Role of Oxytocin in the Natriuresis of Extracellular Volume Expansion* (33772)

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(Introduced by A. Sellers)

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Recent investigations have shown that extracellular volume expansion can cause a marked increase in the renal excretion of sodium despite a significant reduction in its filtered load (1). Micropuncture studies (2) indicate that this phenomenon is associated with a reduction in proximal tubular reabsorption of sodium. Several mechanisms have been suggested to explain this natriuresis; among these is the release of a natriuretic hormone during volume expansion (3).

Cort reported (4) that the hypothalamus of the cat can release a hormone which is directly natriuretic. Evidence exists that in the rat oxytocin can increase sodium excretion probably by decreasing its tubular reabsorption (5). Brooks and Pickford (6) and Chan and Sawyer (7) showed that small doses of oxytocin injected into the carotid artery of a conscious dog is natriuretic when the urine flow is relatively low. In addition, the injection of oxytocin into the third cerebral ventricle of the dog can also enhance renal sodium excretion (8).

The present experiments were designed to test whether oxytocin plays a role in the natriuresis of extracellular volume expansion. The results indicate that oxytocin is not the factor responsible for this natriuresis.

Material and Methods. Eight female mongrel dogs weighing 14–23 kg were studied under pentobarbital anesthesia. The animals were deprived of fluids for 16 hr prior to the experiment. Respiration was controlled by a Harvard respirator pump with ventilation adjusted to maintain arterial pH within normal limits. Glomerular filtration rate (GFR) was measured by exogenous creatinine clearance. Urine was collected from a retention catheter and the bladder was washed with air at the end of each clearance period to assure completeness of collection. Blood was withdrawn at the midpoint of each period from an indwelling needle in the femoral vein. A polyethylene catheter was inserted into the external jugular vein with its tip towards the head, to collect blood samples for oxytocin measurements.

The experiment consisted of five consecutive parts, each lasting 75 min: (i) control; (ii) intravenous infusion of 0.9% NaCl at a rate of 10 ml/min; (iii) intravenous infusion of 0.9% NaCl at a rate of 20 ml/min; (iv) rate of saline infusion adjusted to equal urinary output; at the same time an intravenous priming dose of oxytocin (Syntocinon) 20 mU/kg of body weight, was given and followed by a sustaining oxytocin infusion of 30 mU/min; and (v) sustaining infusion of oxytocin (30 mU/min) continued while the saline infusion was stopped. Clearance periods were obtained for the measurement of GFR and urinrary sodium. After 60 min of parts 2 through 5 of the study and when sodium excretion was stable, three 5-min clearance periods were obtained to correlate the rate of sodium excretion with the levels of oxytocin in jugular blood. Blood samples from the jugular vein were drawn at the end of each part of the experiment. In three of the seven dogs studied GFR and sodium excretion were not measured and only oxytocin in jugular blood was assayed at the end of the control period and after the saline infusion at 10 and 20 ml/min.

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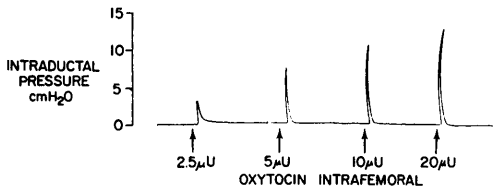

FIG. 1. The changes in intraductal pressure of the mammary gland of a lactating rat after the injection of different doses of oxytocin delivered in an injection volume of 0.2 ml.

Blood and urine samples were analyzed for creatinine and sodium by methods previously reported from this laboratory (9). Jugular blood plasma samples were assayed for oxytocin by measuring their milk-ejection activity as expressed by changes in the intraductal pressure of the mammary gland of ethanol anesthetized lactating rats. The details of this assay procedure as performed in our laboratory have been described previously (10).

The lower limit of sensitivity of this method, using an injection volume of 0.2 ml, is 12.5 μU/ml of oxytocin or 2.5 μU per dose (Fig. 1). Occasionally, smaller amounts of oxytocin (5–6 μU/ml) may be detected when an injection volume of 0.4 ml can be used. The nature of the milk-ejection activity assayed in the blood samples was identified with oxytocin antiserum from rabbits (11). Oxytocin antiserum is a specific inactivator for oxytocin and does not destroy the milk-ejection activity of vasopressin (Fig. 2); therefore, the inactivation of the milk-ejection activity by oxytocin antiserum indicates that this activity was due to oxytocin. In the present study, milk-ejection activity was attributed to oxytocin only when the oxytocin antiserum completely inactivated the activity of the sample.

Results. The results from all experiments are presented in Table I. With extracellular volume expansion, induced by saline infusion, urinary sodium excretion increased from a control value of 27 ± 9 μeq/min (mean ± SE) to 473 ± 205 μeq/min when the infusion of normal saline was 10 ml/min and to 998 ± 224 μeq/min as the rate of infusion was raised to 20 ml/min. The control levels of oxytocin in the jugular blood were low in 5 dogs while high levels of 67 ± 9, 47 ± 3, 87 ± 17 μU/ml were found in the other three animals. The reason for these higher levels is not clear. It is possible that there is wide variation in the fasting jugular blood levels of oxytocin in the female dog. The extracellular volume expansion and the augmented sodium excretion were not accompanied by constant changes in oxytocin levels of jugular blood; oxytocin levels were unchanged in 3 dogs (nos. 3, 4, 6), slightly elevated in 3 animals (nos. 1, 2, 5) and fell markedly in another two (nos. 7, 8).

With the infusion of large amounts of oxytocin, blood levels ranging from 41 to 105 μU/ml were created and maintained for 2.5 hr. Despite the maintenance of high levels of oxytocin in plasma, the rate of sodium excretion did not increase further but fell from 998 ± 224 to 834 ± 199 and 461 ± 119 μeq/min as the saline infusion was first equaled to urine flow and then discontinued.

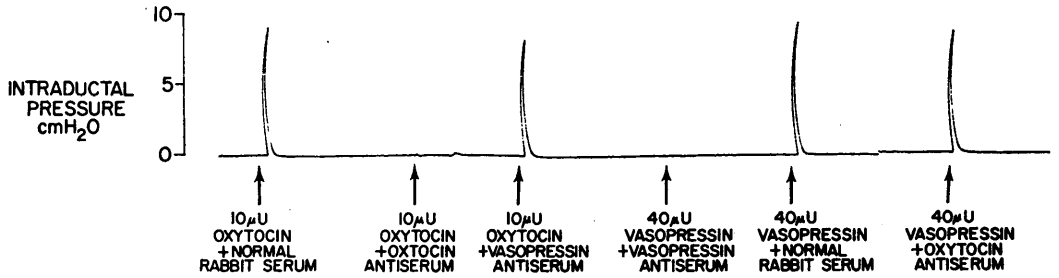

FIG. 2. Recording of intraductal pressure in a lactating rat. Antisera from rabbits against oxytocin or vasopressin do not cross-react. Oxytocin antiserum can only block the biologic activity of oxytocin, and vasopressin antiserum only that of vasopressin. Therefore such antisera are highly suited for the biologic identification of neurophysial hormones. Normal rabbit serum does not alter the activity of the hormones.

TABLE I. Summary of All Experiments.

Dog no.	Control	0.9% NaCl infusion 10 ml/min	0.9% NaCl infusion 20 ml/min	0.9% NaCl infusion Equal to UV + oxytocin	Oxytocin alone
1. C_{cr} (ml/min)	56	66	51	45	42
$U_{Na}V$ (μeq/min)	3	160	163	188	111
Plasma oxytocin (μU/ml)	<6	36 ± 7	12 ± 0	49 ±15	46 ±13
	(2)	(2)	(3)	(3)	(3)
2. C_{cr} (ml/min)	47	54	50	43	45
$U_{Na}V$ (μeq/min)	33	509	1092	609	298
Plasma oxytocin (μU/ml)	<6	<8	12 ± 0	58 ± 3	53 ±13
	(3)	(3)	(2)	(2)	(2)
3. C_{cr} (ml/min)	49	51	55	51	43
$U_{Na}V$ (μeq/min)	35	404	1083	1103	557
Plasma oxytocin (μU/ml)	<12	<6	<12	43 ± 7	58 ± 3
	(2)	(1)	(1)	(3)	(2)
4. C_{cr} (ml/min)	55	65	80	83	73
$U_{Na}V$ (μeq/min)	10	690	1520	1323	538
Plasma oxytocin (μU/ml)	<9	<8	<12	56 ± 0	60 ± 0
	(2)	(1)	(1)	(2)	(2)
5. C_{cr} (ml/min)	57	67	70	65	57
$U_{Na}V$ (μeq/min)	55	604	1132	1026	803
Plasma oxytocin (μU/ml)	9 ± 2	16 ± 3	15 ± 3	105 ±10	88 ±13
	(3)	(2)	(2)	(2)	(2)
6. Plasma oxytocin (μU/ml)	47 ± 3	40 ± 6	47 ±15	—	—
	(3)	(3)	(3)		
7. Plasma oxytocin (μU/ml)	87 ±17	35 ±10	10 ± 2	—	—
	(3)	(2)	(2)		
8. Plasma oxytocin (μU/ml)	67 ± 9	47 ± 2	12 ± 2	—	—
	(4)	(3)	(5)		

[a] C_{cr} = exogenous creatinine clearance, $U_{Na}V$ = sodium excretion, UV = urine volume. Each data point for C_{cr} and $U_{Na}V$ is the mean of three clearance periods. The values for oxytocin are the mean ± SE of several assay values obtained in 1–3 rats. The number of rats used is given in parentheses.

Discussion. The mechanisms underlying the depressed tubular sodium reabsorption are not well delineated. It is believed that a hormonal factor is, at least in part, responsible for this natriuresis. The nature of such a natriuretic hormone is not known. Evidence exists that the hypothalamus may release a polypeptide which can induce natriuresis (4). Oxytocin, a polypeptide, has natriuretic properties in certain animal species (5–8). It was suggested that the action of oxytocin on the renal excretion of sodium might be either a direct one or by stimulating other areas of the central nervous system which secondarily change the renal handling of sodium.

The data from the present study demonstrate that extracellular expansion and the associated high rates of sodium excretion were not accompanied by a simultaneous detectable rise in oxytocin levels of the jugular blood in 5 of 8 experiments and in 2 (no. 2 and 5) out of the remaining three, the rise in oxytocin was only slight. These results suggest that extracellular expansion does not enhance oxytocin secretion. It is possible, however, that an increased secretion of oxytocin

could not be detected if the hormone is being metabolized at a similar rate as it is being released. This postulate seems unlikely since it implies a simultaneous increase in the rate of oxytocin degradation; a process which will defeat the purpose of the increased secretory rate of the hormone.

The failure of the infusion of oxytocin (i) to augment sodium excretion while extracellular volume expansion was not increased by keeping the rate of saline infusion equal to urine flow, and (ii) to prevent the drop in urinary sodium as volume expansion was falling, further suggest that oxytocin is not an important factor in the natriuresis of extracellular volume expansion.

Our results do not necessarily contradict the reported data demonstrating a natriuretic action for oxytocin (5–8). First, it should be emphasized that in most studies the natriuretic response was produced by the injection of oxytocin to cerebral circulation or directly into the third cerebral ventricle. Second, the magnitude of the natriuresis reported after such injections of oxytocin to rats or dogs is small. It is possible, therefore, that the infusion of oxytocin into the systemic circulation in our studies either has no natriuretic effect or caused a small increment in sodium excretion which was masked by the marked changes in urinary sodium induced by volume expansion.

Summary. The effect of extracellular volume expansion on the oxytocin levels in jugular blood and the influence of oxytocin infusion on sodium excretion as the degree of volume expansion was varied, were evaluated in 8 anesthetized dogs. Extracellular volume expansion was not associated by a simualtneous rise in blood levels of oxytocin in 5 of the 8 dogs studied. Oxytocin infusion did not enhance sodium excretion during a steady state volume expansion and was unable to prevent the fall in urinary sodium as volume expansion was falling. The results indicate that oxytocin does not play an important role in the natriuresis of extracellular volume expansion.

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