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THE EFFECT OF INFUSIONS OF PLASMA AND OF SALINE ON THE RENAL RESPONSE TO WATER-LOADING IN SODIUM-DEPLETED DOGS

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SUMMARY

1. Infusion of 150 ml. of plasma to dogs acutely depleted of sodium chloride by peritoneal dialysis with glucose (5 g/100 ml.) does not restore their ability to respond by diuresis when given 2·5 % body weight of water by mouth.

2. Infusion of 300 ml. of saline (0·73 g NaCl/100 ml.) to these animals results in a brisk increase in urinary flow.

3. Infusion of 100 ml. of saline (0·73 g NaCl/100 ml.) to sodium-depleted dogs restores their ability to respond to a water-load of 2·5 % of body weight by diuresis.

4. The results are discussed and a tentative explanation put forward.

INTRODUCTION

Sonnenberg & Pearce (1962) showed that the extent of the natriuresis and diuresis occurring after blood volume expansion could be modified by the degree of hydration of the animal. Thus a dog which had been dehydrated for 24 hr would show no diuresis after blood volume expansion had occurred, whereas a dog which had been given saline by mouth some 18 hr previously would exhibit a considerable increase in urine flow. In both cases the initial blood volume and the degree of its expansion were shown to be similar. Sonnenberg & Pearce interpret these findings to mean that the renal response to blood volume expansion may be modified by the interstitial fluid volume before expansion. The saline-loaded dog would have a normal blood volume, but an increased interstitial fluid volume, whereas the dehydrated dog would have a normal blood volume, but a decreased interstitial fluid volume.

These results have relevance to some of our earlier experiments on salt-depleted dogs (Coxon & Ramsay, 1968), when the effect of giving a water-load of 2·5 % body weight to dogs immediately following peritoneal dialysis (day-one depleted dogs) and 20 hr later (day-two depleted dogs) was described. The difference in the effect of giving the water to day-one and day-two depleted dogs was seen to be accompanied by differences in their plasma and extracellular fluid volumes. In order to decide whether either of these factors plays a part in determining the response of the depleted dog to a water-load, it was decided to test the ability of the day-one depleted dog to excrete a water-load of 2·5 % body weight after prior expansion on the one hand of the blood volume and on the other hand of the extracellular fluid volume. A preliminary report of these experiments has been published (Ramsay, 1963).

METHODS

The experiments were carried out on a group of four episiotomized anoestrous bitches, weighing 15–16·8 kg. The animals were trained to lie quietly on the operating table for up to 6 hr at a time without physical restraint, and were accustomed to the passing of a stomach tube, bladder catheterization, repeated venepuncture and other minor procedures.

Salt depletion was induced as described in the previous paper (Coxon & Ramsay, 1968). The four depleted dogs were then infused with either plasma or with saline before receiving the water-load of 2·5 % of body weight. A minimum period of 10 days was allowed for recovery before using an individual dog again for these experiments.

Plasma infusion. Plasma for infusion was obtained from a sodium-depleted dog which was fully heparinized by the intravenous injection of 30–35 mg heparin/kg body wt. and then bled out through a femoral artery cannula. The plasma was separated after centrifuging the blood, and stored overnight at 4° C. All these steps were carried out using rigid aseptic techniques. Plasma obtained from the donor dog was thus similar in all important respects to the plasma of the experimental animal to be investigated.

The volume of plasma chosen for infusion was 150 ml. This was calculated from the results of previous work (Coxon & Ramsay, 1968), and was designed to increase the plasma volume of all day-one depleted dogs to that expected on the second day of depletion. The plasma was infused into a forelimb vein over a period of 20 min. Blood and urine samples were taken at 20 min intervals for the next hour. Urine samples were collected via a catheter inserted into the bladder using a careful wash-out technique which has been described previously (Ramsay & Coxon, 1967). A water-load of 2·5 % of body weight was then given by stomach tube in a single dose. Urine and blood samples were then collected at approximately 30 min intervals for at least 2½ hr.

Saline infusion. The volume of saline originally chosen for infusion before giving the water-load was 300 ml., as this would have increased the extracellular fluid volume to that expected on the second day of depletion (Coxon & Ramsay, 1968). Similarly, the concentration of the saline was 0·73 g NaCl/100 ml. (125 m-equiv. Na/l.) so that the sodium concentration of the plasma would not be altered as the result of the infusion. Control blood and urine samples were taken and 30 min later the saline infusion was given over a period of 20 min. Immediately after the infusion of this volume of saline had been completed there was a large increase in urine flow, although no water had been given. As this occurred in the first two animals used, it was decided to reduce the amount of infused saline in subsequent experiments.

The volume of saline which could be infused into the day-one depleted dogs without itself promoting an increase in urinary flow was found to be about 100 ml. Accordingly, in four day-one depleted dogs 100 ml. of sodium chloride (0·73g/100ml.) was infused into a peripheral vein over a period of 20 min. Blood and urine samples were taken at 20 min intervals for the next hour. A water-load of 2·5 % of body weight was then given by stomach tube in a single dose. Urine and blood samples were then collected at approximately 30 min intervals for at least 2½ hr.

Analytical methods were identical with those used in the preceding paper (Coxon & Ramsay, 1968).

RESULTS

Plasma infusions. These results are summarized in Table 1. Unfortunately it was only possible to measure the sodium and potassium levels in blood and urine in one of the dogs owing to the scarcity of material.

TABLE 1. Various measurements made on four day-one depleted dogs during the experiments involving the intravenous infusion of 150 ml. of 'depleted' plasma, followed 1 hr later by the administration of a water-load of 2·5 % body weight. The means and standard deviations are shown ($n = 4$ unless otherwise stated)

Observation	Value before infusion of 150 ml. plasma	Value before administration of water-load	Value 2½ hr after administration of water-load
Plasma Na^+ ($n = 1$) (m-equiv/l.)	122	122	120
Urine flow (ml./min)	0·10 ± 0·07	0·14 ± 0·10	0·10 ± 0·05
Na^+ excretion ($n = 1$) (μ-equiv/min)	4·1	8·2	11·0
K^+ excretion ($n = 1$) (μ-equiv/min)	6·8	19·6	24·7
Haematocrit (%)	66 ± 2·9	59 ± 5·5	57 ± 6·4
Plasma protein (g/100 ml)	7·68 ± 0·70	7·33 ± 0·33	7·22 ± 0·40

Administration of 150 ml. of 'depleted' plasma caused no change in the plasma sodium or osmolality in the one dog tested. Also there was no consistent change in plasma protein concentration, the infusion of plasma sometimes causing a small rise, and sometimes a small fall. The rate of urine flow was also unaffected by the infusion in all four dogs.

One hour after completion of the infusion the water-load was given, and during the following 2½ hr there was no change in urine flow. From the mean values in the table it may seem that water had not been absorbed from the gastrointestinal tract as there is no significant fall in plasma protein concentration. However, this is because the absolute values for plasma protein concentration in the four dogs varied. The mean and standard deviation of the fall in concentration was 0·58 ± 0·13 g/100 ml. plasma, showing that water-load had been absorbed from the intestine. Using the sign test (Hoel, 1962) this fall in plasma protein concentration was found to be statistically significant ($P < 0{\cdot}05$).

Thus infusion of plasma to the day-one depleted dogs did not modify the urinary response to a water-load of 2·5 % of body weight.

Infusion of 300 *ml. of sodium chloride* (0·73 *g*/100 *ml.*). These results are summarized in Table 2. The experiments were planned in the same way as those just described, the intention being to follow the infusion of saline by the administration of a water-load. However, infusion of the saline caused a considerable increase in urine flow, accompanied by a natriuresis and kaluresis. The plasma protein concentration showed a fall of 1·00 ± 0·10 g/100 ml. of plasma.

Thus, although administration of plasma plus water, a total of about 450 ml. of fluid, caused no change in urine flow in the day-one depleted dogs, intravenous infusion of 300 ml. of saline in the same animal caused an immediate diuresis (Fig. 1), accompanied by an increase in sodium and potassium excretion.

TABLE 2. Various measurements made on two day-one depleted dogs during the experiments involving intravenous infusion of 300 ml. of sodium chloride solution (0·73 g/100 ml.). The individual values are shown for the two dogs

	Value before infusion of 300 ml. NaCl (0·73 g/100 ml.)		Value 2 hr after infusion of 300 ml. NaCl (0·73 g/100 ml.)	
Observation	Dog *A*	Dog *B*	Dog *A*	Dog *B*
Urine flow (ml./min)	0·10	0·05	2·30	1·79
Sodium excretion (μ-equiv/min)	2·3	1·5	8·4	9·3
Potassium excretion (μ-equiv/min)	3·5	1·7	18·6	21·8
Haematocrit (%)	71	66	62	54
Plasma protein (g/100 ml.)	6·71	8·33	5·94	7·10

Infusion of 100 *ml. of sodium chloride* (0·73 *g*/100 *ml.*) *followed by* 2·5% *body weight of water.* These results are shown in Table 3. The infusion of 100 ml. of sodium chloride (0·73 g/100 ml.) caused no striking change in the rate of urine flow, although there was a tendency for sodium and potassium excretion to increase. The water-load was administered 1 hr later, and this was followed by a brisk diuresis, with an increase in sodium excretion and no change in potassium excretion. The water-load caused a fall in plasma protein concentration of 0·94 ± 0·22 g/100 ml.

Thus infusion of only 100 ml. of sodium chloride (0·73 g/100 ml.) changes the diuretic response of a day-one depleted dog to an oral water-load of 2·5% body weight, in contrast to the infusion of 150 ml. of depleted plasma. The administration of the water results in an increase in urinary flow in this group of animals. The differing responses to infusion of 300 ml. of saline, infusion of 100 ml. of saline plus water administration, and infusion of 150 ml. of plasma plus water administration are shown for one dog in Fig. 1.

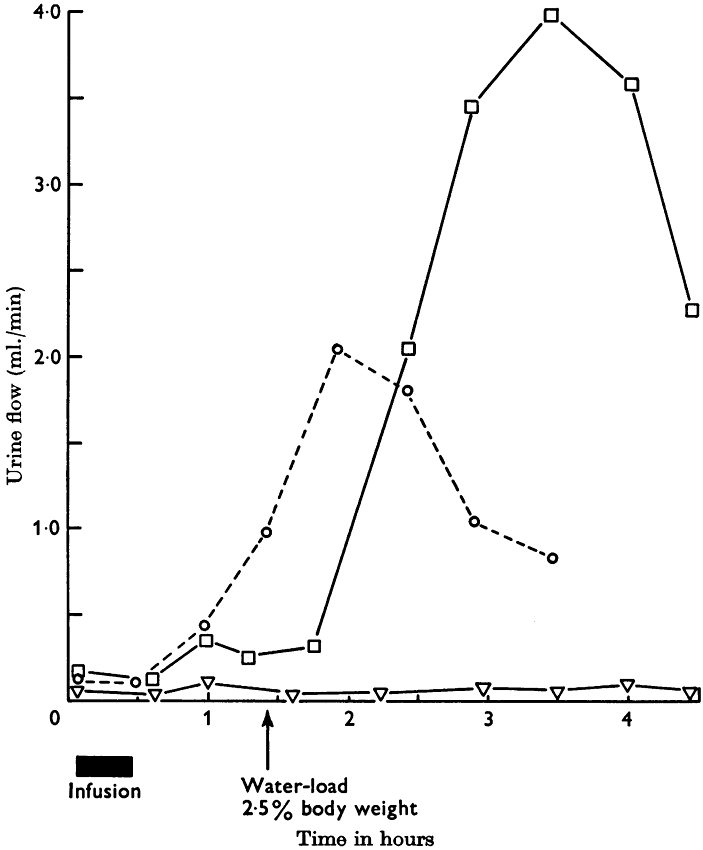

Fig. 1. To show the effect of plasma and saline infusions on the rate of urine flow following a water-load of 2·5 % of body weight in one of the four sodium-depleted dogs: (*a*) ▽—▽ intravenous infusion of 150 ml. of 'depleted' plasma, followed by the water-load: (*b*) □—□ intravenous infusion of 100 ml. of saline (0·73 g/100 ml.), followed by the water-load: (*c*) O . . . O intravenous infusion of 300 ml. of 0·73 % saline.

TABLE 3. Various measurements made on four day-one depleted dogs during the experiments involving the intravenous infusion of 100 ml. of sodium chloride solution (0·73 g/100 ml.), followed 1 hr later by the administration of a water-load of 2·5 % body weight. The means and standard deviations are shown ($n = 4$)

Observation	Value before infusion of 100 ml. NaCl (0·73 g/100 ml.)	Value before administration of water-load	Value 2½ hr after administration of water-load
Plasma Na^+ (m-equiv/l.)	126 ± 0·9	126 ± 0·9	122 ± 1·6
Urine flow (ml./min)	0·06 ± 0·08	0·22 ± 0·06	2·40 ± 1·22
Sodium excretion (μ-equiv/min)	0·6 ± 0·9	4·4 ± 0·9	11·3 ± 4·5
Potassium excretion (μ-equiv/min)	4·3 ± 7·5	15·2 ± 5·3	17·1 ± 1·0
Haematocrit (%)	64 ± 1·4	58 ± 4·7	54 ± 4·6
Plasma protein (g/100 ml.)	7·84 ± 0·37	7·11 ± 0·19	6·17 ± 0·32

DISCUSSION

It has often been pointed out that in certain pathological hyponatraemic states, such as congestive heart failure, the osmoregulatory system appears to be 'set' so as to induce a diuresis only at a lower plasma osmolality than usual (Takasu, Lasker & Shalhoub, 1961). For example, in a typical patient described by these workers, a diuresis only occurred when the plasma osmolality fell below about 260 m-osmoles/kg, a fall induced by the administration of water. In experiments previously described on day-one and day-two depleted dogs (Coxon & Ramsay, 1968) a small fall in osmolality of about 8 m-osmoles was observed on the second day of depletion, which could have allowed an administered water-load to reduce the osmolality below the value necessary for a diuresis to be initiated in these animals.

This interpretation is not supported by the experiments just described. Infusion of 300 ml. of sodium chloride solution (0·73 g/100 ml.) should cause no fall in the plasma osmolality in the day-one depleted dogs and yet caused an obvious diuresis. A similar, or greater, volume of water when given by mouth caused a decrease in plasma osmolality, but no diuresis. Secondly, both the infusion of 150 ml. of plasma and 100 ml. of saline (0·73 g/100 ml.) caused no change in plasma osmolality, and yet the latter caused a water-load to produce a diuretic response, whereas the former did not. Hence the response of the day-one depleted dog to water loading must depend on something other than plasma osmolality.

Our data do not allow exclusion of changes in plasma protein concentration from being of importance in the phenomenon just described (O'Connor, 1962). The total fall in plasma protein concentration in the dogs receiving saline and water was greater than in those receiving plasma and water. However, there is much evidence in the literature to show that diuresis following intravenous administration of colloid-containing fluids occurs independently of changes in plasma protein concentration (Levinsky & Lalone, 1963). There is no reason to suppose that in the salt-depleted dog this should not also be the case.

It has been shown that the day-one depleted dog will exhibit a diuresis when a water-load of 5 % body weight is given, but not after one of half that volume (Coxon & Ramsay, 1968). Perhaps the ability to produce a diuresis depends in some way on the distribution of the volume of administered water as well as on the reduction in osmolality. One question which must be answered is why 300 ml. of sodium chloride (0·73 g/100 ml.) produces a diuresis in the day-one depleted dog, while a similar volume of water does not. This is unlikely to be due to the different routes of administration of the two fluids, since dilution of plasma protein, after the water-load, shows that water is rapidly absorbed from the intestine. Secondly, O'Connor (1955) has shown that neither the dilution of the plasma protein concentration, nor the magnitude of the diuresis in normal dogs receiving similar quantities of saline, depends upon whether the fluid was given orally or intravenously.

When water is given to the dog, the volume will be distributed through the body water. However, when sodium containing solutions are given, they will be restricted to the extracellular fluid compartment. If, as is believed by many, expansion of the total extracellular fluid volume can cause diuresis, then the graded expansion of this compartment induced by saline infusion would be more likely to cause a diuresis. Atkins & Pearce (1959), among others, have shown that infusion of 200 ml. of plasma causes a rise in urinary flow in normal dogs. Sonnenberg & Pearce (1962) have demonstrated that blood volume expansion will cause a diuresis and natriuresis only if the interstitial compartment is normal in volume or expanded. In our dogs this compartment was shown to be reduced in volume, so that plasma infusions would not be expected to produce a diuresis. However, the infusion of the sodium chloride (0·73 g/100 ml.) should cause an acute expansion of the total extracellular fluid compartment, both plasma and interstitial fluid. From the work of Sonnenberg & Pearce (1962) the differing effects of saline and plasma infusions in our experiments may be accounted for by their differing effects on the interstitial fluid volume.

A water-load of 2·5 % of body weight when given a day-one depleted dog after administration of 150 ml. of 'depleted' plasma will not cause a diuresis, but after 100 ml. of 0·73 % saline will result in increased urinary flow. The water-load may be expected to cause similar expansion of the extracellular fluid compartment in both cases. However, the animal receiving the saline infusion will have an interstitial compartment of larger volume than the one receiving plasma. From the experiments of Sonnenberg & Pearce (1962), it would be predicted that the animal with the larger interstitial fluid volume would be more likely to show a diuresis after fluid administration.

The results presented in this paper, therefore, give further support to the ideas of Sonnenberg & Pearce (1962). It would appear reasonable that the behaviour of any receptors sensitive to blood volume changes might be modified by conditions in the interstitial fluid. A change in the volume of interstitial fluid in the wall of a blood vessel might be expected to alter the intramural tension. Both passive effects, due to a change in the elastic elements, and active effects, due to a response of the smooth muscle elements, could contribute to this change in intramural tension. The behaviour of stretch receptors in the wall of the blood vessel will depend upon the conditions in the tissue in which they are embedded. In this way, a change in interstitial fluid volume could alter the sensitivity of the receptors and thus modify their response to the stretch initiated by blood volume expansion.

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