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THE EFFECT OF 5-HYDROXYTRYPTAMINE ON THE EXCRETION OF WATER IN CONSCIOUS DOGS

BY

V. C. ABRAHAMS AND MARY PICKFORD

From the Department of Physiology, University of Edinburgh

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5-Hydroxytryptamine (5-HT) is present in a number of tissues, but its physiological role is still undetermined. Erspamer (1954a, b,) found that 5-HT was powerfully antidiuretic and that, in rats, the subcutaneous route of administration was the most effective, as little as 4 μg./kg. producing definite and fairly long-lasting antidiuresis in the most sensitive individuals. By means of clearance measurements he found that glomerular filtration rate (GFR) was reduced and that there might also be some reduction in renal plasma flow (RPF). He concluded that 5-HT antidiuresis was due to preferential constriction of the afferent glomerular arterioles and, further, that the posterior pituitary played no part in the antidiuresis. He believes that 5-HT is a hormone designed for the physiological regulation of renal function (1953). Since most work on 5-HT has been done on rats, and little on dogs (Erspamer and Ottolenghi, 1951; Sala and Castegnaro, 1953), and since it is important to determine whether 5-HT is a renal hormone, as Erspamer believes, or merely an antidiuretic substance, we have carried out a number of different studies on the dog.

METHODS

Observations were made on conscious bitches during water diuresis. The methods of collecting urine and inducing diuresis have previously been described (Abrahams and Pickford, 1954). 5-HT was administered in the form of the creatinine sulphate dissolved in 1.0 ml., or less, of 0.9% NaCl solution. All doses are calculated and given as weight of base/kg. body weight of dog. The drug was injected subcutaneously, intramuscularly, intra-arterially or intravenously. The intra-arterial injections were made either into the sinus-denervated carotid artery lying in a previously prepared van Leersum loop, or into the aorta through a catheter inserted, under local anaesthesia, *via* the femoral artery. The catheter was inserted to a measured length immediately before giving the experimental dose of water. The position of its tip was ascertained later by reintroducing the catheter when the animal was killed. When intra-aortic injections were made the substance to be injected was dissolved in a volume of 0.9% NaCl solution less than that of the dead space of the catheter, namely, 0.8 ml. The test solution was injected into the catheter and then washed into the circulation with 1 or 2 ml. 0.9% NaCl solution.

Some observations were made on the renal clearances of diodone and creatinine before and after the intravenous injection of 5-HT. The methods used have already been described (Pickford and Ritchie, 1945). They avoid interference with the dog except for the collection of blood samples, and provide a period of 20 to 25 min. at the plateau of diuresis when the plasma concentrations of diodone and creatinine remain relatively constant. If antidiuresis occurs the period of steady plasma concentration is prolonged.

When required, blood pressure was measured in the conscious dog through a side-arm of the aortic catheter, and recorded by means of a mercury manometer.

RESULTS

Subcutaneous and Intramuscular Administration of 5-HT.—Only 4 observations were made on the effect on water diuresis of subcutaneously administered 5-HT. One bitch (Angela) received 22 μg./kg. 36 min. after the ingestion of water. The course of the diuresis thereafter was not noticeably different from normal. It was, however, possible that there had not been sufficient time for the drug to be absorbed and produce its effect. Therefore, in another animal (Darkie) 5-HT was given at the time of water administration. On one day the dose was 32 μg./kg. and on 2 others 74 μg./kg. subcutaneously. On no occasion did antidiuresis occur (Fig. 1).

Two animals were given 13.5 and 36 μg./kg. 5-HT intramuscularly and showed no hint of antidiuresis. On the other hand, 32 μg./kg. given intramuscularly to Darkie caused on this occasion an immediate and marked antidiuresis. The short latency of the response (1.0 min.) makes it probable that this positive response of Darkie to an

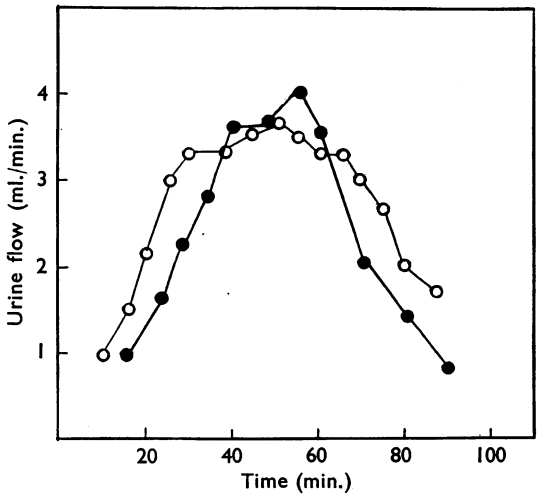

FIG. 1.—Record of water diuresis (Darkie). 300 ml. water by mouth at zero time. ●——● normal water diuresis. O——O, water diuresis when 74 μg./kg. 5-HT was given subcutaneously at zero time. In all graphs, ordinate is rate of urine flow in ml./min., and abscissa is time in min.

intramuscular injection when this animal gave consistently negative responses to subcutaneous injections was coincidental.

Administration of 5-HT into the Malleolar Vein.—A single injection of 5-HT given into the malleolar vein during water diuresis caused antidiuresis to a variable extent. The doses tested ranged from 0.6 μg./kg. to 84 μg./kg. Since the effect in any one dog varied from time to time (Fig. 2) despite apparently constant conditions, which included the time of day and the anoestrous condition of the animal, it was difficult to determine the minimum effective dose. Some dogs showed more variability of response than others. It was, however, clear that, in 11 normal dogs, true antidiuresis, as contrasted with momentary cessation of flow due to ureteric spasm (Abrahams and Pickford, 1956a), was not regularly seen with doses under 10 μg./kg. (Table I). Only one animal (Smokey) showed a sensitivity greater than this, and at post mortem this dog was found to have only the left kidney. On the right there was nothing but a fibrous cord in place of the ureter. The one kidney was large, dimpled on the surface, and showed, on histological examination, many areas of considerable fibrosis. In life there had been nothing to suggest that this dog was congenitally abnormal. This animal was one of the first on which observations were made, and unfortunately, before it was killed, information was given to Professor Erspamer that, in dogs, the sensitivity to intravenously administered 5-HT ranged from 4 to 20 μg./kg. Later experience amends these figures to 10–20 μg./kg.

TABLE I

MINIMUM INDIVIDUAL EFFECTIVE ANTIDIURETIC DOSES OF 5-HT WHEN INJECTION WAS MADE INTO THE MALLEOLAR VEIN

No. of Observations	Dog	Dose 5-HT μg./kg.	No. of Observations	Dog	Dose 5-HT μg./kg.
15	Frisk	10	6	Bouncer	14
2	Topsy	18·5	4	Darkie	16
3	Sheila	20	8	Angela	21·8
5	Jess	12 7	5	Kit	9·4
4	Chris	13 5	10	Judy	10
4	Lady[1]	18·5	5	Thisbe	13
6	Smokey[2]	4·0			

[1] With diabetes insipidus. [2] Congenital absence of right kidney.

Some observations were made on one dog at a time when it had a prolapsed uterus. It could be seen that, when antidiuresis occurred in response to an injection of 5-HT, there was a perceptible paling of the vaginal mucous membrane, lasting about 5 min.; when antidiuresis did not occur there was no pallor. Furthermore, all dogs which subsequently showed antidiuresis sighed, panted, or

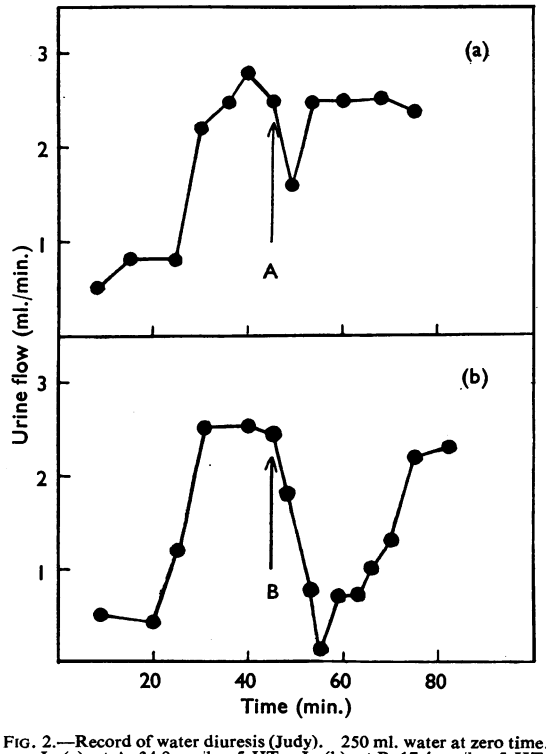

FIG. 2.—Record of water diuresis (Judy). 250 ml. water at zero time. In (a), at A, 34.8 μg./kg. 5-HT. In (b), at B, 17.4 μg./kg. 5-HT. Injections made into malleolar vein on both occasions.

yawned some seconds after the injection of 5-HT. If this respiratory response was minimal or absent antidiuresis did not occur.

Administration of 5-HT into the Carotid Artery.—Intracarotid injections of 5-HT were given 4 times in the following doses: 8.6 μg./kg., 9.2 μg./kg., 9.4 μg./kg., and 18.8 μg./kg. The results were variable, but it was clear that the effect of 5-HT was no greater nor was the minimum effective dose smaller when the drug was given into the common carotid instead of the malleolar vein (Fig. 3). These findings agree with those of others, who state that the action of 5-HT is not a central one (Erspamer, 1954a). With regard to the respiratory effects, these were no greater, and perhaps less, on intracarotid than on intravenous injection. This agrees with the findings of Douglas and Toh (1953) and of Schneider and Yonkman (1954).

Renal Clearances Following the Administration of 5-HT.—Renal clearances of diodine and creatinine were measured 15 times on 5 dogs before and after the injection into the malleolar vein of doses of 5-HT ranging from 9.2 to 18.5 μg./kg. The responses varied considerably, antidiuresis being observed in 9 of the 15 experiments. In the 9 experiments in which antidiuresis occurred, its degree varied from one or more transitory depressions to a prolonged inhibition of urine flow

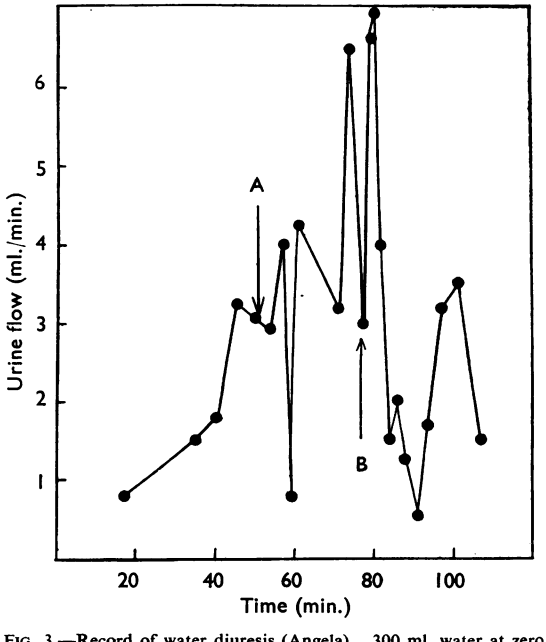

FIG. 3.—Record of water diuresis (Angela). 300 ml. water at zero time. At A, 18.8 μg./kg. 5-HT into the left common carotid artery. At B, 18.8 μg./kg. 5-HT into the malleolar vein.

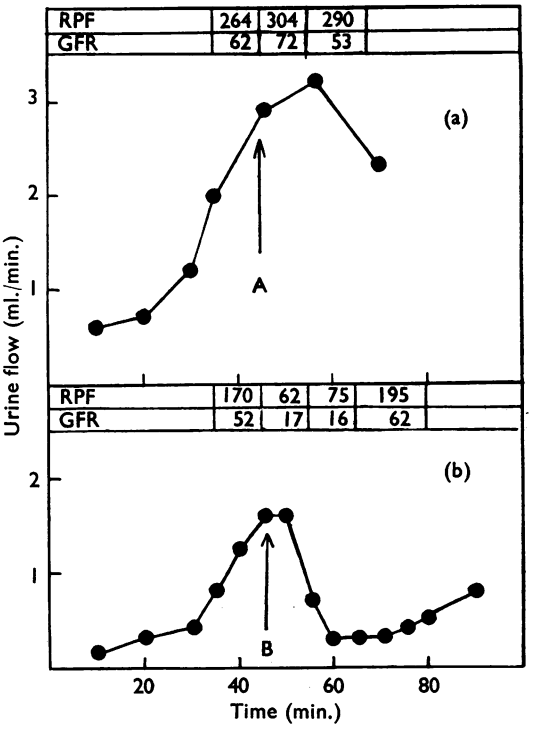

FIG. 4.—Record of water diuresis and renal clearances in ml./min. of diodone (RPF) and creatinine (GFR) in 2 dogs before and after injection into the malleolar vein of 5-HT. (a) Bouncer; at A, 10.2 μg./kg. (b) Judy; at B, 15 μg./kg.

(Fig. 4). When depression was transitory both clearances rose and fell roughly to the same extent and in parallel with the urine flow, suggesting a purely vascular origin for the alterations in renal activity. When there was prolonged inhibition of urine flow, both clearances fell in 7 out of 9 experiments; once the GFR alone and once the RPF alone decreased. After the initial depression which lasted for 20 to 25 min. the RFP rose towards or above the preinjection level, even though the urine flow was still inhibited. On three occasions the GFR also increased (Fig. 4).

When urine flow was not inhibited by the administration of 5-HT both clearance values rose to a greater or lesser extent (Fig. 4).

Thus 5-HT, in contrast to posterior pituitary lobe extract, is uncertain and variable in its action on dog kidney unless given in fairly large doses. The initial phase of 5-HT antidiuresis seems to depend on decreased plasma flow and glomerular filtration rate, the latter especially tending to persist. The fact that antidiuresis persisted after recovery of both clearances suggested that the preliminary reduction of blood supply to the kidney

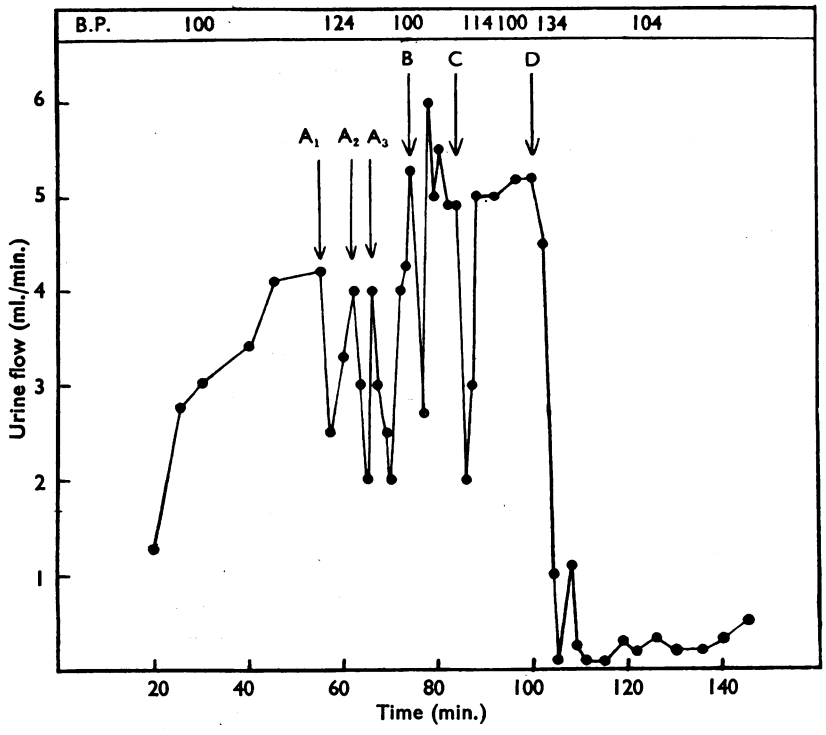

FIG. 5.—Record of water diuresis (Thisbe). 300 ml. water at zero time. A_1, A_2, and A_3, three separate intra-aortic injections of 10 μg. adrenaline. B, 8 μg./kg. 5-HT intra-aortically. C, 40 μg./kg. 5-HT intra-aortically. D, 20 μg./kg. 5-HT into the cubital vein. At top, blood pressure in mm. Hg.

gave rise to some other and more long-lasting reaction (Verney and Vogt, 1938, 1943), possibly reflex. Therefore, the reaction of the kidney to 5-HT injected into either the aorta or the cubital vein was examined. By this means information might be obtained about the origin of the vascular changes occurring in the kidney, i.e., whether the kidney shows a particular sensitivity to the drug, or whether it simply responds to a change in vascular conditions elsewhere in the body.

Administration of 5-HT into the Aorta.—The minor operation of aortic catheterization did not usually delay the onset of water diuresis. In five out of six experiments there was no difference from the normal pattern of diuresis; only once was its onset delayed by 30 min. In all instances the catheter tip was one or more inches above the origin of the right renal artery. Control observations showed that the injection of 2 ml. saline alone into the aorta had no effect on the rate of urine flow.

One animal (Jess) received an intra-aortic injection of 22 μg./kg. 5-HT. Three min. after this dose the urine flow fell from its previous rate of 6 ml./min. to 5.3 ml./min., and 3 min. later was again 6 ml./min. This was the only noticeable response. Respiration was in no way disturbed. Owing to a clot in the catheter it was not possible to repeat the injection. The negative result could have occurred because the 5-HT was swept past the renal arteries and did not reach the kidneys. Another dog (Thisbe) received 8 μg./kg. 5-HT into the aorta, showed no change in blood pressure and inhibition of urine flow for one minute; 40 μg./kg. caused a small rise of blood pressure and another transitory fall in the rate of urine flow (Fig. 5). On both these occasions the reduction in the rate of urine flow seemed to be due to ureteric spasm. In this dog it was unlikely that the 5-HT failed to reach the kidneys, since three consecutive injections of 10 μg. adrenaline given intra-aortically (Fig. 5) immediately before the 5-HT injections caused the type of urinary inhibition always seen after the intravenous injection of adrenaline. In a third dog (Chris) the intra-aortic injection of 36 μg./kg. 5-HT caused a large rise in blood pressure and inhibition of urine flow (Fig. 6).

Administration of 5-HT into the Cubital Vein.—When 5-HT was injected into the malleolar vein the appearance of antidiuresis was correlated to the degree of the respiratory response (see top of p. 37). It was therefore possible that both antidiuresis and panting depended on changes in the vascular bed in the thorax, or on direct stimulation of sensory

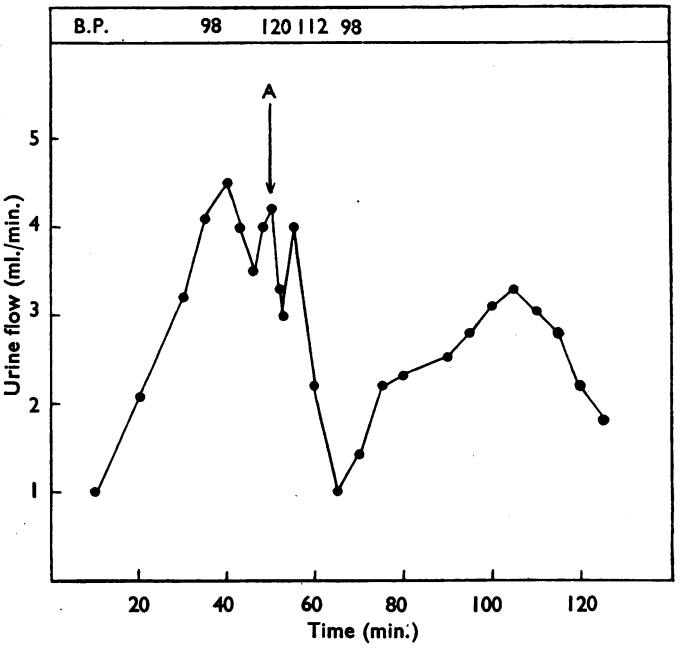

FIG. 6.—Record of water diuresis (Chris). Effect of intra-aortic injection, at A, of 36 μg./kg. 5-HT. At top, blood pressure in mm. Hg.

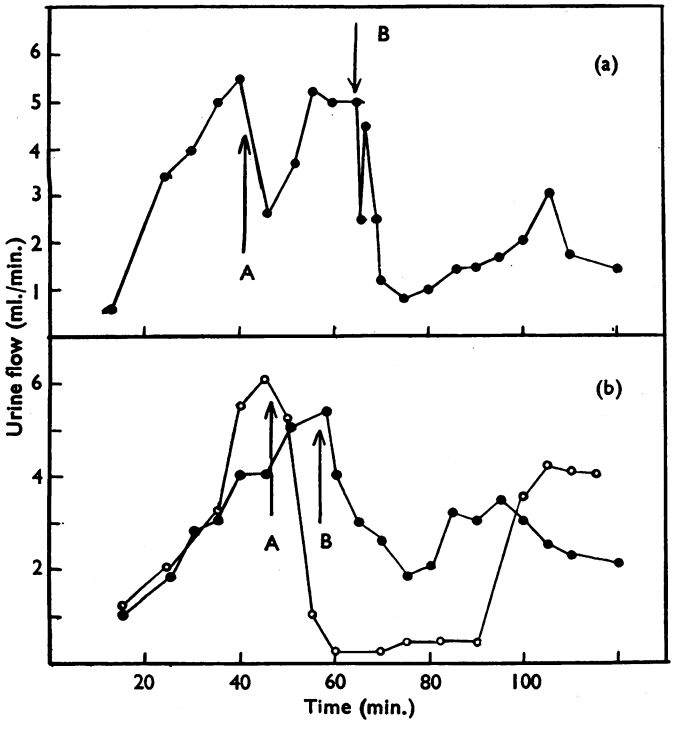

FIG. 7.—Record of water diuresis (Jess). Comparison of the effect of 5-HT injected into the malleolar and cubital veins. (a) At A, 13.4 μg./kg. into malleolar vein; at B, 13.4 μg./kg. into cubital vein. (b) O——O at A, 13.4 μg./kg. into cubital vein; ●——● at B, 13.4 μg./kg. into malleolar vein.

receptors there (Comroe, Van Lingen, Stroud, and Roncorini, 1953; MacCanon and Horvath, 1954; Mott and Paintal, 1953; Schneider and Yonkman, 1953, 1954)—that is, that both phenomena were caused by reflexes arising in the same area. It was also possible that the variability of the response after injection of 5-HT into the malleolar vein depended on the rate at which this substance was picked up by the platelets, and therefore on the final concentration of 5-HT reaching some part of the thoracic viscera. If these hypotheses were valid, then an injection into the cubital vein should be more effective than one into the malleolar, because the path and time to the thorax are shorter; and

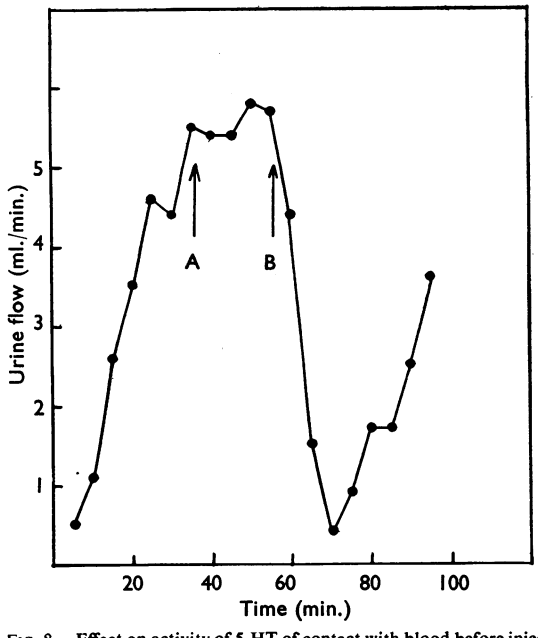

FIG. 8.—Effect on activity of 5-HT of contact with blood before injection into the circulation. Record of water diuresis (Chris). At A, 18 μg./kg. after 16 sec. contact with dog's own blood; at B, 18 μg./kg. without preliminary admixture with blood. Both injections into cubital vein.

5-HT should be inactivated by contact with blood for a short time. It has been confirmed in 5 dogs that a given dose of 5-HT is more effective as an antidiuretic when given into the fore- as compared with the hind-limb vein, and that a smaller dose is effective by the former route (see Fig. 7). Furthermore, a dose injected into the fore-limb vein was more powerfully antidiuretic than twice that amount injected into the aorta earlier the same afternoon (Fig. 5).

Fig. 8 shows the effect of an injection of 5-HT after contact with blood. For the first injection at A, after inserting the hypodermic needle in the cubital vein, 2 ml. blood was withdrawn into the syringe which already contained 18 μg./kg. 5-HT in 1.0 ml. 0.9% NaCl solution. The mixture of blood and 5-HT containing saline was then immediately re-injected. The whole procedure was completed in 16 sec. For the second injection at B, 18 μg./kg. 5-HT in 1.0 ml. 0.9% NaCl solution was given into the same vein without preliminary admixture with blood. In the first instance the change in rate of urine flow was negligible, but in the second there was marked antidiuresis. This shows that contact with blood for 16 sec. is sufficient to reduce the amount of free 5-HT below that necessary to produce antidiuresis. This interval is roughly equal to that between the injection into the hind-limb vein of 5-HT or acetylcholine and the respiratory response—that is, the circulation time from leg to thorax or head in dogs of 12 to 16 kg. body weight is about 14–16 sec.

The Effect of 5-HT on Blood Pressure.—It was evident from the intra-aortic records of blood pressure that in the conscious dog 5-HT produced the same response as in the anaesthetized animal—that is, a sharp rise in pressure lasting 2 to 3 min. and then a gradual fall. In the conscious dog the preinjection level was re-attained in 11 to 13 min. It was also clear that there was no inhibition of urine flow unless there was a change in general blood pressure (Figs. 5 and 6).

The Effect of 5-HT in the Dog with Diabetes Insipidus.—Fig. 9 shows that, in a diabetic dog (Lady), drinking between 5 and 6 l. of water daily, an intravenous injection of 15.5 μg./kg. 5-HT caused a brief inhibition of urine flow, probably due to ureteric spasm, followed by recovery and then a moderate but longer-lasting inhibition. 31 μg./kg. produced a similar response. Unfortunately there is no information about the prediabetic response of this dog. Post-mortem histological examination of the hypothalamus and pituitary showed that few supraoptic or paraventricular cells remained. Those cells present, when stained with toluidine blue, were pale and agranular, and when stained with chrome-alum-haematoxylin and phloxin were loaded with dark material. The posterior lobe and median eminence were atrophic.

The Effect of 5-HT after Renal Denervation.—In one dog (Jess) the kidneys were denervated by stripping the renal pedicles and freeing the kidneys from all peritoneal connexions. 11 days later an intravenous injection of 13.5 μg./kg. 5-HT induced antidiuresis.

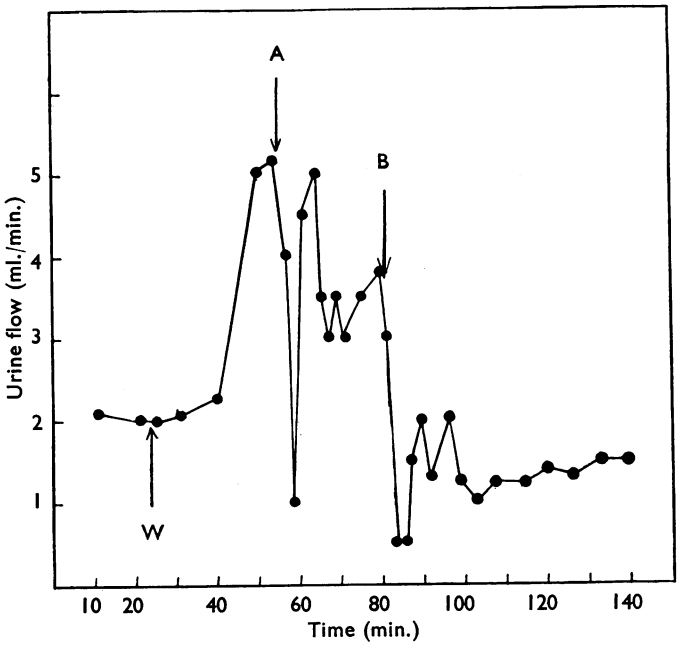

FIG. 9.—Effect of intravenous 5-HT on water diuresis in dog (Lady) with diabetes insipidus. At W, 350 ml. water by mouth. At A, 15.5 μg./kg. 5-HT. At B, 31 μg./kg. 5-HT. Both injections into malleolar vein.

Appearance of the Kidney after the Administration of 5-HT.—Once, immediately before killing an anaesthetized dog (Bouncer), the abdomen was opened and the kidney watched during the injection into the malleolar vein of 26 μg./kg. 5-HT. Some seconds after the injection the surface of the organ paled markedly. The colour began to return 2 to 3 min. later. After waiting 15 min. to allow time for recovery, a further dose of 26 μg./kg. was injected intravenously, followed 1 min. later by a concentrated solution of bromphenol blue in 0.9% NaCl solution. As quickly as possible after this the left renal pedicle was clamped, the kidney removed and bisected, and examined under low-power binocular magnification. Dye was seen plentifully in the medulla, but in only a few radial streaks in the cortex. Juxtamedullary glomeruli were empty of dye. These findings were confirmed later by histological examination of both kidneys.

DISCUSSION

The experiments described show that, in the conscious dog, single intravenous injections of 5-hydroxytryptamine (5-HT) given during water diuresis cause an inhibition of urine flow. In normal dogs, the minimum individual effective dose given into the malleolar vein varied from 10 to 20 μg./kg. In one dog with congenital absence of the right and fibrosis of the left kidney, the minimal effective dose was only 4 μg./kg. In any one dog the degree of antidiuresis induced by a given dose varied from day to day, even under constant conditions, and on some days no antidiuresis would be seen. Subcutaneous doses of up to 74 μg./kg. caused no antidiuresis. These results in the dog are similar to those of Erspamer (1954a and b) working on rats. They differ, however, in the degree of sensitivity of the two species, in the most effective route of administration and in the regularity of response. Erspamer found that in some rats as little as 4 μg./kg. 5-HT given subcutaneously caused antidiuresis. Clearly dogs do not exhibit anything like this degree of sensitivity to subcutaneously administered 5-HT. On the other hand, rats appear to be fairly insensitive to its intravenous administration (Erspamer, 1954b), though we have been unable to trace any published work on the intravenous use of a salt of the pure base in a study on water diuresis in rats.

Measurements of diodone and creatinine clearances in dogs showed that during antidiuresis the values of both RPF and GFR fell rapidly. 20 to 25 min. later RPF rose towards or above pre-injection levels, even though urinary inhibition persisted. The GFR, too, might recover during the phase of urinary inhibition, but usually it remained depressed for a longer period than the RPF. When antidiuresis failed to appear in response to an injection of 5-HT the clearances of

diodone and creatinine rose. Here, then, dogs and rats showed similar reactions, in that, when antidiuresis occurred, it seemed to depend on a reduction in GFR rather than in RPF. That blood pressure rose and vaginal mucous membrane paled when antidiuresis followed injection of 5-HT, and, on the other hand, that clearance values rose when antidiuresis failed to occur, all suggest that vasoconstriction, both generally and in the kidney, is a prerequisite for antidiuresis. In other words, the kidney is no more sensitive to 5-HT than are other areas, and 5-HT, unlike the vasopressor fraction of posterior pituitary extracts, does not specifically induce water reabsorption. This agrees with Erspamer's conclusion that the antidiuresis is vascular in origin, but is contrary to the idea that 5-HT is a specific renal vascular hormone. Sala and Castegnaro (1953) believe it is a water reabsorbing hormone. They used large doses given subcutaneously to dogs, and report that antidiuresis occurred, on occasion, in the absence of any change in GFR. There was, however, always a reduction in RPF. They interpret this as meaning that 5-HT induces specific reabsorption of water. Unfortunately no observations were made on the blood pressure which would be greatly increased by such doses, which would cause complex and variable changes in the kidney and possibly other remote effects such as release of antidiuretic hormone.

Why, in the present experiments, the reaction of the kidney to 5-HT varied from day to day is unknown. There seemed to be no relationship to the size of dose used. The variability may have depended on the proportion of injected 5-HT affecting the circulatory system and the proportion finally reaching the kidney.

No observations were made on the effect of infusions of 5-HT as was done by Corcoran, Masson, Del Greco, and Page (1954). They infused dogs intravenously at rates of 2 to 13 μg./kg./min. 5-HT, and found no hint of antidiuresis with the smaller doses and hypotension with the larger. Judging from the present results the low doses were probably too small to cause antidiuresis, even when given steadily over a period of time, since 5-HT is so rapidly removed from the circulation (Gaddum, Hebb, Silver, and Swan, 1953) that its concentration is unlikely to rise. The higher doses were within the antidiuretic range for some dogs, but hypotension would confuse the issue. The last complication was absent from the experiments described in this paper.

The present results on intracarotid injections in a dog with diabetes insipidus accord with those of Erspamer (1954a, b) and Barac (1953), who concluded that an intact posterior lobe was unnecessary for an antidiuretic reaction to 5-HT administration, and that no direct central stimulation was involved.

Certain observations make it unlikely that 5-HT can be considered a renal hormone. In the dog the uncertainty and variability of its effect on the kidney raise the suspicion that its most important action is at some other site. Compared with the kidney, the response of the systemic blood pressure, the ureter (Abrahams and Pickford, 1956a), and uterus (Abrahams and Pickford, 1956b) show greater consistency and sensitivity. When 5-HT is in contact with blood its activity is rapidly reduced, as was shown by Gaddum, Hebb, Silver, and Swan (1953) and in the present experiments. When 5-HT is given by intravenous injection the time during which it is in contact with blood before it reaches the ureter, uterus or kidney must be nearly the same ; yet the smallest injected dose to which the kidney responds varies from 10 to 20 μg./kg., whereas the other two organs react to doses of 0.5 μg./kg. and 5 μg./kg. respectively—and are thus more sensitive than the most sensitive kidney. Yet it might be expected that a hormone would act on its target organ in lower concentration than that necessary to affect other organs. The systemic blood pressure is altered by doses of 5-HT which are wholly without effect on the rate of urine flow (Abrahams and Pickford, 1956a). Further, when 5-HT is injected into the aorta, and there was reason to suppose that the drug was reaching the kidney, the renal reaction to 40 μg./kg. was insignificant, but there was a marked response to the intravenous injection of 20 μg./kg. (Fig. 5). Furthermore, antidiuresis only occurred when the general blood pressure was raised, and was never seen unless there was evident respiratory reaction to the injection. All these facts made it necessary to look beyond the kidney for the origin of the effect of 5-HT on urine flow. Mott and Paintal (1953) found that 5-HT stimulates vagal fibres whose origins lie between the great veins and left atrium ; and 5-HT is more strongly antidiuretic when injected into the cubital vein instead of the malleolar vein or aorta (Fig. 7). It would thus appear that 5-HT produces antidiuresis mainly by setting up reflexes from the thorax, probably from the pulmonary bed, which, by altering the general blood pressure, affect the kidney.

This does not exclude other modes of action as well. Page (1952) found that the perfused kidney shows vasoconstriction in response to 5-HT, though the reaction is less marked than that to

adrenaline. There is, too, the present observation that the denervated kidney responded by antidiuresis to an injection of 5-HT. This could be explained as due, in part, to the direct vasoconstrictor action of 5-HT ; but also, almost certainly, to the powers of autoregulation displayed by the denervated kidney (Sellwood and Verney, 1955). No substance can strictly be called a renal hormone because it is active on the denervated kidney, unless, at the same time, the general blood pressure is unchanged.

Finally, there is the problem of why the antidiuretic effect of 5-HT sometimes greatly outlasts an effective blood concentration. Verney and Vogt (1938, 1943) found that in some dogs a long-lasting suppression of urine flow followed short periods of renal arterial occlusion. It may be that injected 5-HT, by depriving the renal cortex of blood for as long as 2 or 3 min., which it was observed to do, has much the same effect as renal arterial occlusion. Possibly, too, the sharp changes in blood pressure may cause the release of antidiuretic hormone from the posterior lobe of the pituitary.

SUMMARY

1. Observations were made on conscious dogs of the effect during water diuresis of injecting 5-hydroxytryptamine (5-HT) subcutaneously, intramuscularly, into the malleolar or cubital vein, or the aorta or carotid artery.

2. 5-HT was most effectively antidiuretic when injected into the cubital vein, less so when injected into the malleolar vein or carotid artery, and still less so when given into the aorta at a point above the origin of both renal arteries. It was least effective when administered subcutaneously or intramuscularly.

3. When injected into the malleolar vein the minimum effective antidiuretic dose varied from 10 to 20 μg./kg.

4. Antidiuresis was not regularly seen after a given dose of 5-HT. When it did occur it was accompanied by obvious respiratory reactions. When aortic pressure was measured this was seen to rise at the onset of antidiuresis. The vaginal mucous membrane also paled. If the respiratory and vascular reactions were inconspicuous or absent antidiuresis did not occur.

5. During antidiuresis the renal clearances of diodone and creatinine fell. One or both values might increase towards or above preinjection level before urine flow recovered. When 5-HT failed to cause antidiuresis both clearance values rose.

6. The meaning of the results is discussed ; it is concluded that there are several reasons for the antidiuretic action of 5-HT, but that it is not a specific renal hormone.

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