Brit. J. Pharmacol. (1956), **11**, 44.

THE EFFECT OF 5-HYDROXYTRYPTAMINE ON THE URETER AND ON THE BLOOD PRESSURE OF DOGS; AND OF ADRENALINE, NORADRENALINE, AND POSTERIOR PITUITARY EXTRACTS ON THE URETER

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(RECEIVED OCTOBER 12, 1955)

When observing the action of 5-hydroxytryptamine (5-HT) on the rate of urine flow in conscious dogs it was often noticed that almost immediately after an intravenous injection of this substance there was a brief marked slowing of urine flow, followed by an equally brief period of rapid flow before the appearance of the long-lasting antidiuresis described by Erspamer (1954) (Fig. 1). These fluctuations in rate of urine flow lasted no more than 2–3 min. and could be most easily explained as due to temporary spasm of the ureters. It was decided, therefore, to examine the response of the ureter *in situ* to 5-HT. Moreover, it was of interest in connexion with the antidiuresis seen after 5-HT to know whether renal function was affected by smaller or greater doses than those which had an action on smooth muscle such as that of ureter, uterus and of the vascular system. At the same time, the opportunity was taken of observing the effect of some other drugs on the ureter, and of the effect of 5-HT on the blood pressure of the anaesthetized dog.

METHODS

Nine dogs were anaesthetized either with chloralose, 0.1 g./kg., or with pentobarbitone sodium, 0.033 g./kg., intravenously. The abdomen was opened through a midline incision and a length of ureter, of 2 inches or more, was prepared for perfusion through its lumen by inserting one cannula into its upper end just below the renal pelvis, and another into its lower end either immediately above the bladder, or, from within the bladder, through the ureteric orifice. Care was taken when tying in the cannulae to leave the main ureteric blood vessels outside the ligatures so that the ureter kept its normal blood supply and, to some extent, its normal innervation. This arrangement made it possible for solutions injected into distant veins to reach the ureter by the normal route. The lumen of the ureter was perfused with 0.9% NaCl solution from a Mariotte bottle connected with one or other cannula, so that the pressure and direction of perfusion could be controlled. Inflow and outflow from the ureter were connected to the exterior by fine rubber tubes

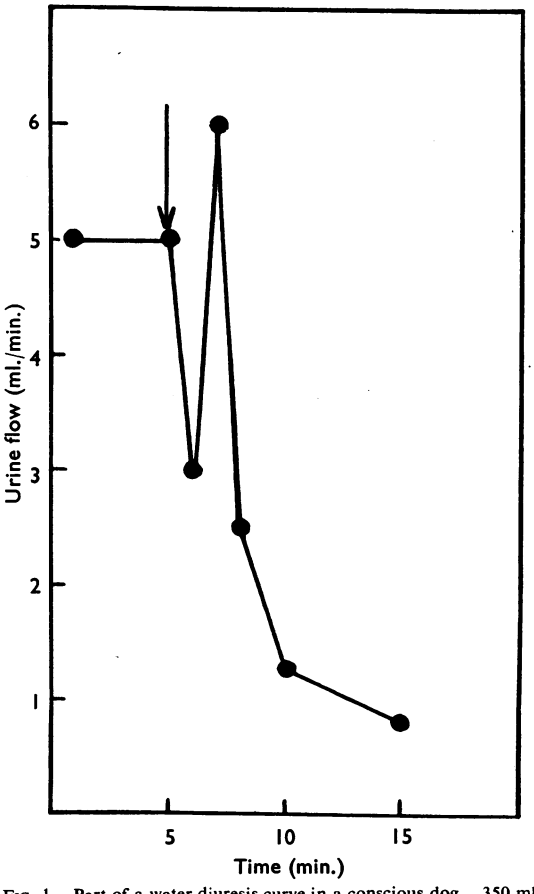

FIG. 1.—Part of a water diuresis curve in a conscious dog. 350 ml. water given by mouth 65 min. before the intravenous injection, at arrow, of 12.7 μg./kg. body weight 5-HT. Ordinate, urine flow in ml./min. Abscissa, time in min.

passing either through the midline incision or through stab wounds in the flank. The rate of flow of fluid through the ureter was measured by means of a drop recorder. Carotid or femoral arterial pressure was recorded from a mercury manometer. The abdomen was closed before observations were begun.

5-HT was administered in the form of the creatinine sulphate, but all doses are calculated and given as the weight of base/kg. body weight. Posterior lobe extracts used were "Pitressin" and "Pitocin" of Parke, Davis & Co. Synthetic (−)-adrenaline and (−)-noradrenaline bitartrate were made up shortly before use in 0.9% NaCl solution in such concentration that the volume injected was never more than 1.0 ml. All injections were made intravenously.

Results

It was found that no fluid passed through the ureter when the perfusion pressure was below a critical level which varied somewhat in different dogs. Usually the limiting pressure was about 20 cm. water, but in some dogs it was as low as 15 cm. Just above the minimum effective pressure, drops appeared at regular intervals in ones, twos or threes. At somewhat higher pressures a number of drops passed through quickly, regularly followed by a short pause (Fig. 2). Further increase of perfusion pressure increased the number of drops between pauses until a point was reached when the drops came steadily and continuously. This pressure varied greatly between dogs, ranging from 40–60 cm. water. In any one experiment the pattern of flow through the ureter remained constant for a given perfusion pressure.

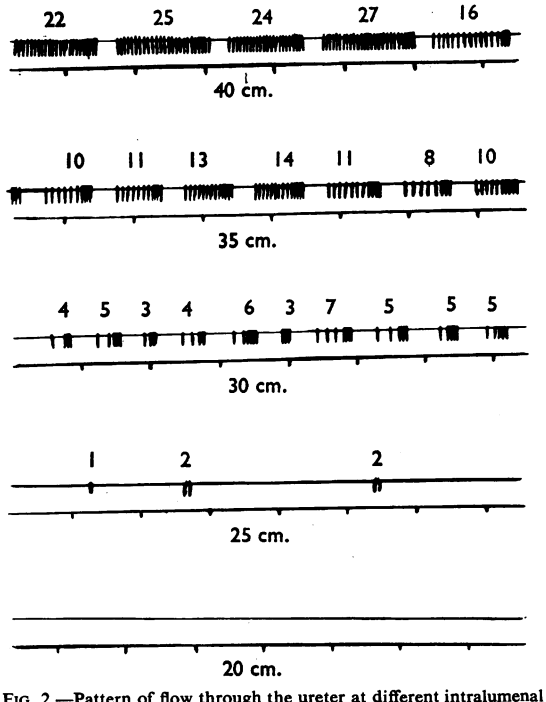

Fig. 2.—Pattern of flow through the ureter at different intralumenal pressures. Upper line is drop record of ureteric flow, the numerals above which indicate the number of drops appearing from the ureter at each outflow-spurt of the perfusion fluid. Lower line, time in 10 sec. Intralumenal pressures in cm. water.

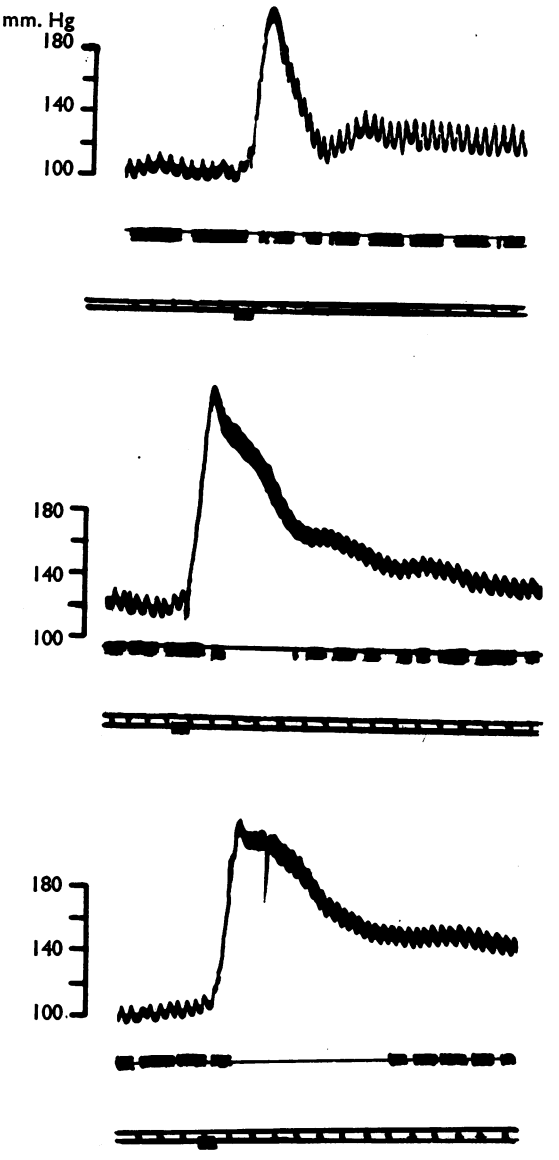

Fig. 3.—Effect of intravenous 5-HT on flow through the ureter, and on arterial pressure. Top record, 3.6 μg./kg. 5-HT; middle record, 10.8 μg./kg. 5-HT; bottom record, 18 μg./kg. 5-HT. In each record: top line, arterial pressure; 2nd line, drop record of ureteric flow; 3rd line, time in 10 sec.; bottom line, signal marker.

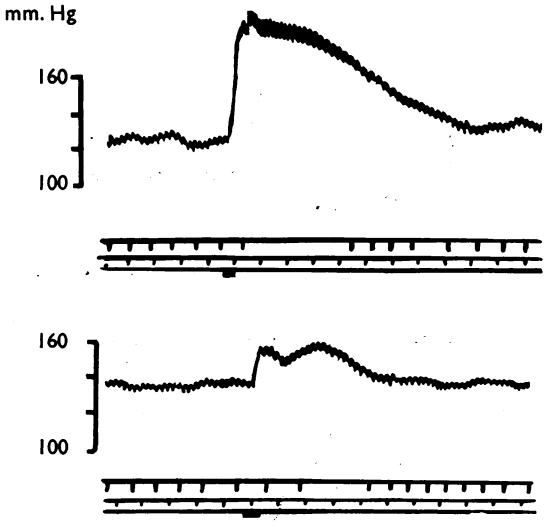

FIG. 4.—Effect of intravenous adrenaline and noradrenaline on flow through the ureter. Upper record, 5 μg. (−)-noradrenaline Lower record, 5 μg. (±)-adrenaline. In each record: top line, arterial blood pressure; 2nd line, ureteric flow; 3rd line, time in 10 sec.; bottom line, signal marker.

Intermittency was not due to resistance in the perfusion system, since at any pressure above zero a steady, more or less rapid, stream of fluid passed. If the blood supply of the ureter was occluded, or if anaesthesia was deep, there was no intermittency of flow, and instead a continuous series of drops emerged from the lower cannula. The results were the same whether chloralose or pentobarbitone sodium was the anaesthetizing agent. On two occasions the ureter was perfused from its lower end. Despite this reversal of direction the pattern of flow was unchanged.

With this information available, observations on the actions of drugs on the ureter were made at perfusion pressures between 25–30 cm. water unless otherwise stated, and only on ureters that showed intermittency of flow.

Effect of 5-HT.—Fig. 3 shows the effect on flow through the same ureter of three different concentrations of 5-HT given into the saphenous vein. With increase in amount of the drug, flow was held up for a longer period. Since, in the conditions of the experiments, the pressure above a ureteric block did not build up as it would have done in natural circumstances (see Fig. 1), no secondary rush of fluid could be expected, and none was seen. The minimum intravenous dose observed to have an effect on the ureter was 3.6 μg./kg. (Fig. 3). It can also be seen from Fig. 3 that the cessation of ureteric flow began just after the onset of the blood-pressure rise, and that flow returned before the blood pressure fell to its initial level. If, during the inhibition of flow caused by 5-HT, the perfusion pressure was quickly raised to 55 or 60 cm. water, then ureteric flow started again immediately.

Effect of Adrenaline and Noradrenaline.—Fig. 4 shows that both adrenaline and noradrenaline caused a short-lasting cessation of transureteral flow which occurred during the period of increased arterial pressure. On one occasion, 2 min. after the intravenous administration of 2 mg. of phentolamine, (2-*N*-*m*-hydroxyphenyl-*p*-toluidinomethyliminazoline, " Rogitine ") neither ureter nor blood pressure reacted to 10 μg. adrenaline.

Effect of Extracts of Posterior Lobe of Pituitary.—Doses of vasopressor extract up to 10 mU. were without effect on the pattern of flow through the ureter. On the other hand, 50 sec. after 50 mU. of the oxytocic fraction had been given there was a temporary decrease in the rate of flow, whilst following 100 mU. the number of drops in a series

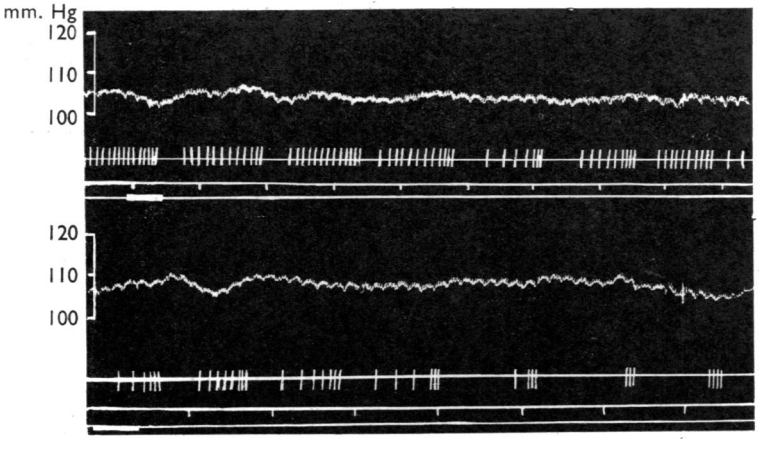

FIG. 5.—Effect of intravenous oxytocin on flow through the ureter. Upper record, 50 mU. at signal; lower record 100 mU. at signal. In each part: top line, arterial pressure; 2nd line, drop record of ureteric flow; 3rd line, time in 10 sec.; bottom line, signal marker.

decreased and the length of the pauses between series increased for more than 5 min. (Fig. 5).

Effect of 5-HT on Arterial Blood Pressure.—In 9 dogs given 41 injections of 5-HT ranging from 3.6 μg. to 84 μg./kg., only twice (Fig. 6) was there any fall of blood pressure. Both occurred in the same dog following the injection of 4 μg./kg. 5-HT. Later, this animal gave a pure

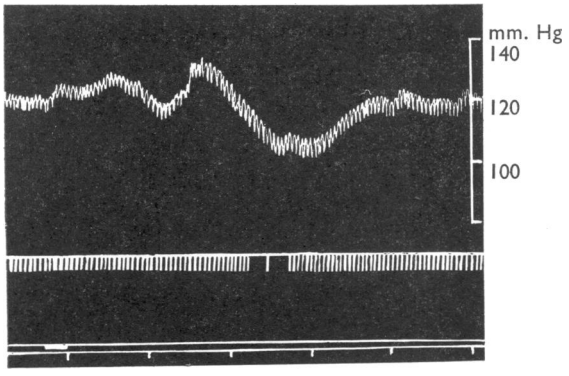

FIG. 6.—Blood-pressure record. Dog, pentobarbitone sodium. At signal, 3.6 μg./kg. 5-HT intravenously. Illustrates the only occasion on which any fall of pressure occurred after the initial rise.

pressor response to the same or larger doses. Two other dogs given 4 μg. and 2 μg./kg. of 5-HT showed only a rise of blood pressure. On all other occasions 5-HT caused an immediate rapid rise in blood pressure which lasted about 60 to 70 sec. The pressure then fell to within 8–10 mm. Hg of the preinjection level, thereafter falling slowly over some minutes. This occurred after moderate as well as after large doses of 5-HT (Fig. 7). Table I gives four examples, picked at random from the records, showing the time before the blood pressure recovered completely. Thus, in anaesthetized dogs, the intravenous administration of 5-HT had a pure pressor action which lasted some minutes. The response to the intracarotid injection of 5-HT was always a marked, but short-lived, pressor effect (Fig. 7).

TABLE I

TO SHOW TIME FOR FALL OF BLOOD PRESSURE TO NORMAL AFTER INTRAVENOUS 5-HT

Four examples picked at random

Dose (μg./kg.)	Time (min.)
7·3	5·0
7·3	3·0
21·0	4·8
49 0	6·0

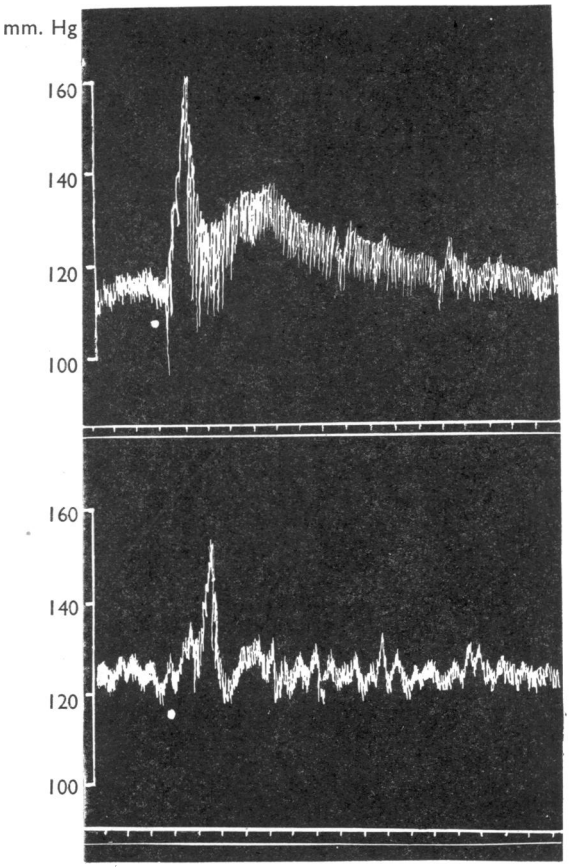

FIG. 7.—Blood pressure record. Dog, pentobarbitone sodium. Comparison of the effect in the same dog of 12.5 μg./kg. 5-HT given into the femoral vein (upper record), and into the carotid artery (lower record).

DISCUSSION

The preliminary observations on ureteric activity showed that between certain perfusion pressures fluid emerged from the lower end of the ureter in small rushes with regular pauses between. Since the abdomen was closed, peristalsis was not actually seen ; but the observations are in accord with clinical and experimental work showing that the ureters have peristaltic activity, and that urine enters the bladder in spurts. Much of the experimental work on the ureter has been done on the excised organ observed in a bath, but Trattner (1932) noted the response of the human ureter *in situ* and found that contractions appeared in it with an intralumenal pressure of 0–12 cm. water and were maximal between 3 and 18 cm. water. He also found that peristalsis disappeared at 38–70 cm. pressure. Lucas (1908) found that a pressure of 15 cm. water applied at the lower end of the isolated

ureter of dogs was not transmitted to a higher level —that is, the muscle was able to remain contracted against this force. Morales, Crowder, Fishman, and Maxwell (1952) observed in dogs with exteriorized trigones that at high rates of urine flow, which presumably means at high renal pelvic pressures, the urine came in a continuous jet and not in spurts. All these pressure values and reactions are similar to those recorded here, namely, that intermittent flow began at about 15 cm. water and became continuous at various pressures from 40 cm. upward. It is surprising that the ureter seems to work as well in reverse as in the normal direction, but Gruber (1930) noticed the same phenomenon in the isolated ureter of pigs. The preparation used may thus be considered a reasonably normal one, and consequently suitable for study of the action of 5-HT and other drugs.

The ureter of the dog was sensitive to as little as 3.6 μg./kg. 5-HT given intravenously, and reacted by a spasm lasting 1 to 2 min. which began almost immediately after injection. It appeared that the ureteric muscle relaxed sooner than that of the vascular system, but it may be that the perfusion pressures used were sufficient to force open the ureter during the phase of recovery from spasm. It seems clear that the rapid swings in rate of urine flow seen immediately after the intravenous injection of 5-HT can be fully explained by its action on the ureter; the contraction holds back the urine, which accumulates in the renal pelvis, so that, when relaxation occurs, a considerable volume is delivered in a short time.

Several workers (Gruber, 1930; Lucas, 1908; Roth, 1917) have found that the isolated ureter responds to adrenaline by an increase in tone or strength of contraction. This accords with the present findings on the intact ureter, that both adrenaline and noradrenaline temporarily inhibit transureteral flow during the phase of greatest increase in arterial pressure.

Ross and Stehle (1930) showed that an intravenous injection of 1 mg. of a laboratory-made posterior pituitary lobe extract had a constrictor action on the ureter that was inadequate to account for antidiuresis. The observations described above show that an antidiuretic dose (10 mU.) of the vasopressor fraction has no perceptible effect on the ureter, whereas the oxytocic fraction, in amounts that may well occur in a limited number of normal circumstances (Abrahams and Pickford, 1954), does cause contraction of the ureteric, as of the uterine, muscle.

With regard to the effect of 5-HT on blood pressure, the results were only in part the same as those obtained by other workers. Only in one dog was there any secondary hypotensive effect. On all other occasions the response was purely pressor, and no late sustained fall of pressure was seen even after large doses (Page and McCubbin, 1953). Why these results were different is unknown. Intracarotid injections of 5-HT caused a sharp rise of blood pressure, with return to normal in about 1 min. The response was immediate, and no secondary fall of pressure was ever seen. Thus 5-HT may have a transient central action (cf. Heymans and Heuvel-Heymans, 1953). That the responses to intracarotid and intravenous injection of 5-HT were somewhat different may depend on the rate at which 5-HT is removed from the circulation (Gaddum, Hebb, Silver, and Swan, 1953).

The object of the observations on blood pressure was not to re-examine the mechanism of action of 5-HT but to determine the dose which, given intravenously, had a measurable effect on the blood pressure, and to compare it with the dose to which other systems or tissues reacted. In Fig. 3 the response of the ureter is clearly a threshold one, yet the pressor response is well developed; thus it may be concluded that the ureter is less sensitive than the arterial pressure to 3.6 μg./kg. The uterus of the conscious and anaesthetized dog contracts in response to an even lower concentration than that which affects the blood pressure (Abrahams and Pickford, 1956a). As described in another paper (Abrahams and Pickford, 1956b), antidiuresis is rarely seen after single intravenous doses of 5-HT of less than 10 μg./kg. Thus, whatever may be the reason or reasons for the hypertensive action of 5-HT, a rise in general blood pressure is provoked by a smaller dose of 5-HT than affects either ureter or kidney, but needs a larger one than causes contraction of the uterus.

Summary

1. In the anaesthetized dog observations were made on the activity of the ureter left *in situ*, with blood supply intact, and the lumen perfused with 0.9% NaCl solution.

2. At perfusion pressures of about 15 cm. water, or more, small volumes of fluid at regular intervals passed through the ureter.

3. At pressures of 40 cm. water and upward, the actual pressure varying with the individual, a continuous series of drops passed through the ureter.

4. Intravenous 5-hydroxytryptamine, by causing contraction of the ureteric muscle, completely prevented the passage of fluid through its lumen for

1 to 2 min. and slowed the flow for a further period of 1 to 2 min.

5. Both adrenaline and noradrenaline caused a transitory contraction of the ureteric muscle.

6. Given in adequate antidiuretic dose, the vasopressor fraction of posterior lobe extract was without effect on the ureter. The oxytocic fraction caused contraction of the muscle.

7. In dogs, anaesthetized with either chloralose or pentobarbitone sodium, 5-hydroxytryptamine rarely caused other than a pure pressor response, whether given into the carotid artery or intravenously.

A few days before our manuscript was submitted a paper appeared in *J. Physiol.* (1955, **129**, 436) on " The Behaviour of the Intact Ureter in Dogs, Rabbits and Rats " by D. W. Gould, A. C. L. Hsieh and L. F. Tinckler. There is no disagreement between the conclusions reached by these authors and by us.

We wish to express our gratitude to the Upjohn Company for a generous supply of 5-hydroxytryptamine creatinine sulphate, and to Messrs. Ciba for a supply of " Rogitine."

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