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Received May 18, 1962. P.S.E.B.M., 1962, v110.

Natriuresis in Conscious Dogs during Arginine Vasopressin Infusion and after Oxytocin Injection.* (27621)

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Both vasopressin and oxytocin can enhance electrolyte excretion by conscious dogs(1-4). Brooks and Pickford(2) observed that low doses of arginine vasopressin cause natriuresis only if administered during water diuresis. Oxytocin, however, is natriuretic only when the rate of urine flow is low. We have confirmed both these observations(4). The peculiar relation of the rate of urine flow to natriuretic responses suggests that endogenous vasopressin may enhance the natriuretic response to oxytocin while it may inhibit the response to exogenous vasopressin. In this paper we describe the influence of prolonged infusion of arginine vasopressin on natriuretic responses of conscious hydrated dogs to oxytocin.

Materials and methods. All experiments were performed on 4 trained female dogs weighing between 15 and 21 kg. They were not fed but were allowed water *ad lib.* for 12 hours preceding each experiment. Diuresis was induced by oral administration of 40-50 ml/kg of water.

In the experiments on electrolyte excretion, arginine vasopressin was injected intravenously in a priming dose of 0.5 to 1.0 mU and then infused at 15-20 mU/hr. After the rates of urine flow and electrolyte excretion became stable, 100 to 150 mU of oxytocin were given intravenously. Urine was collected from an indwelling bladder catheter at 10-minute intervals. The bladder was rinsed with water and air at the end of each period. Sodium and potassium were measured by internal standard flame photometry.

Glomerular filtration rate was measured by exogenous creatinine clearance. Renal plasma flow was estimated by either para-aminohippurate or iodopyracet (Diodrast) clearance. The indicators were infused intravenously.

The hormones used were purified arginine vasopressin (Pitressin of bovine origin) supplied by the late Dr. D. A. McGinty of Parke, Davis and Co., and synthetic oxytocin (Syntocinon) supplied by Dr. R. Bircher of Sandoz Pharmaceuticals. Both preparations were standardized in this laboratory against USP Reference Standard by rat vasopressor or rat uterus assays.

Results and discussion. Low doses of arginine vasopressin cause a marked increase in rate of sodium excretion by conscious dogs during water diuresis(2,3,4). There is also a variable increase in potassium excretion. Vasopressin infusion, however, at 1 mU/kg $\times$ hr provokes a transient natriuresis that begins to subside even before antidiuresis becomes maximal (Fig. 1A). Sodium excretion returns to the control rate within an hour, although antidiuresis persists as long as the infusion is maintained (up to 4 hours). This indicates that the kidney adapts rapidly to the natriuretic influence of vasopressin, becoming refractory despite persistent antidiuresis. Such development of resistance to the natriuretic action could be of adaptive value to the organism, allowing maintained antidiuresis in response to endogenous vaso-

* Supported by grants from Nat. Inst. of Arthritis and Metab. Dis., U.S.P.H.S., and from the Lowell M. Palmer Foundation.

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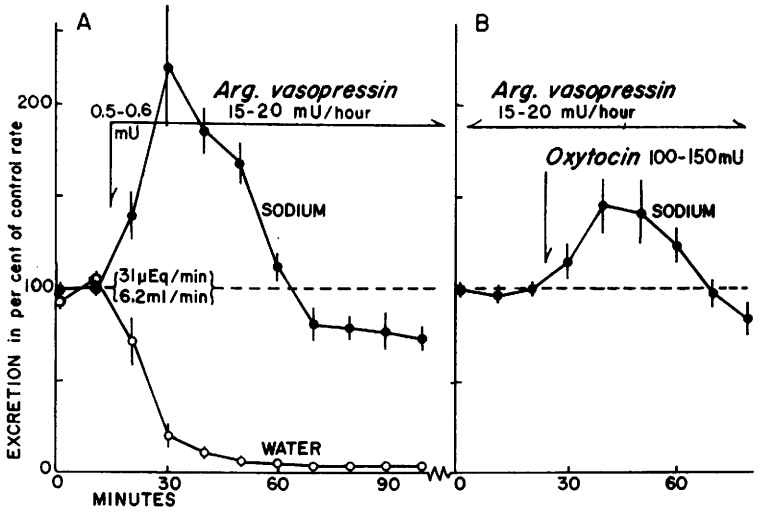

FIG. 1. A. Influence of vasopressin infusion on sodium and water excretion in conscious hydrated dogs. Excretory rates are expressed as percent of the rates determined for 30 min prior to start of infusion. Points are mean values for 6 experiments. Vertical lines through points are standard errors of means. B. Response to oxytocin injected during sustained vasopressin infusion. Points are means from 5 experiments.

pressin without excessive sodium loss. An alternative hypothesis is possible since natriuresis wanes as antidiuresis becomes established. This could merely be another manifestation of the previously observed phenomenon that vasopressin is not natriuretic when urine flows are low(2,4).

Neither of the interpretations offered above affords much new insight into the mechanism of vasopressin natriuresis. This response could result either from decreased tubular sodium reabsorption of from a slight increase in the rate that sodium is filtered by the glomeruli. We have been unable to detect consistent changes in glomerular filtration rate or renal plasma flow in dogs receiving natriuretic doses of vasopressin. Fluctuations in filtration rate adequate to explain natriuresis of the observed magnitude could, however, easily escape detection since they could be much smaller than the inherent variations in measurements of exogenous creatinine clearances.

Oxytocin, 7 mU/kg, produces a consistent natriuresis in conscious dogs with low urine flows(2,3,4). During water diuresis, however, this dose has no effect. If 7 mU/kg of oxytocin is injected intravenously into water-loaded dogs during prolonged vasopressin infusion, after sodium excretion has returned to rates close to those existing prior to infusion, it exerts a weak but consistent natriuretic effect (Fig. 1B). The intensity and duration of this effect are less than those observed when this dose of oxytocin is injected into dogs with normally low urine flows. It is possible that the degree of overhydration in these vasopressin-infused dogs partially inhibits the response to oxytocin.

The natriuretic response to these low doses of oxytocin, therefore, appears to depend upon the presence of vasopressin, either endogenous or exogenous. This would be consistent with the observation by Brooks and Pickford(2) that oxytocin is only natriuretic in dogs with diabetes insipidus if vasopressin is also administered. Higher doses of oxytocin, however, that produce antidiuresis themselves, do produce natriuresis in hydrated dogs(4). This suggests that it is antidiuresis, not vasopressin, that is prerequisite if oxytocin is to be natriuretic.

The mechanism of the renal response to oxytocin remains obscure. Oxytocin is more effective when injected into a carotid artery (2) or into the third cerebral ventricle (Chan and Sawyer, unpublished). This implies an intracranial site of action of the peptide in causing natriuresis. Although Brooks and

Pickford(2) reported that doses of oxytocin comparable to those used in the present study markedly enhance Diodrast clearance, approximately doubling it in some instances, we were unable to detect significant changes in either Diodrast or para-amino hippurate clearances after injection of oxytocin into our dogs. Ali(3) also reported increased glomerular filtration rate after oxytocin. We could not detect any consistent changes in exogenous creatinine clearances in our dogs after natriuretic doses of oxytocin. An undetectable increase in glomerular filtration rate could, however, account for the observed small increase in sodium excretion. Enhancement of either glomerular filtration or renal plasma flow comparable in magnitude to that reported by Brooks and Pickford(2) and Ali (3) should, nonetheless, have been clearly evident if they occurred in our clearance experiments. They did not. The significance of this discrepancy is not evident at this time. Our results are, however, more consistent with those of Heidenreich *et al.*(5) who observed that oxytocin had minimal effects on renal hemodynamics in normal dogs.

Natriuretic responses of dogs to vasopressin and oxytocin are relatively small and of uncertain physiological significance. Similar responses have not been demonstrated in man. These phenomena appear, however, of sufficient interest to merit further investigation. Many aspects of the humoral regulation of renal sodium excretion remain quite mysterious. Study of those factors that can be related to this important renal function can only serve to reduce the area of mystery.

Summary. Low doses of arginine vasopressin cause natriuresis in conscious dogs only if administered during water diuresis. If vasopressin is infused there is an initial natriuresis which rapidly subsides, although antidiuresis persists for the duration of the infusion. Oxytocin, in low doses, produces natriuresis only at low urine flows produced by withholding water or by infusing vasopressin. Antidiuresis appears to be a prerequisite for the natriuretic response to oxytocin.

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Received May 21, 1962. P.S.E.B.M., 1962, v110.

Placental Transfer of L-Thyroxine and Tri-iodo-L-thyronine in Rats During Late Pregnancy.* (27622)

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The fetal requirement of thyroid hormones can be met in two ways: either by the fetal thyroid gland or by placental transfer of hormones from the mother. Clinical observations have demonstrated the likelihood of placental transfer of thyroid hormones(1) and in a manner similar to rabbits(2). In rabbits, Hall and Myant(3) and Myant(4) report that thyroid hormones are transferred and that tri-iodothyronine passes more readily than thyroxine in all stages of pregnancy. In guinea pigs, Peterson and Young(5) present evidence for transfer of thyroxine whereas Hirvonen and Lybeck(6) present evidence to the contrary.

This problem has not been studied in detail in the rat. Knobil and Josimovich(7) gave indirect evidence of greater placental permeability to thyroxine than tri-iodothyronine based on the greater suppressive action of

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† Supported in part by a grant from the Population Council and a contract with Atomic Energy Commission.