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SODIUM AND WATER METABOLISM UNDER THE INFLUENCE OF PROLACTIN, ALDOSTERONE, AND ANTIDIURETIC HORMONE

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SUMMARY

1. Rabbits were placed in metabolism cages in order to measure their intakes of food, water, and sodium chloride (as 1 % saline solution), and to measure urinary and faecal excretion of sodium, potassium, and water.

2. Antidiuretic hormone (0·2 i.u./day) caused a reduction in urine volume and no change in sodium excretion. There was full compensatory reduction in water intake so that no accumulation of water occurred.

3. Aldosterone (4 mg/day) caused a reduction in renal sodium excretion for 1–2 days. The saline intake was reduced, though this was insufficient to prevent some sodium accumulation.

4. Renal mineralocorticoid 'escape' resulted in a large increase in sodium excretion at the end of the aldosterone treatment period. This was fully compensated through increased saline intake, and balance was maintained.

5. Prolactin (200 i.u./day) caused a reduction in urine volume and in renal sodium excretion and since there were no compensatory changes in water and sodium intake, this led to substantial accumulation of both water and sodium.

6. The effects of smaller doses of both aldosterone and prolactin were investigated and found to be similar but smaller.

7. It is suggested that whereas prolactin may have little or no role to play in the sodium homoeostasis of the normal animal, the hormone may well be responsible for the substantial increase in body fluids in pregnancy.

INTRODUCTION

Although there have been many studies showing that mineralocorticoid steroids enhance salt appetite (Rice & Richter, 1943; Herxheimer & Woodbury, 1960; Wolf & Handal, 1966; Weisinger & Woods, 1971), these experiments did not include simultaneous measurement of sodium excretion. Denton (1967), reviewing the evidence for mineralocorticoid induced salt appetite concluded that the salt appetite mechanism is less sensitive than the kidney to mineralocorticoid stimulation. However, two years later Denton, Nelson, Orchard & Weller (1969) demonstrated salt appetite stimulation with doses of desoxycorticosterone which apparently caused no change in renal sodium excretion.

Sodium depletion following adrenalectomy is a powerful stimulus to sodium ingestion, but subsequent mineralocorticoid replacement was shown to reduce saline

intake to that of normal animals when lower doses were used, though increased saline intake was observed with the highest doses (Fregly & Waters, 1966). In addition, patients suffering from Conn's syndrome and having a high circulating aldosterone titre do not typically exhibit either excessive sodium intake or salt craving (Denton *et al.* 1969). Although mineralocorticoids are capable of altering sodium intake under certain conditions, the relationship of this effect to the simultaneous sodium excretion is far from clear, and the physiological importance of these hormones in the regulation of sodium intake is in doubt (Fitzsimons, 1975).

Kozłowski & Szczepanska-Sadowska (1975) have looked for a role for antidiuretic hormone in the control of water intake. They found that in the dog antidiuretic hormone increased the osmotic sensitivity of the thirst mechanism, but did not cause drinking. Neither did antidiuretic hormone stimulate water intake in the rat.

Prolactin has been shown to reduce sodium and water excretion in the perfused cat kidney (Lockett, 1965), and in rat (Lockett & Nail, 1965), man (Horrobin, Burstyn, Lloyd, Durkin, Lipton & Muiruri, 1971) sheep (Burstyn, Horrobin & Manku, 1972), and rabbit (Burstyn, McKillop & Lloyd, 1974). The administration of prolactin to human volunteers gave rise to a sensation of thirst and salt craving in some individuals (Horrobin *et al.* 1971). Shulkes, Covelli, Denton & Nelson (1972) reported that prolactin caused a substantial increase in the sodium intake of rabbits, but they, in disagreement with previous workers, observed increased renal sodium excretion during treatment.

Experiments were performed here to verify the renal sodium retaining action of prolactin in rabbits, and to look for concomitant changes in their sodium intake. In addition, groups of animals were treated with doses of aldosterone and antidiuretic hormone selected to cause changes in renal sodium and water excretion similar to those caused by prolactin. The effects of these three hormones on thirst and salt appetite, and hence on water and sodium metabolism, could then be compared.

METHODS

Rabbits were housed in metabolism cages permitting the separate collection of urine and faeces. The animals were given two drinking bottles, one containing water, and the other 1% saline (w/v). The bottles were equipped with ball valve nozzles, and the drips were collected. The positions of the bottles were exchanged at intervals of 2–4 days to ensure that the animals chose on the basis of taste rather than location.

The urine was collected at a fixed time each day and analysed for sodium and potassium content by flame photometry. The daily faeces were weighed, and samples preserved for analysis. These samples were oven-dried to determine water content, and then dissolved in hot nitric acid for sodium and potassium measurement by flame photometry. Water and saline intakes were measured daily by weighing to the nearest gram, and subtracting spillage. Food intake was determined by weight, and samples of food were analysed periodically for sodium and potassium content in the same way as the faecal samples. The animals were weighed daily to the nearest 5 g.

Each experiment was preceeded by a long period of 1–2 months during which the animals became accustomed to drink from both water and saline bottles. The animals were handled to tame them, but no measurements were made at this time. The experiments all began with a control period of two weeks duration, the last 5–9 days of which were selected to yield mean control values of all the measured variables. The animals were injected with hormone-free vehicle for the last 3 days of the control period. The experimental period was of 5 or 10 days duration, during which the animals were injected with hormone twice daily. The experimental period was followed by a second control period of 7–9 days, during the first 3 days of which the animals were injected with hormone-free vehicle.

The prolactin (ovine prolactin, Ferring) was injected in an aqueous medium buffered to pH 8. One mg of this preparation is approximately equivalent to 25 i.u. The aldosterone (D-aldosterone-free alcohol, Ciba) was injected dissolved in arachis oil. Dissolution was assisted by ultrasonic emulsification for 20–30 sec. The antidiuretic hormone (Pitressin tannate in oil, kindly donated by Parke-Davis) was diluted to appropriate strength with arachis oil. All injections were given in a volume of either 0·2 or 0·25 ml., I.M., into a hind leg.

All the results were expressed as mean values over a stated period of time, averaged for all of the animals in the group. In two experiments, the experimental periods were further subdivided to conform to the pattern of response of the animals.

Sodium balance was computed simply by subtracting the total excretion from the total intake. Water balance is not so accurately determined owing to cutaneous and respiratory evaporation. Therefore water balance was estimated by subtracting excretion from intake in the control period to obtain a value for insensible water loss. This value was subtracted from the difference between intake and excretion in subsequent experimental periods to yield an estimate for water balance. This procedure assumed that water losses remained constant during the experimental treatments.

Blood samples were taken from the animals at the end of the control period and at the end of the experimental treatment. This was done only in the two prolactin experiments. The plasma was analysed for sodium and potassium concentration.

In all the experiments, the results were examined by the paired t test, and, in the Figures, where statistical significance is achieved, the value of P is given.

RESULTS

Prolactin was administered at two dose levels. The high dose of prolactin (200 i.u./day for 5 days, seven rabbits) reduced urine volume, but left the water intake virtually unchanged (Fig. 1). This gave rise to a large accumulation of water. The animals' weight gain for the whole period of treatment was small and not statistically significant owing to loss of appetite during the final 2–3 days of treatment (Table 1). However, the weight gain for the first 2 days of treatment, when food intake was normal, was 24 ± 8 g/day ($P < 0{\cdot}05$).

In the post-experimental period, both urine volume and water intake increased to slightly above control values. Appetite improved promptly, and food intake also increased to above control values. Although the animals were apparently in water balance, some of the previously accumulated water may have been lost because body weight remained constant despite the increased appetite.

The dose of antidiuretic hormone (0·2 i.u./day for 5 days, seven rabbits) was chosen to match closely the reduction in renal water excretion produced by the high dose of prolactin. The reduction in urine volume and in water intake were similar, resulting in small and not statistically significant increases in both water balance and body weight (Table 1). Sodium excretion, intake, and balance were unaltered by antidiuretic hormone. All parameters returned to control values in the post experimental period.

The high dose of prolactin reduced renal sodium excretion, leaving the saline intake unchanged (Fig. 2). This resulted in a very large accumulation of sodium (Table 2).

In the post-experimental period, sodium excretion returned to control values, leaving the animals very nearly in sodium balance. The sodium previously accumulated was not excreted during the period of observation.

Aldosterone was administered at two dose levels. The high dose of aldosterone was chosen to match closely the reduction in renal sodium excretion produced by the high dose of prolactin. This dose (4 mg/day for 5 days, six rabbits) reduced the renal

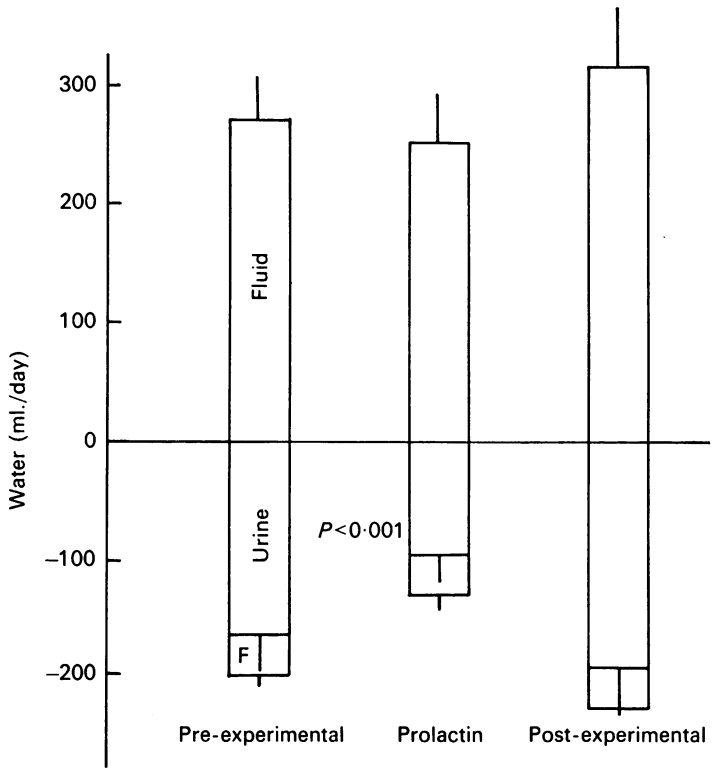

Fig. 1. The effects of 200 i.u./day prolactin on the water intake and excretion of seven animals. Fluid was water plus saline, F represents faecal water. The pre-experimental period was 7 days, prolactin was administered for 5 days, and the post-experimental period was 8 days. P values refer to statistical significance between the experimental and the pre-experimental data as determined by a paired t test.

TABLE 1. Comparison between the changes in renal water excretion, water intake, and estimated water balance after treatment with antidiuretic hormone (0·2 i.u/day), or prolactin (200 i.u./day or 20 i.u./day*). The values given are followed by their standard errors, and the % changes are given in brackets below. The statistical significance of the changes was determined by paired t test from which the P value is given unless it is not significant (n.s.)

Change from control value	Antidiuretic hormone 0·2 i.u./day	Prolactin 200 i.u./day	Prolactin 20 i.u./day
Urine volume ml./day	−51·0 ± 9·8 (−35%) $P < 0·01$	−67·2 ± 12·8 (−41%) $P < 0·001$	−15·0 ± 7·0 (−17%) $P < 0·05$
Water intake ml./day	−54·5 ± 9·6 (−20%) $P < 0·01$	−19·5 ± 10·4 (−7%) n.s.	−9·6 ± 4·5 (−4%) n.s.
Water balance ml./day	9·0 ± 6·0 n.s.	37·0 ± 6·0 $P < 0·01$	13·5 ± 5·5 $P < 0·05$
Weight g/day	6 ± 11 n.s.	5 ± 8 (see text)	15 ± 5·5 $P < 0·05$

* First 3 days of treatment only.

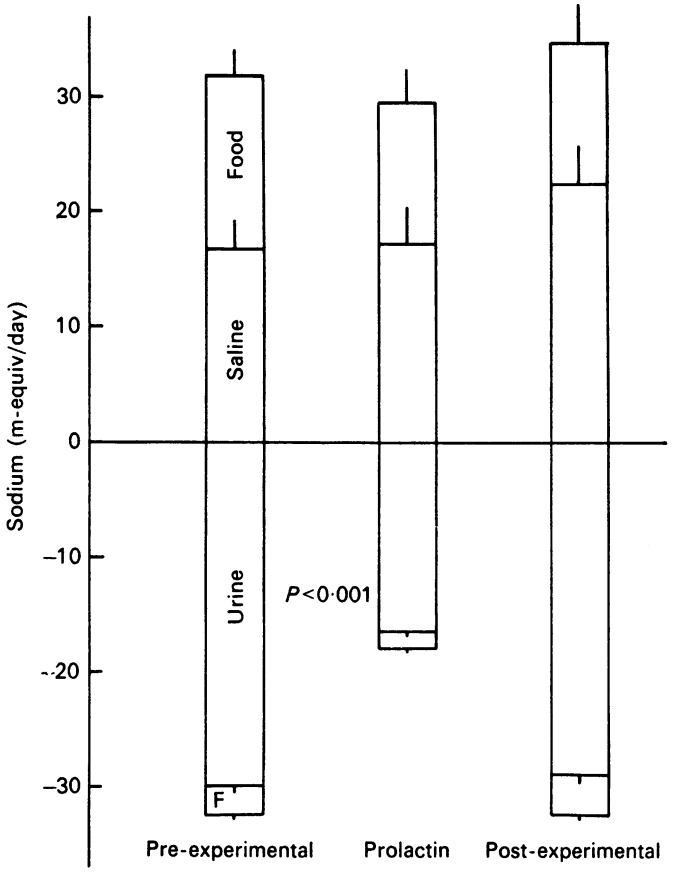

Fig. 2. The effects of 200 i.u./day prolactin on the sodium intake and excretion of seven animals. Food indicates dietary sodium, F represents faecal sodium. The pre-experimental period was 7 days. Prolactin was administered for 5 days, and the post-experimental period was 8 days. The *P* values are as in Fig. 1.

TABLE 2. Comparison between the changes in renal sodium excretion, voluntary sodium (saline) intake, and sodium balance after treatment with aldosterone (4·0* or 0·25 mg/day), or prolactin (200 or 20 i.u./day*). The values given are followed by their standard errors, and the % changes are given in brackets below. The statistical significance of the changes was determined by paired *t* test from which the *P* value is given unless it is not significant (n.s.)

Change from control value	Aldosterone 4·0 mg/day	Prolactin 200 i.u./day	Aldosterone 0·25 mg/day	Prolactin 20 i.u./day
Urine sodium m-equiv/day	$-6·8 \pm 0·9$ (−48%) $P < 0·01$	$-13·3 \pm 3·1$ (−45%) $P < 0·001$	$-5·4 \pm 1·3$ (−27%) $P < 0·05$	$-5·5 \pm 1·5$ (−21%) $P < 0·01$
Saline intake m-equiv/day	$-2·9 \pm 1·2$ (−52%) $P < 0·05$	$0·5 \pm 4·4$ (3%) n.s.	$-3·9 \pm 1·4$ (−65%) $P < 0·05$	$-4·3 \pm 2·6$ (−16%) n.s.
Sodium balance m-equiv/day	$4·6 \pm 2·3$ n.s.	$12·3 \pm 2·8$ $P < 0·01$	$2·7 \pm 1·2$ n.s.	$0·8 \pm 1·8$ n.s.

* The data is given only for the reduced renal sodium excretion phase of the hormone's action.

sodium excretion in five of the six rabbits for 1 or 2 days (Table 2). For the remainder of the period of treatment (and for the whole of the treatment period in one animal) the renal sodium excretion was increased 75 % ± 25 ($P < 0{\cdot}05$) above control values. During the sodium retention phase of the aldosterone response the saline consumption was halved (Table 2) and there was some sodium retention, though this was not statistically significant. During the phase of increased renal sodium excretion (+94 % ± 17, $P < 0{\cdot}05$) the saline intake was increased by 150 % ± 48 ($P < 0{\cdot}05$) and the animals were in sodium balance. Faecal sodium excretion was approximately halved in all animals ($P < 0{\cdot}02$).

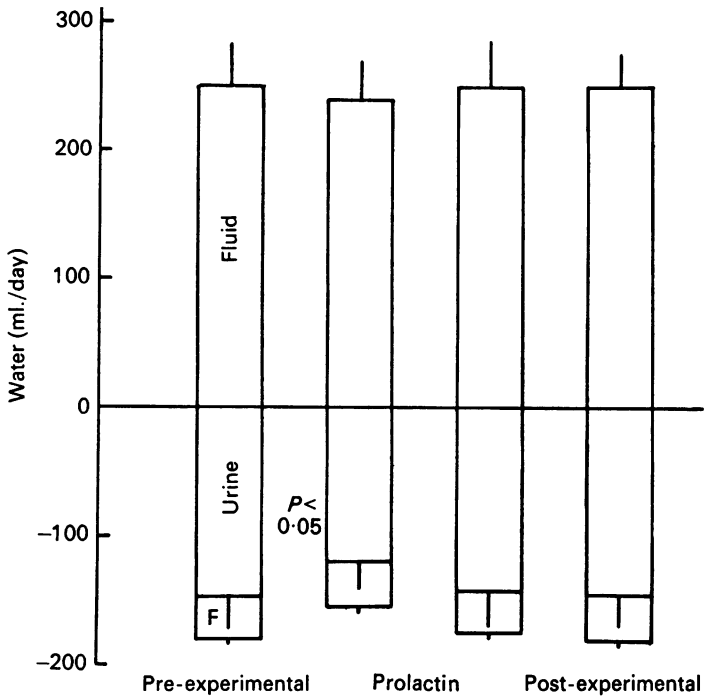

Fig. 3. The effects of 20 i.u./day prolactin on the water intake and excretion of seven animals. Fluid was water plus saline, F represents faecal water. The pre-experimental period was 8 days. The 10 day treatment period was divided into a 3 day phase of reduced renal water excretion and a 7 day phase during which renal water excretion had returned to control values. The post-experimental period was 8 days. The P values are as in Fig. 1.

The magnitude and duration of the initial period of reduced renal sodium excretion was related to the sodium intake of the animals. The animals which consumed least sodium in the control period showed the largest and longest lasting reduction in sodium excretion. The animal with the highest sodium intake responded to this dose of aldosterone with increased sodium excretion on the first day.

During the post-experimental period, sodium excretion and intake returned to control values. Initially, there was some loss of sodium, though this was not statistically significant.

The low dose of prolactin (20 i.u./day for 10 days, seven rabbits) reduced urine

volume, but left the water intake virtually unchanged (Fig. 3), resulting in water accumulation which was well matched by weight gain (Table 1). The water accumulation persisted for 3 days of treatment. In the remaining 7 days, urine volume returned to control values, and the animals were in water balance. There was some water loss in the first 2 days of the post-experimental period through increased urine volume and reduced water intake.

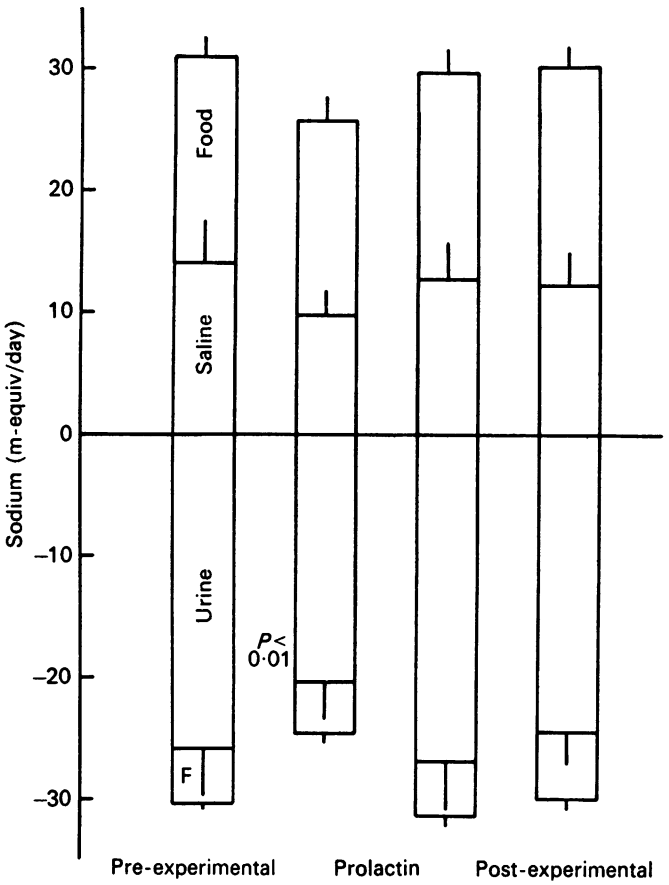

Fig. 4. The effects of 20 i.u./day prolactin on the sodium intake and excretion of seven animals. Food indicates dietary sodium, F represents faecal sodium. The pre-experimental period was 8 days. The 10 day treatment period was divided into a 3 day phase of reduced renal sodium excretion and a 7 day phase during which renal sodium excretion had returned to control values. The post-experimental period was 8 days. The *P* values are as in Fig. 1.

The low dose of prolactin reduced renal sodium excretion, and this was accompanied by a similar reduction in saline intake (Fig. 4), resulting in a trifling sodium accumulation for the first 3 days of treatment (Table 2). In the remaining 7 days both renal sodium excretion and saline intake returned to control values and the animals were in sodium balance. In the post-experimental period, there was an initial slight sodium loss, followed by a positive sodium balance caused by increased food consumption and weight gain.

The low dose of aldosterone was chosen to match the reduction in renal sodium excretion produced by the low dose of prolactin. This dose (0·25 mg/day for 3 days) reduced renal sodium excretion in four animals, increased sodium excretion in one animal, and had no effect on seven animals. The four animals responding with reduced renal sodium excretion also reduced their saline intake so that sodium accumulation was small and not statistically significant (Table 2). The single animal increased renal sodium excretion by 200 % and saline intake by 400 %, remaining in sodium balance. Its saline intake was three times the mean value for the rest of this group. The seven animals not responding to that dose of aldosterone exhibited no change in saline consumption and a slight sodium accumulation of $1·9 \pm 1·3$ m-equiv/day (not significant). All of the animals approximately halved their faecal sodium excretion ($P < 0·02$). There was no consistent change in water excretion, intake, or balance in this group of animals with the exception of the single individual whose sodium excretion was increased. In this animal urine volume increased by 65 % and water intake by 36 %. There was an estimated water loss of 35 ml./day which agreed well with the simultaneous weight loss of 40 g/day.

TABLE 3. Plasma sodium and potassium concentrations before and after treatment with two doses of prolactin. The changes with the high dose are not statistically significant

	Na^+ (m-equiv/l.)		K^+ (m-equiv/l.)	
	Control	Prolactin	Control	Prolactin
200 i.u./day	$141·4 \pm 0·4$	$142·6 \pm 0·6$	$4·33 \pm 0·28$	$3·14 \pm 0·34$
20 i.u./day	$149·3 \pm 1·9$	$126·4 \pm 1·7$ ($P < 0·001$)	$5·60 \pm 0·26$	$6·69 \pm 0·23$ ($P < 0·02$)

Plasma sodium and potassium concentrations were measured in the prolactin treated animals only (Table 3). The high dose of prolactin caused no statistically significant change in either the plasma sodium or potassium concentration. The low dose of prolactin caused a large reduction in the plasma sodium concentration, an expected consequence of water accumulation in the absence of sodium accumulation. The plasma potassium concentration was reduced.

The change in voluntary sodium intake (saline consumption) was compared to the change in renal sodium excretion for both doses of aldosterone and both doses of prolactin. The correlation coefficients (r) and the probability that these arose by chance (P) were calculated. The two doses of aldosterone were taken together since there was no significant sodium accumulation with either dose, and $r = 0·89$, and $P < 0·001$, showing that voluntary intake closely parallels renal sodium excretion.

With the low dose of prolactin results gave $r = 0·70$ ($0·05 < P < 0·10$), showing that here voluntary sodium intake is far less closely related to renal sodium excretion despite the absence of any sodium accumulation. With the high dose of prolactin, where there was considerable sodium accumulation, $r = 0·67$, and $P = 0·10$, showing that voluntary sodium intake is virtually independent of renal sodium excretion.

Similarly, changes in water intake were compared to changes in urine volume for both doses of prolactin and for antidiuretic hormone. With antidiuretic hormone there was no significant accumulation of water, and $r = 0·86$, and $P < 0·02$, showing that water intake and excretion are closely related. With the two prolactin doses

taken together, both having caused significant water accumulation, $r = 0{\cdot}46$, and $P = 0{\cdot}10$, showing that water intake is virtually independent of water excretion.

Neither of the prolactin treatments, nor the low dose of aldosterone, nor antidiuretic hormone caused any consistent change in the renal potassium excretion. The high dose of aldosterone produced a fall in potassium excretion from $23{\cdot}9 + 9$ to $14{\cdot}9 + 6$ m-equiv/day (not significant), upon withdrawal of hormone treatment.

DISCUSSION

The results reported here indicate differences between the actions of prolactin and antidiuretic hormone on water metabolism, and between prolactin and aldosterone on sodium metabolism.

The reduction in renal water excretion caused by antidiuretic hormone was accompanied by, and well correlated with, the reduction in water intake, preventing any statistically significant accumulation of fluid by the animals (Table 1). In contrast to this, much the same reduction in renal water excretion was caused by the larger prolactin dose. This was associated with an unchanged water intake so that the animals gained a substantial volume of water. The smaller dose of prolactin produced qualitatively similar results (Table 1).

Kozłowski & Szczepanska-Sadowska (1975) reported that I.V. antidiuretic hormone has no direct effect on spontaneous water intake. This suggests that the reduction in water intake during chronic treatment with antidiuretic hormone is a compensatory response to the smaller renal water excretion, and not a primary action of the hormone. On the other hand, the reduction in renal water excretion caused by prolactin was uncompensated, indicating that prolactin may have a direct effect on thirst.

The reduction, and subsequent increase in renal sodium excretion caused by the higher dose of aldosterone were accompanied by a reduction, and subsequently, an increase in saline consumption. Similarly, the lower dose of aldosterone caused parallel changes to occur in both renal excretion and intake of sodium. There was some accumulation of sodium observed with both doses of aldosterone, but these were not statistically significant (Table 2).

Chronic mineralocorticoid treatment greatly elevates saline consumption (Rice & Richter, 1943; Gross & Schmidt, 1958; Hall & Hall, 1968). However, none of these authors described the changes in saline consumption during the first days of treatment, nor made any estimates of sodium excretion. It is likely that their animals were in the 'escape' phase of mineralocorticoid response, and that their results do not differ from those reported here. Moreover, apart from the experiments of Gross & Schmidt, in which mineralocorticoids produced oedema, ascites, and rapid death, the other authors reported no obvious fluid accumulations in their animals as gauged by rapid weight gains. Likewise, neither volunteers treated with large doses of aldosterone, nor patients with primary aldosteronism suffer large fluid accumulations (August, Nelson & Thorn, 1958; Ross, 1975, p. 84), which again agrees with the results reported here.

Therefore, although mineralocorticoids may be able to stimulate salt appetite directly (Wolf & Handal, 1968; Weisinger & Woods, 1971), they do not seem to

produce large accumulations of fluid in the body. Prolactin, on the other hand, caused substantial accumulation of fluid in the experiments reported here. The low dose caused the accumulation of hypotonic fluid so that plasma sodium concentration fell. The high dose caused the accumulation of fluid with an excess of sodium. Since the plasma sodium concentration remained unchanged, some of the excess sodium must have been stored outside the extracellular compartment.

It must be pointed out that mineralocorticoids do not always increase salt appetite. Rice & Richter (1943) produced indirect evidence that desoxycorticosterone reduced salt appetite in animals maintained on sodium deficient diets. Fregly & Waters (1965) showed that in adrenalectomized animals, replacement doses of aldosterone reduced saline intake, though large doses increased it. Weisinger & Woods (1971) reported that animals raised with constant access to saline did not respond to aldosterone with increased salt appetite. In the experiments described here, aldosterone reduced saline intake initially, increasing it only in animals which had moved into the 'escape' phase of the mineralocorticoid response.

The role of prolactin in the normal regulation of body fluid balance is not established. Buckman & Peake (1973), and Buckman, Kaminsky, Conway & Peake (1973) have reported that plasma prolactin levels are suppressed in hydration. According to the results reported here, this would assist in the excretion of the water load. On the other hand, Adler, Noel, Wartofskoy & Frantz (1975), and Berl, Brautbar, Ben-David, Czaczkes & Kleeman (1976) have been unable to substantiate these observations, and deny prolactin a role in normal body fluid homoeostasis.

It is known that blood volume and total body water increase substantially in pregnancy, most of the increase occurring in the third trimester (Tatum, 1953; Campbell & MacGillivray, 1972). During pregnancy, plasma prolactin titres increase tenfold, the bulk of the increase occurring in the third trimester (Berle & Apostolakis, 1971; Tyson, Hwang, Guyda & Friesen, 1972; L'Hermite, Stauric & Robyn, 1972). Moreover, in pregnancy, relatively more water than sodium is gained (Gray, Munro, Sims, Meeker, Solomon & Watanabe, 1964), resulting in hyponatremia (Newman, 1957). A similar hyponatremia has been observed in the pregnant rat (Lichton, 1961), and in the pregnant rabbit (P. G. Burstyn, unpublished).

In the results reported here, the high dose of prolactin caused relatively greater sodium accumulation than water accumulation, but no change in plasma sodium concentration. However, the low dose of prolactin resulted in water accumulation only, and a substantial decrease in plasma sodium concentration. It is obviously not possible to relate the dose of ovine prolactin used in these experiments on rabbits with the plasma concentrations of human prolactin found in pregnancy. In view of the results reported here, and the increase in total body water in prolactin-treated rabbits (Lloyd, 1973) and rats (P. G. Burstyn, unpublished) it seems possible that prolactin is responsible for at least some of the fluid accumulation in pregnancy.

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