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THE PERSISTENCE OF A DEPRESSOR RESPONSE TO OXYTOCIN IN THE FOWL AFTER DENERVATION AND BLOCKING AGENTS

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The effects of oxytocin and vasopressin on the blood pressure of the fowl have been studied after surgical or chemical interruption of parts of the central and peripheral nervous systems, and after the administration of stilboestrol and progesterone. An augmented and prolonged depressor response to oxytocin was seen after atropine, bretylium, tetraethylammonium or decapitation, but not after decerebration, dihydroergotamine or dibenamine. There was a tendency for the pressor action of vasopressin to disappear after decapitation, decerebration, and all the blocking agents used, except tetraethylammonium. The differences between these results and those which have been obtained in rats are discussed.

It was shown in a recent paper (Lloyd & Pickford, 1961) that the effects of posterior pituitary hormones on the vascular system of the rat may be altered by chemical or surgical interruption of certain parts of the central and peripheral nervous systems. For example, although oxytocin was without effect on the blood pressure of the male or dioestrous female, despite dilatation of some vascular beds (Lloyd, 1959a), it acted as a pressor substance after pithing, decerebration, or sympathetic blockade at either the ganglionic or peripheral level. The pressor effect of vasopressin was greater than normal after such procedures.

A similar pressor response to oxytocin, and an increased response to vasopressin, were seen in the oestrous female, during late pregnancy, or after the administration of ovarian hormones to male or female rats (Lloyd, 1959a & b). It was therefore of interest to determine whether any changes in response to oxytocin and vasopressin could be induced by such procedures in other species. For this purpose the fowl was chosen, since a marked fall in blood pressure normally follows the injection of oxytocin, with little or no tachyphylaxis to small doses, and hence any conversion to a pressor response could be easily detected.

METHODS

White Leghorns of approximately 2 kg body weight were used, anaesthetized with sodium phenobarbitone (200 mg/kg) injected intramuscularly. All injections were made into a cannulated wing vein in a total volume of 0.4 ml. of 0.9% NaCl solution. Blood pressure was recorded on a kymograph from a mercury manometer connected to the cannulated ischiatic artery as described by Coon (1939). Sodium citrate (8% w/v) solution was used in the connecting pieces of the recording system. Stilboestrol dipropionate and progesterone (Progestin, B.D.H.) were injected subcutaneously in oil 24 or more hr before observations were

made. The oxytocin used was the synthetic brand Syntocinon (Sandoz) and the vasopressin was the Parke Davis product Pitressin. Occasionally the highly purified arginine vasopressin of du Vigneaud was employed. No difference was noticed in the effects of the commercial or highly purified extracts. The blocking agents used were bretylium tosylate (Darenthin, Wellcome Research Laboratories), dihydroergotamine (Sandoz), reserpine (Ciba Serpasil), dibenamine, and tetraethylammonium iodide. Decapitation was carried out by the method described for the duck by Paton (1912). Decerebration was carried out by opening the skull with a dental drill and bone forceps, reflecting the dura while leaving the longitudinal sinus intact, and removing the cerebrum by suction whilst an assistant compressed the carotid arteries against the transverse processes of the vertebrae. The cavity was then packed with gelatin sponge (Whitteridge, unpublished).

RESULTS

Normal hens

In this group the results were obtained from 20 hens, some of which were subsequently subjected to other procedures. In all cases oxytocin gave rise to an immediate and short-lasting depression of the blood pressure (Fig. 1A), and in any

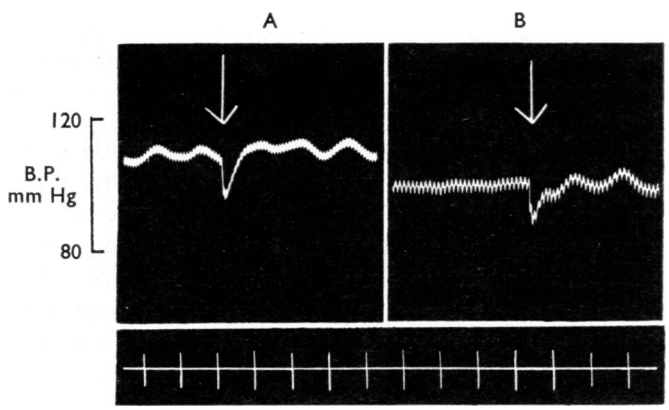

Fig. 1. The effect of 40 m-u. oxytocin on the blood pressure of the fowl (A) before and (B) after decerebration. Time, 30 sec.

one bird the magnitude and duration of this response remained constant, showing no hint of tachyphylaxis. In different birds, however, the dose needed to produce a depressor response of 10 mm Hg varied from 5 to 60 m-u. oxytocin. This may have been due, in part at least, to differences in basal blood pressure levels, which ranged from 85 to 115 mm Hg (mean 98 mm Hg). The type of response to vasopressin varied. In some cases a pure pressor response was obtained, and in others a transient depressor response, which might or might not be followed by a pressor response. In most instances 40 to 80 m-u. vasopressin was required to produce any alteration in blood pressure, but in some birds no response was obtained with up to 240 m-u. vasopressin. Whichever type of response was obtained, it tended to decrease during the course of the experiments, even when as long a period as 20 min was allowed between consecutive injections.

The effect of surgical interference with the nervous system

Decerebration. Decerebration was carried out on three hens after the normal responses to oxytocin and vasopressin had been established. In all three the blood pressure after decerebration was 5 to 10 mm Hg lower than before operation.

In all three experiments oxytocin remained depressor after operation, and in each case, allowing for the somewhat lower initial blood pressure, the magnitude and duration of the depressor response were unaltered (Fig. 1B). For example, in one bird, 40 m-u. oxytocin depressed the blood pressure by 10 mm Hg both before and after decerebration. In all three birds before operation, vasopressin caused a slight increase in blood pressure. After extirpation of the cortex, and giving the same dose of vasopressin, no pressor effect was seen ; instead there was a slight depression of 4 and 6 mm Hg respectively in two birds, and no response in the third (Fig. 2).

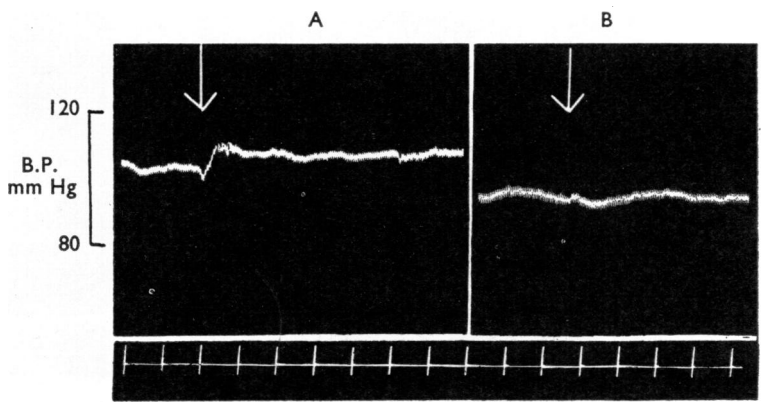

Fig. 2. The effect of 80 m-u. vasopressin on the blood pressure of the fowl (A) before and (B) after decerebration. Time, 30 sec.

Decapitation. A total of four hens was decapitated after the completion of control observations. After operation, the blood pressures were 70, 40, 50 and 45 mm Hg respectively, with the birds maintained on artificial respiration. In all four, oxytocin caused a fall in blood pressure both before and after decapitation (Fig. 3). In the bird in which the blood pressure was 70 mm Hg after operation, the depressor response to oxytocin was augmented and prolonged (Fig. 3 (i)), while in the birds with the lower blood pressures the response was prolonged, but reduced in magnitude (Fig. 3 (ii)). In all four after decapitation, vasopressin in doses of 80 m-u. caused a small depression in the blood pressure. This dose, before decapitation, had caused a similar fall in blood pressure in three of the hens, but a small rise in the fourth.

The effects of autonomic blocking agents

Atropine. Atropine, 1 to 2 mg, was administered intravenously to three normal hens after control observations were complete. This dose was sufficient to abolish all depressor responses to injected acetylcholine. The blood pressure was transiently elevated immediately following the injection of atropine, but rapidly returned to the normal level. In all three birds the depressor response to oxytocin was augmented

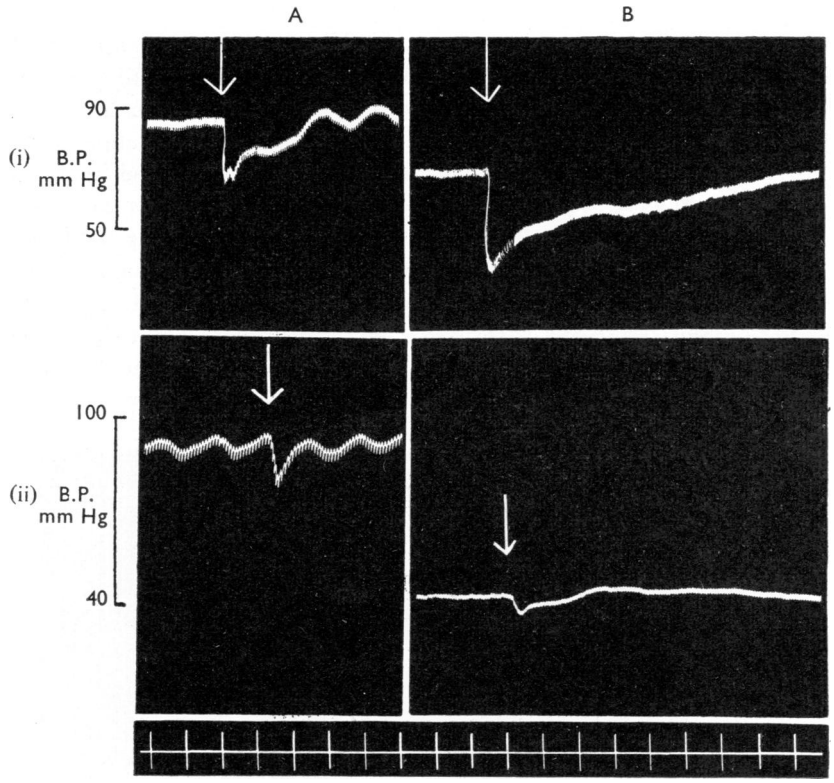

Fig. 3. The effect of 20 m-u. oxytocin on the blood pressure of two hens (A) before and (B) after decapitation. Time, 30 sec.

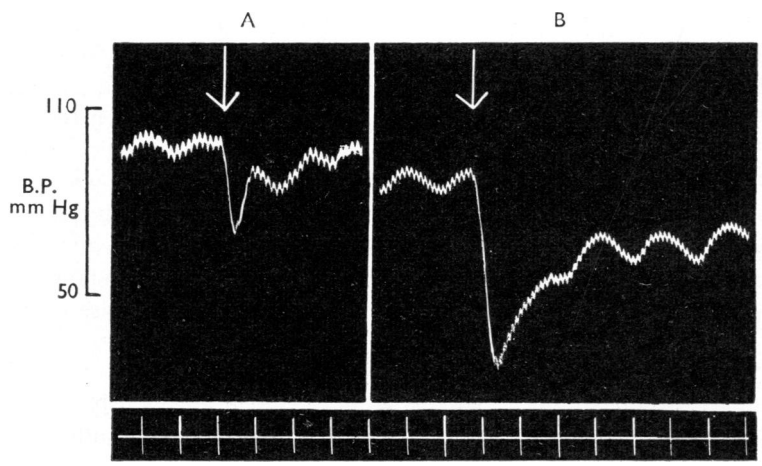

Fig. 4. The effect of 20 m-u. oxytocin on the blood pressure of the fowl (A) before and (B) after the intravenous injection of 1 mg atropine. Time, 30 sec.

and prolonged after atropine (Fig. 4). For example, in one hen 10 m-u. oxytocin caused a fall in blood pressure of 28 mm Hg before atropine, and a fall of 37 mm Hg after atropine. In two of the hens before treatment vasopressin had caused a diphasic response, a transient fall being followed by a slight but prolonged rise, while the third showed only the depressor phase of the response. After atropine, the pressor effect was reduced while the depressor phase was unaffected in the first two, and in the third the depressor effect was increased.

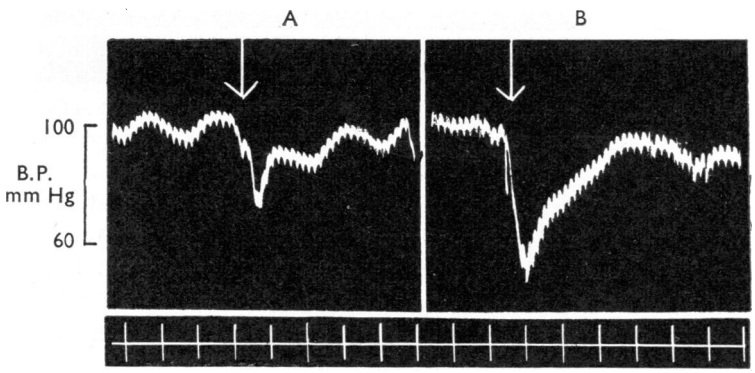

Fig. 5. The effect of 10 m-u. oxytocin on the blood pressure of the fowl (A) before and (B) after the intravenous injection of 6 mg bretylium tosylate. Time, 30 sec.

Bretylium tosylate. Bretylium tosylate (6 mg) was given intravenously to three hens after the normal vascular responses had been tested. In all three, after the blocking agent, the depressor response to oxytocin was increased and prolonged (Fig. 5). This increase in effect was noted immediately after the bretylium was given, and became maximal 50 to 60 min later, when the response was 50 to 55% greater than normal in all cases.

In one bird 80 m-u. vasopressin was without effect on the blood pressure either before or after bretylium. In the other two, a rise in blood pressure of 10 and 40 mm Hg respectively was produced by 80 m-u. before the administration of the blocking agent, and a fall of 40 mm Hg and a rise of 20 mm Hg respectively after bretylium.

Dihydroergotamine. Dihydroergotamine was given intravenously, in a dose of 1 to 1.3 mg, during observations on three hens. One of these had previously been treated with bretylium. The dose used was sufficient to abolish the pressor response to injected noradrenaline. In all three the depressor response to oxytocin was slightly reduced after the administration of the blocking agent (Fig. 6). For instance, 20 m-u. oxytocin gave a fall of 30 mm Hg in the blood pressure of one bird before blocking, and a fall of 25 mm Hg consistently afterwards. The small pressor response to vasopressin seen in all three birds when they were normal was absent after the administration of the dihydroergotamine.

Tetraethylammonium iodide. Three hens were treated with 8, 10, and 40 mg tetraethylammonium respectively. In all three the blood pressure fell some 5 to 10

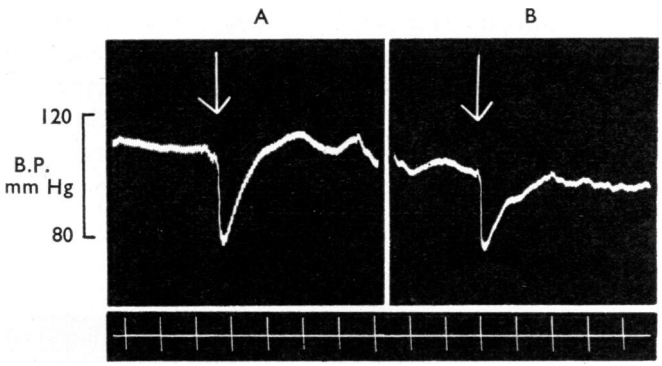

Fig. 6. The effect of 20 m-u. oxytocin on the blood pressure of the fowl (A) before and (B) after the intravenous injection of 1.3 mg dihydroergotamine. Time, 30 sec.

mm Hg below the pretreatment level. In one hen (which had received 40 mg tetraethylammonium) the depressor response to 20 m-u. oxytocin was only 6 mm Hg as compared with a fall of 28 mm Hg before tetraethylammonium. In the two which had received the smaller doses, the depressor responses to 20 m-u. oxytocin were increased from 28 to 34 mm Hg, and from 19 to 40 mm Hg respectively. In all three birds the small pressor response to vasopressin seen before tetraethylammonium administration was unchanged.

Dibenamine. Two hens were given dibenamine intravenously during the course of observations. In one bird the dose given was 20 mg, which was sufficient to abolish the pressor effect of injected noradrenaline, while in the other the dose was 5 mg, which reduced, but did not abolish, the adrenaline response. In both birds the blood pressure remained at the pre-injection level. In the bird given the larger dose of dibenamine the depressor response to 40 m-u. oxytocin was reduced from 16 mm Hg to 10 mm Hg, and in the bird given the smaller dose the fall in blood pressure in response to 20 m-u. oxytocin was reduced from 14 mm Hg to 10 mm Hg. In both birds before dibenamine, 80 m-u. vasopressin was slightly depressor, but after the blocking agent vasopressin had no effect at all on the blood pressure.

Reserpine. One hen was treated with 10 mg reserpine injected subcutaneously in divided doses on two consecutive days. On the following day the vascular responses were tested. No response was obtained to the injection of tyramine, while the responses to oxytocin and vasopressin did not appear to differ from those seen in untreated birds. 20 m-u. oxytocin gave a depression of the blood pressure of 10 mm Hg, while a slight depression was also seen in response to 80 m-u. vasopressin. The subsequent infusion of noradrenaline for 30 min at a rate of 2 μg/min did not affect the response to either oxytocin or vasopressin.

The effects of stilboestrol and progesterone administration

Stilboestrol dipropionate was injected subcutaneously or intramuscularly in five hens, in doses ranging from 50 to 100 μg/kg. This dose was more than adequate for the induction of the altered response to oxytocin in rats (Lloyd, 1959a). Observations were made 24 hr after treatment in four of the hens, and 48 hr after in the

fifth. In all five, oxytocin was depressor, 10 m-u. oxytocin giving a fall in blood pressure of 18 to 32 mm Hg. This appeared to be a larger response than that obtained with similar doses of oxytocin in normal hens, but the numbers are too limited to permit a more definite comparison. In all five birds vasopressin caused a preliminary fall in blood pressure, and in three of them this was followed by a pressor response. A sixth bird was treated with progesterone (1 mg), and a seventh given both stilboestrol (100 μg) and progesterone (1 mg). In these two birds the responses to both oxytocin and vasopressin were in every way similar to those seen in untreated birds.

DISCUSSION

The results described show that the dilator action of oxytocin in the normal hen remains dilator after extirpation of parts of the central nervous system, or ganglionic or peripheral blockade of the autonomic nervous system. This is in marked contrast to the rat, where a pressor and constrictor response to oxytocin was regularly seen after all such procedures, except the administration of atropine (Lloyd & Pickford, 1961). The persistence of the depressor response to pituitary extracts after decerebration in the hen has been described by Hogben & Schlapp (1924). In the present experiments the only marked differences induced in the action of oxytocin by any procedure were the prolongation (and in one instance augmentation) of the depressor response after decapitation, and a prolongation and augmentation after atropine, bretylium, and tetraethylammonium iodide. A similar effect has been noted in the duck after atropine by Paton & Watson (1912), who used whole posterior pituitary extract (Pituitrin), and in the chicken, again after atropine, by Coon (1939), who used the oxytocic fraction (Pitocin). All these workers attributed the greater and more prolonged effect following atropine to its ability to block a cardiac stimulating effect of the pituitary preparations. However, Woodbury & Abreu (1944) did not find that Pitocin augmented cardiac contraction in chickens. It is not possible to say whether a cardiac effect was concerned in the experiments described here, where the depressor response to oxytocin was increased and prolonged by very dissimilar agents and procedures, namely, atropine, bretylium, tetraethylammonium, and once after decapitation.

On the other hand dibenamine and dihydroergotamine somewhat reduced the depressor response to oxytocin. The only obvious difference between these two groups of agents is that noradrenaline is still constrictor in the presence of bretylium, tetraethylammonium and atropine, but is inactive following the administration of dibenamine or dihydroergotamine. It is wholly obscure how the possibility of a constrictor response to noradrenaline can be linked with an enhanced depressor response to oxytocin. No helpful information was provided by the use of reserpine, since this substance did not alter the response to either oxytocin or vasopressin, whether or not noradrenaline was infused. In this last respect at least, the chicken behaves like the rat (Lloyd & Pickford, 1961).

The effects of the procedures on the vascular responses to vasopressin were less well marked, but following decerebration, decapitation, and all the drugs used except tetraethylammonium, any pressor response previously seen was reduced or abolished, and in a few cases was even replaced by a depressor effect. In only a few experiments

did the normal response contain a depressor component, namely, three of the four experiments in which decapitation was performed, three experiments in which atropine was later given, and two in which dibenamine was given. After decapitation the depressor response was unchanged, after atropine it was in one case greater than before, and after dibenamine it was abolished. However, since vasopressin gives somewhat variable results in control experiments on normal birds, little can be said with certainty save that in no case was an increase in the pressor response to vasopressin seen. This is again in contrast to the rat, where the response to vasopressin was almost invariably increased after surgical or chemical denervation. The administration of stilboestrol, alone or in combination with progesterone, caused, if anything, a greater depressor response to oxytocin, and certainly no increase in the pressor effect of vasopressin, although the doses of ovarian hormones used were the same as, or greater than, those which in the rat regularly sensitized the animal to vasopressin and caused oxytocin to become a pressor substance (Lloyd, 1959a). It is not known, however, whether stilboestrol and progesterone would of themselves produce any vascular effects in chickens as they do in rats and many other mammals, or at what site such actions would occur.

Summarizing, the action of oxytocin on the blood pressure in the fowl is unchanged by decerebration, and slightly reduced by substances with properties like those of dibenamine and dihydroergotamine, but its depressor effect is greater and more prolonged after decapitation, or the administration of bretylium, tetraethylammonium, or atropine. In contrast, the pressor component of the action of vasopressin is reduced by all procedures except giving tetraethylammonium. If it were not for this exception it might be suggested that the pressor activity of vasopressin is in some way dependent on the connexion of the blood vessels with the nervous system. In most respects the results obtained in the fowl are the exact reverse of those found in the rat (Lloyd & Pickford, 1961).

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