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THE EFFECT OF A HIGH WATER INTAKE ON THE KIDNEY'S ABILITY TO CONCENTRATE THE URINE IN MAN

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In compulsive polydipsia the kidney's ability to concentrate the urine, in response to parenteral pitressin or to fluid deprivation, may be decreased (de Wardener, 1956). This paper shows that a similar decrease occurred in two normal subjects after drinking about 10 l. of water a day for eleven days.

METHODS

Experimental procedure

The experiments were made on two men, subject 1, aged forty, weighing 82·5 kg, and subject 2, aged thirty, weighing 65·8 kg. The observations covered an uninterrupted period of 22 days (28 May–18 June 1956), which was divided into three parts. The first (the control period), during which the water intake was normal, lasted 5 days in subject 1 and 6 days in subject 2; the second (the experimental period), in which the intake of water (in addition to tea and coffee) was 10–12 l./24 hr in subject 1 and 7·5–9 l./24 hr in subject 2, continued for 12 days; the third (the post-experimental period) began with an initial period of 26 hr fluid deprivation, and ended with a period of normal water intake lasting 4 days in subject 1, and 3 days in subject 2. As far as was possible both subjects carried on with their normal activities throughout the 22 days.

During the control period and the latter part of the post-experimental period, the intake of fluids (including tea and coffee) was only governed by the subjects' inclinations, and was not measured. During the experimental period the average intake of water was approximately the same for both subjects (122 and 124 ml./kg/24 hr); the consumption of tea and coffee was about the same as in the control period. The intake of water was spread fairly evenly throughout the 24 hr; 250–500 ml. was taken every 30–60 min, except for two interruptions, one of 2½ hr from 5 to 7.30 p.m., and the other, during the night, lasting 4 hr in subject 1, and up to 5 hr in subject 2. Alcohol was not taken during the experiment.

Lunch, tea and dinner were prepared without added salt by the hospital diet kitchen. These meals were the same for both subjects, and, apart from minor variations in the type of vegetable and fruit, were the same every day. Breakfasts (toast, butter and tea) were eaten at home but were slightly different for the two subjects. All food was weighed and its composition calculated from the tables of McCance & Widdowson (1946). The average dietary intake of calories per day was 1720 in subject 1 and 2070 in subject 2; of protein 56 g in subject 1, and 62 g in subject 2; and of sodium 59 m-equiv in subject 1 and 72 m-equiv in subject 2. In addition, the subjects were allowed to add as much salt as they wished, the salt-cellars being weighed and refilled each day by a third person.

Urine was collected in 24 hr periods from 8 a.m. The volume, osmolarity, and the sodium and creatinine content were measured daily. The daily sodium balance was calculated by adding the dietary sodium intake to the sodium taken from the salt-cellar, and subtracting the sodium excreted in the urine; sodium losses in the faeces and sweat were not included. In the experimental period, when the urine output was about 10 l./day, the bladder was emptied at intervals of 30–45 min during the waking hours; freedom of movement was only obtained by carrying about suitable containers. Each subject was weighed between 7 and 7.30 p.m., no fluid having been taken for 2 hr. The bladder was emptied immediately before weighing.

Renal function tests

The ability of the kidneys to concentrate the urine was measured (*a*) during an infusion of pitressin, (*b*) during a mannitol osmotic diuresis, induced while pitressin was being infused, and (*c*) following deprivation of fluids. These tests were performed before, and at the end of the period of high water intake.

On the fourth day of the control period each subject was given 50 m-u. of pitressin I.V. in 30 sec, followed by an intravenous infusion (antecubital vein) of 3 m-u./min for 1 hr. At the end of the hour the infusion was continued at the same rate, and in addition 600 ml. (subject 1) and 450 ml. (subject 2) of 25% mannitol was given intravenously at the rate of 10 ml./min into the other arm. The bladder was emptied naturally 10 min after the beginning of the pitressin infusion, and at 15–20 min intervals thereafter. Blood was collected immediately before and at the end of the mannitol infusion.

This procedure was repeated on the twelfth day of the experimental period (i.e. after 11 days of high water intake), but with greater amounts of pitressin and mannitol. Subject 1 received 200 m-u. pitressin followed by 4 m-u./min and 675 ml. of 25% mannitol; subject 2 was given 100 m-u. pitressin followed by 4 m-u./min and 575 ml. of the mannitol solution. The high water intake continued until the beginning of the pitressin infusion. Urine was collected at 10 min intervals through an indwelling catheter in the bladder.

The fluid deprivation test was first performed four weeks before the experiment was begun, and repeated on the twelfth day of the experimental period, immediately after the second pitressin mannitol test. Fluids were withheld for 26 hr ending at 7.30 p.m. The urines that have been compared were collected during the last 2–3 hr of each period of fluid deprivation.

The daily creatinine clearance was measured throughout the experiment.

Other observations. Plasma osmolarity and plasma sodium and potassium concentrations were measured on 2 days during the control period, on 4 days in the experimental period, and on 2 days in the post-experimental period. The bromide space, haematocrit value, plasma proteins, chloride and bicarbonate, and the blood urea were estimated on the third day of the control period and the eleventh day of the experimental period.

Analytical methods. Sodium and potassium were measured with a flame photometer; osmolarity was calculated from measurement of the freezing-point depression (de Wardener & del Greco, 1955); plasma and urine creatinine were determined by the method of Bonsnes & Taussky (1945); plasma proteins by that of Harrison (1947); and plasma chloride, plasma bicarbonate and blood urea by those of Peters & Van Slyke (1932). The bromide space was calculated from the plasma ^{82}Br concentration 24 hr after an oral dose (Gamble, Robertson, Hannigan, Foster & Farr, 1953).

RESULTS

Renal function

Concentrating capacity

At the end of the experimental period the ability to concentrate the urine was grossly impaired in both subjects. The results are shown in Table 1 and Figs. 1–3.

TABLE 1. Urine and plasma osmolarity, urine flow and solute output following the intravenous administration of pitressin, and after a 26 hr period of fluid deprivation; each test was performed before, and at the end of, drinking about 10 l. of water a day for 11 days

	Subject 1				Subject 2			
	Osmolarity		Urine flow (ml./min)	Solute output (μ-osmole/min)	Osmolarity		Urine flow (ml./min)	Solute output (μ-osmole/min)
	Urine (m-osmole/l.)	Plasma (m-osmole/l.)			Urine (m-osmole/l.)	Plasma (m-osmole/l.)		
Pitressin I.V.								
Before drinking	865	287	0·42	364	885	280	0·35	310
After drinking	512	261	0·95	487	407	269	0·97	395
Fluid deprivation								
Before drinking	1042	291	0·39	407	1185	292	0·37	438
After drinking	468	292	0·58	272	453	290	0·57	258

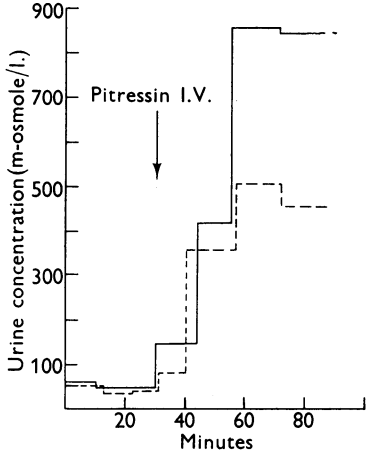

Fig. 1

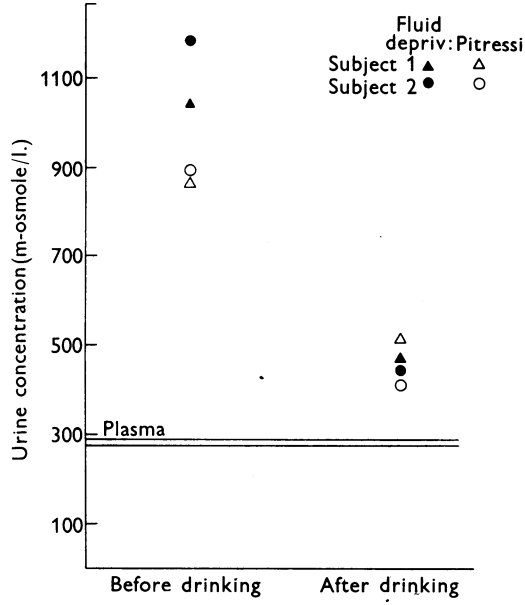

Fig. 2

Fig. 1. Subject 1. Changes in urine osmolarity following the administration of pitressin after drinking large amounts of water for varying periods, (i) for 1 hr (——), and (ii) for 11 days (- - -). The first observation was made 3 months before the second. On the first occasion pitressin was given 1 hr after drinking 1 l. water; thereafter amounts were drunk equal to the volumes of urine passed.

Fig. 2. Urine concentrations following the intravenous administration of pitressin, and after a 26 hr period of fluid deprivation, before, and at the end of, drinking about 10 l. of water a day for 11 days. The plasma osmolarity varied between the limits indicated by the two lines.

Pitressin test. During the control period the urine concentrations following the intravenous administration of pitressin were 865 m-osmole/l. in subject 1, and 885 m-osmole/l. in subject 2; at the end of the experimental period they were 512 and 407 m-osmole/l. respectively, despite the use of larger quantities of pitressin. The U/P osmolar ratios during the control, and at the end of the experimental periods, were 3·02 and 1·96 in subject 1; and 3·16 and 1·51 in subject 2. Such a change in the ability to concentrate the urine does not occur after a short period of excessive water intake (Fig. 1).

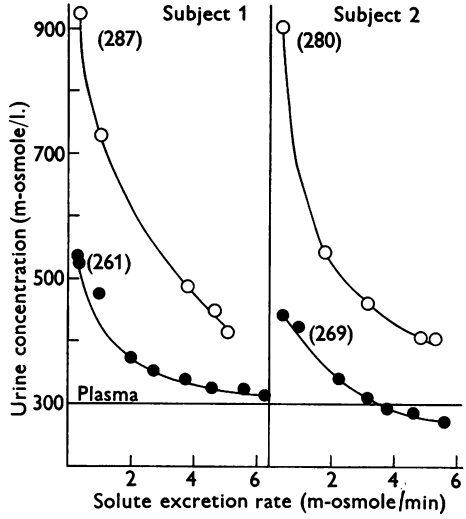

Fig. 3. Diuresis induced by a mannitol infusion during the intravenous administration of pitressin before, and at the end of drinking about 10 l. of water a day for 11 days. The individual results have been adjusted to a common plasma osmolarity of 300 m-osmole/l. by multiplying the observed urine osmolarity by $300/p$, where p is the plasma osmolarity. ○, before, and ●, after 11 days of high water intake. The plasma osmolarity at the start of each mannitol infusion is shown in brackets.

Fluid deprivation. The concentrations of the urine at the end of the control period of fluid deprivation were 1042 m-osmole/l. in subject 1, and 1185 m-osmole/l. in subject 2, whereas with fluid deprivation immediately after the experimental period they were 468 and 453 m-osmole/l. respectively, despite the fact that on this occasion the rise in plasma osmolarity (see Table 1), and the loss of weight were greater. Subject 1 lost 2·2 kg, and subject 2 lost 3·4 kg, whereas each lost 0·9 kg during the control test. The U/P osmolar ratios in the control observations and after the experimental period were 3·59 and 1·60 in subject 1; and 4·06 and 1·56 in subject 2.

Pitressin mannitol test. Fig. 3 shows the changes in urine osmolarity which occurred in this test during the control period, and at the end of the experimental period. In both subjects the urine osmolarity, over the same wide

range of solute outputs, was always greater during the control period; the difference being particularly noticeable in subject 2 in whom the urine, during the experimental period, became hypotonic to plasma at the higher rates of solute output.

Diluting capacity. The ability to dilute the urine remained unchanged throughout the experimental period; on the eleventh day of this period a specimen of urine obtained from subject 1 contained 44 m-osmole/l. and one from subject 2, 42 m-osmole/l. at urine flows of 11·5 and 13 ml./min respectively.

Creatinine clearance

During the last 3 days of the control period, when the urine flow averaged 0·97 ml./min in subject 1 and 1·04 ml./min in subject 2, the mean creatinine clearances were 83 and 87 ml./min. In the last 3 days of the experimental period, when the urine flow averaged 8·2 ml./min in subject 1 and 6·4 ml./min in subject 2, the mean creatinine clearance rose to 114 and 101 ml./min respectively.

Bromide space, plasma sodium concentration, sodium balance and weight

At the end of the experimental period both subjects showed an increase in bromide space and plasma sodium concentration, in spite of a net loss of sodium in subject 1, and no significant change in the sodium balance in subject 2. The results are shown in Figs. 4 and 5.

On the eleventh day of the experimental period the increase in the bromide space was 3·3 l. in subject 1, and 3·4 l. in subject 2. The increase in the plasma sodium concentration was 5 m-equiv/l. in subject 1, and 3 m-equiv/l. in subject 2. The net loss of sodium was 250 m-equiv in subject 1, and 8 m-equiv in subject 2. Each subject's weight fell sharply after the experimental period and thereafter remained substantially below the weight at the end of the experimental period; four days after the experimental period the change in weight was 2·0 kg in subject 1 and 1·5 kg in subject 2.

Plasma osmolarity; plasma chloride, bicarbonate, potassium and protein concentrations; blood urea concentration; packed cell volume

Excluding the days on which pitressin was administered, and the day of fluid deprivation, the plasma osmolarity during the experimental period fell from 287 to 278 m-osmole/l. in subject 1, but showed no consistent trend in subject 2.

During the experimental period the plasma chloride and blood urea concentrations were decreased in both subjects. The chloride fell from 109 to 103 m-equiv/l. in subject 1, and from 111 to 105 m-equiv/l. in subject 2; the blood urea from 23 to 16 mg/100 ml. in subject 1 and from 35 to 19 mg/100 ml.

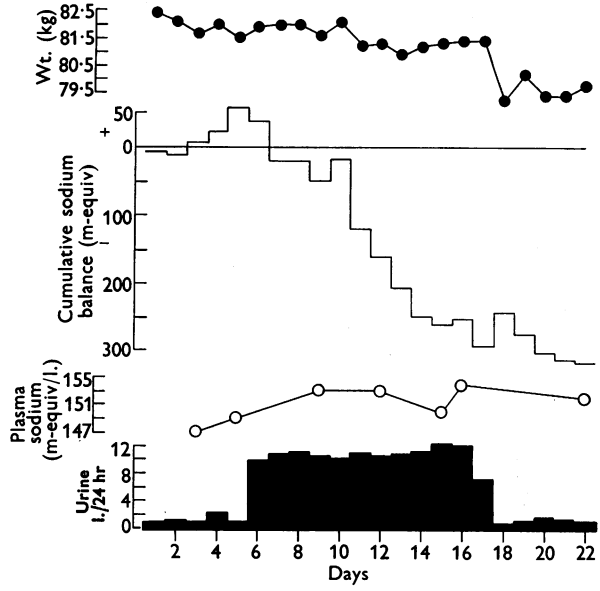

Fig. 4. Subject 1. Changes in weight, cumulative sodium balance, plasma sodium concentration and urine volume throughout the experiment. The plasma sodium concentration rose, though there was a negative cumulative sodium balance, and no change in weight.

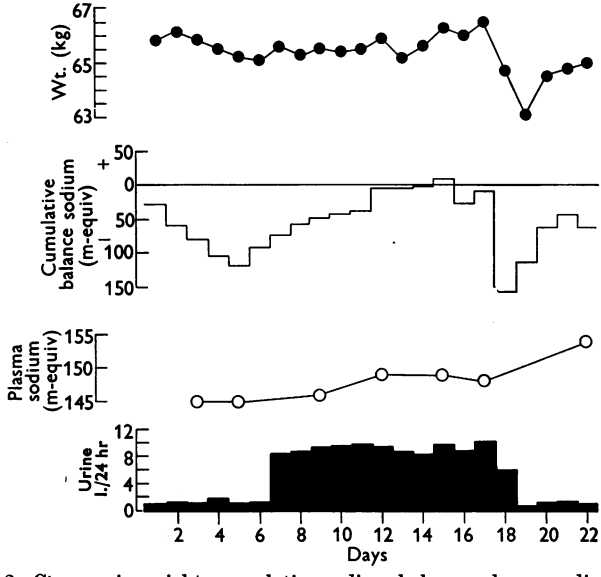

Fig. 5. Subject 2. Changes in weight, cumulative sodium balance, plasma sodium concentration and urine volume throughout the experiment. The plasma sodium concentration rose, though the cumulative sodium balance was in equilibrium and there was a slight gain in weight.

in subject 2. Changes in the concentrations of plasma bicarbonate and potassium were variable.

There was also a slight decrease in the plasma protein concentration and in the packed cell volume during the experimental period. The plasma proteins fell from 7·9 to 7·6 mg/100 ml. in subject 1, and from 7·5 to 7·1 mg/100 ml. in subject 2; the packed cell volume from 47 to 45% in subject 1, and from 47 to 44% in subject 2.

Subjective sensations during and after the experimental period

The most striking feature was a feeling of coldness associated with pallor. This varied in intensity and lasted throughout the experimental period; it continued to a less extent for 2–3 weeks thereafter. The skin was cold to touch, and during the experimental period the face was puffy.

Throughout the experimental period both subjects showed pronounced emotional lability, with alternating bouts of hilarity and moroseness; venepunctures at this time gave rise to exaggerated apprehension. During the last 6–7 days of the experimental period, simple intellectual activity became an effort.

Appetite was excellent during the experimental period, though from the second to the fourth day the food was tasteless unless large amounts of salt were added; on these days the thought of adding salt caused profuse salivation. At the beginning of the experimental period the drinking water was flavoured with fruit squashes in an attempt to make its ingestion more palatable. It was soon found, however, that plain water was just as easy to drink. The drinking of large volumes of water was found to be tedious rather than unpleasant, and the lips often felt dry without any accompanying feeling of thirst.

The beginning of the 26 hr period of fluid deprivation, which followed the experimental period, was experienced with a sense of relief and mild exhilaration, and though it followed immediately after an infusion of over 500 ml. of 25% mannitol, there was a singular lack of thirst. Later, however, there was increasing tiredness, depression, headache and thirst. Two hours after rehydration all these symptoms, except tiredness, had disappeared. During the post-experimental period there was a mild revulsion to water which continued for some days.

DISCUSSION

The results show that a period of high water intake reduced the kidney's ability to concentrate the urine over a wide range of solute excretion rates. The change in the ability to concentrate following the administration of pitressin, therefore, was due to a change in the renal tubules; that this was also the reason for the reduced concentration found after fluid deprivation is suggested by the fact that the rise in urine concentration, and the fall in urine flow which followed fluid deprivation, were almost the same as those obtained

on the preceding day with large doses of pitressin. This suggests that the limited concentrating capacity of the tubules was being used to a maximum extent on both occasions, and that with fluid deprivation therefore the release of anti-diuretic hormone was not less than normal. By contrast, in diabetes insipidus, in which the tubules respond normally to pitressin, the urine osmolarity after fluid deprivation does not approach that obtained with pitressin (Leaf, Mamby, Rasmussen & Marasco, 1952).

It is unlikely that the small increase in glomerular filtration rate that occurred during the period of high water intake was in any way responsible for the kidney's reduced ability to concentrate the urine. When the period of excess drinking ended, the filtration rate during the subsequent period of fluid deprivation was considerably lower than during the administration of pitressin, yet the urine concentrations were almost the same.

It has been previously shown that when the fluid intake is normal the concentration of the urine following the administration of pitressin is lower than after a period of fluid deprivation, and that this discrepancy is not due to any difference that may exist between pitressin and anti-diuretic hormone (Jones & de Wardener, 1956). It seems, therefore, that compared with a state of normal hydration, a high fluid intake decreases, and fluid deprivation increases, the tubule's ability to concentrate the urine in response to pitressin. It is suggested that these variations represent different aspects of the same mechanism.

The low urine concentration obtained with fluid deprivation, 24 hr after excessive drinking had ceased, demonstrates that the effects produced by this mechanism are slow to change. Similarly, following fluid deprivation, the increased ability to concentrate persists for some hours after a large drink of water is taken (Jones & de Wardener, 1956). These observations are in keeping with the fact that when the water intake is normal the kidney's ability to respond to pitressin is not influenced by an increased intake of only a few hours duration.

The cause of the diminished tubular response to pitressin following a high water intake is obscure. It does not appear to be due to sodium deficiency, changes in plasma osmolarity or plasma electrolyte concentrations, but changes in the extracellular fluid volume may be responsible.

In both subjects the increase in bromide space, the slight fall in plasma protein concentration and packed cell volume, and the sudden and maintained loss of weight after the period of high water intake, indicate that drinking large amounts of water caused an increase in the total body water and expansion of the extracellular fluid volume. As this change occurred together with an unexpected rise in plasma sodium concentration and without a positive balance of sodium, it is concluded that there was a transfer of sodium into the extracellular fluid.

There are several reports that in animals acute expansion of the extracellular fluid space by intravenous saline infusions may cause a substantial decrease in the renal response to pitressin (Mudge, Foulks & Gilman, 1949; Wesson, Anslow, Raisz, Bolomey & Ladd, 1950; del Greco & de Wardener, 1956). It is suggested that the kidney's decreased ability to concentrate after drinking large amounts of water may have been related to the expansion of the extracellular fluid space. The mechanism responsible for this change is not known, but in view of the transfer of sodium into the extracellular fluid which occurred, it is possible that changes in the electrolyte composition of the tubule cells were finally responsible.

Gamble *et al.* (1953) have reported that the ratio of the radioactive bromide space to the radioactive chloride space is 1·02, and to the sucrose space is 1·33; the greatest difference between the bromide and the chloride space in any one of their subjects was 7%. In the experiments reported here the bromide space after drinking had increased by 19% in subject 1, and 18% in subject 2. Some of the increase may have been due to a greater amount of bromide entering the cells when the second determination was made. If, however, the ratios found by Gamble *et al.* (1953) are applicable, the transfer of sodium into the extracellular fluid was 720 m-equiv in subject 1 and 410 m-equiv in subject 2. It is possible that some of this sodium came from bone. Teleologically the transfer of sodium into the extracellular fluid can be interpreted as an attempt to prevent cellular overhydration. A similar rise in plasma sodium concentration and extracellular fluid volume, without a rise in cumulative sodium balance, has been observed by Luft, Sjogren, Ikkos, Ljunggren & Tarukoski (1954), and by F. T. G. Prunty (personal communication), following the prolonged administration of deoxycorticosterone and corticotrophin.

A rise in plasma sodium concentration when drinking large quantities of water has previously been described by Kunstmann (1933), who drank similar amounts to those described here and, like subject 1, also developed a negative sodium balance. Other reports (Regnier, 1916; Strauss, 1922) in which less water was drunk, describe no change in plasma sodium concentration though on most occasions a negative sodium balance developed. The increased excretion of sodium, which produced these negative sodium balances, may be related to a decreased secretion of aldosterone, in response to the expansion of the extracellular fluid space (Bartter, Liddle, Duncan, Barber & Delea, 1956).

The subjective sensation of coldness associated with a cold, pale skin is sometimes seen in patients suffering from compulsive polydipsia soon after a sudden increase in water ingestion. It appears to be due to skin vasoconstriction, the mechanism of which is unexplained. In the experiments described here the blood pressure, electrocardiogram and electroencephalogram were unaffected by the high water intake.

Previous investigators who have studied the effect of a long period of high

water intake were investigating the stimulus for polydipsia in compulsive cases. Their main purpose was to find out whether a period of voluntary excessive drinking was followed by an addiction to water, and in some instances they reported that there was indeed some difficulty in reducing the intake of water at the end of the experiment. It is emphasized that in the present experiments the sudden cessation of water drinking was greeted with relief and that subsequently there was a mild distaste for plain water.

In conclusion, if the cause of the decreased ability to concentrate the urine in voluntary excessive drinking is the same as in compulsive polydipsia, it follows that the change in tubular function in the latter is directly related to the high water intake and not to the psychological disturbance which induces the polydipsia.

SUMMARY

1. The effect of drinking about 10 l. of water a day for 11 days has been studied in two normal subjects.

2. At the end of this period there was a considerable decrease in the kidney's ability to concentrate the urine, following either the administration of pitressin intravenously, or a period of fluid deprivation. It is concluded that the kidney's ability to concentrate the urine is related to the individual's average intake of water.

3. There was also an increase in the plasma sodium concentration and an expansion of the extracellular fluid space, without retention of sodium. It is concluded that there was a substantial transfer of sodium into the extracellular fluid.

4. It is suggested that the decrease in the kidney's ability to concentrate was related to the expansion of the extracellular fluid space.

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