investigate this possibility and its implications.

SUMMARY

1. The blood pressure responses of rats to oxytocin and vasopressin were studied during the infusion of vasodilator substances, and after surgical or chemical interruption of autonomic nervous pathways.

2. None of the vasodilators tested altered the responses to the posterior-lobe hormones.

3. On ten out of twelve occasions following pithing or decerebration in the male or dioestrous rat oxytocin, which normally did not affect the blood pressure, acted as a pressor substance. The pressor response persisted even when the blood pressure was raised by infusion of vasoconstrictor substances. In most instances the pressor response to oxytocin was accompanied by an increased sensitivity to the pressor action of vasopressin.

4. Similar changes in response were seen after ganglionic or peripheral sympathetic blockade, but not after atropine.

5. It is suggested that the smooth muscle of the vascular system is caused to contract by a direct action of oxytocin, and that the absence of any change in blood pressure and the vasodilatation seen in dioestrous and male rats is due to an overriding central activity.

6. The similarity of action of oestrogens and of sympathetic blockade on the responses of the rat to oxytocin are discussed.

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