Extracellular fluid volume and thirst

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...receptors also stimulates thirst. Many other authors have suggested that the underlying stimulus is, instead, the decrease in extracellular fluid (ECF) volume which occurs concomitantly with the swelling of the cells, and volume receptors mediating this effect have been considered and generally accepted. However, the evidence that ECF volume contraction leads to thirst is still controversial (cf. 8, 12, 31 and 19, 34). The present study attempts to clarify this issue by determining whether increased intracellular fluid (ICF) volume will produce thirst in the absence of ECF volume contraction, and whether decreased ECF volume will produce thirst in the absence of ICF volume changes.

METHODS

Subjects and Pretreatment Maintenance

Male albino rats of the Sprague-Dawley strain, approximately 120-150 days old and weighing 350-430 g, were used in all experiments. They were maintained and tested in a well-illuminated room in which temperature averaged 77°F with little variation. They were individually housed in mesh-wire cages (8 x 11 x 8 inches), with Purina lab chow and distilled water available ad lib.

Procedure

Group I. Each morning for four successive days 20 rats were weighed and then transferred to metabolism cages where neither food nor water was available. Urine was collected and the volume measured in a graduated tube attached to the base of each cage. Each day, after 6 ½ hr of food and water deprivation, the rats were given a 5% of body wt stomach load of water through an orally inserted catheter. The water was prewarmed to body temperature. A drinking tube was then made available, and water intake and urine output were recorded at 15-min intervals for 3 hr. At the end of this period the rats were returned to their home cages. On the 4th day, the rats were injected ip with either 4 mU Pitressin (40 mU/ml, diluted from a 20-U/ml solution; Parke, Davis & Co.) or 0.1 ml isotonic saline per 100 g body wt immediately following the water loading. (These animals will henceforth be referred to as tubed/Pitressin and tubed/saline rats, respectively.)
were weighed and then transferred to metabolism cages where neither food nor water was available. After 8 hr, a drinking tube was presented for 1 hr, following which the rats were returned to their home cages. Urine was collected and its volume measured as above, the bladder being emptied by suprapubic pressure at the start and finish of each daily session. The volumes of water consumed and of urine excreted in the metabolism cages were recorded and the average of the 2nd and 3rd day's readings were used as the preinjection control measure. On the 4th day the animals were injected subcutaneously in the abdominal midline (under light ether anesthesia) with either 2.5 ml 1.5% Formalin (0.6% formaldehyde in distilled water adjusted to pH 7.4 by a phosphate buffer) (Formalin rats, N = 8), 5.0 ml of 10% polyethylene glycol (Carbowax, compound 40-M; Union Carbide & Chemicals Co.) solution in isotonic saline (PG rats, N = 10), or comparable volumes of the vehicles (N = 8, 10). They were then placed in the metabolism cages and the above procedures resumed.

**Tissue Analyses**

To determine the effects of these procedures on the distribution of fluid and electrolytes in the cellular, interstitial, and intravascular compartments, blood and muscle samples were obtained from similarly treated rats sacrificed 90 min after the fourth water intubation (group I, N = 12), or 8 hr after the injection of Formalin or polyethylene glycol (group II, N = 18). Identical determinations were also performed on nine samples obtained from rats after 8 hr of food and water deprivation alone, and from a final nine rats receiving neither injection nor deprivation. The data from these last animals (referred to as deprived and nontreated rats, respectively) were used as a base line to which the effects of all experimental procedures could be compared.

Each rat was anesthetized with Nembutal (40 mg/kg) injected intraperitoneally. The abdominal cavity was exposed and 5-6 ml blood were withdrawn from the aorta, centrifuged immediately, and the hematocrit determined. Two sections of diaphragm muscle were then quickly removed, weighed in tared 10-ml volumetric flasks to the nearest 0.1 mg, and dried in an oven at 100-105°C until constant weight. Peripheral portions of the muscle were chosen to avoid the central tendon and the larger blood vessels, thus providing a fat-free and relatively blood-free tissue sample.

Subcutaneous injections of Formalin or polyethylene glycol (PG) produced an acute edema localized at the injection site. In these animals the abdominal wall containing the edematous tissue (approx. 3 sq inches) was removed and weighed on a tared piece of aluminum foil to the nearest 0.01 g. This tissue was then dried in an oven at 100-105°C until constant weight and the results compared with those obtained from comparable tissue samples of the 10 nontreated and deprived rats.

Great care was taken to develop a uniform and consistent operating procedure. Unnecessary delay was particularly avoided, and only 120-150 sec usually elapsed from the first incision until the muscle samples were weighed.

After preliminary acid digestion of the dried muscle, chloride was determined by a Volhard titration. The sodium and potassium concentrations of both tissue and serum were determined by flame photometry, using lithium as the internal standard. Serum chloride was determined by a Cotlove automatic chloridometer, serum protein by a refractometer, and serum water by drying to constant weight. Total blood CO2 was determined with the Van Slyke manometric gas apparatus in six Formalin rats, and blood pH was also measured in three of these rats. Finally, serum protein was determined by a biuret reaction in three PG rats. All serum and muscle analyses were made in duplicate. A more detailed description of these procedures is presented in the original study on which this report is based.

**Calculations**

The mass of the extracellular phase and the concentration of water in the intracellular phase of muscle were calculated from the chloride and water contents of the tissue and serum. The assumptions, principles, and equations for these determinations have been discussed elsewhere (17 and unpublished study).
RESULTS

Table 1. Effects of water loading, Formalin, or polyethylene glycol on various measures of blood and serum constituents

<table>
<thead>
<tr>
<th>No. of Rats</th>
<th>(HOH)\textsubscript{m}</th>
<th>g/100 ml Prot.</th>
<th>Hct</th>
<th>mEq/liter Serum Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated</td>
<td>9</td>
<td>925.6±2.8</td>
<td>5.91±0.15</td>
<td>46.1±2.7</td>
</tr>
<tr>
<td>Deprived</td>
<td>9</td>
<td>926.5±3.4</td>
<td>5.89±0.24</td>
<td>47.1±1.1</td>
</tr>
<tr>
<td>Tubed/saline</td>
<td>6</td>
<td>930.8±1.9</td>
<td>5.83±0.14</td>
<td>47.8±0.1</td>
</tr>
<tr>
<td>Tubed/Pitressin</td>
<td>6</td>
<td>931.3±2.0</td>
<td>5.85±0.14</td>
<td>48.2±2.1</td>
</tr>
<tr>
<td>Formalin</td>
<td>9</td>
<td>934.5±3.4</td>
<td>5.89±0.17</td>
<td>50.7±2.5</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>9</td>
<td>918.7±3.9</td>
<td>6.96±0.23</td>
<td>53.5±3.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. (HOH)\textsubscript{m} = g HOH/kg serum. Hct = hematocrit.

Table 2. Effects of water loading, Formalin, or polyethylene glycol on various measures of muscle constituents

<table>
<thead>
<tr>
<th>No. of Rats</th>
<th>(HOH)\textsubscript{m}</th>
<th>(HOH)\textsubscript{e}</th>
<th>(E)</th>
<th>mEq/100 g Dry Solids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated</td>
<td>9</td>
<td>761.9±5.3</td>
<td>720.8±4.9</td>
<td>150.7±12.0</td>
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<tr>
<td>Deprived</td>
<td>9</td>
<td>762.2±5.8</td>
<td>718.3±5.9</td>
<td>160.1±20.8</td>
</tr>
<tr>
<td>Tubed/saline</td>
<td>6</td>
<td>773.5±4.5</td>
<td>726.7±4.8</td>
<td>179.0±14.2</td>
</tr>
<tr>
<td>Tubed/Pitressin</td>
<td>6</td>
<td>782.8±4.0</td>
<td>734.7±7.7</td>
<td>188.2±14.0</td>
</tr>
<tr>
<td>Formalin</td>
<td>9</td>
<td>773.0±5.4</td>
<td>731.7±8.9</td>
<td>176.3±19.3</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>9</td>
<td>760.0±5.0</td>
<td>717.6±5.6</td>
<td>155.7±10.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. (HOH)\textsubscript{m} = g HOH/kg muscle. (HOH)\textsubscript{e} = g HOH/kg intracellular phase of muscle. (E) = g extracellular phase of muscle/kg muscle.

RESULTS

Group I

Water consumption. None of the 32 water-loaded rats drank during the period following intubation, either on the 3 days of pretesting or on the 4th day when they also received intraperitoneal injections of Pitressin or the vehicle. In comparison, all nine deprived rats drank 0.3-1.0 ml of water in the 1 hr following 8 hr of food and water deprivation. The difference in water intake between the deprived rats and either of the water-loaded groups is statistically significant (P < .001; all P values reported are based on two-tailed tests) as determined by the nonparametric median test.

Urine excretion. Figure 1 shows the mean urine outputs of 20 water-loaded rats. The diuresis of the tubed/saline rats was more prompt and copious than that of the tubed/Pitressin animals during the 3-hr period of observation. These curves obtained from slightly deprived rats are similar to, but displaced slightly to the right of, corresponding curves for satiated rats (40).

Ninety minutes after intubation, excretion of the administered water load was approximately 50% in the tubed/saline rats, but less than 10% in the tubed/Pitressin rats. Thus, in similarly treated animals sacrificed at this time, considerable portions of the administered water are still retained. Since water absorption from the gastrointestinal tract is almost complete within 30-45 min after direct stomach loading (32), and is uninfluenced by Pitressin (18), much of this water should appear in the blood and tissues of these animals.

Shifts in body fluids and electrolytes. A summary of the data obtained from analyses of the serum and muscle of nondeprived, deprived, tubed/saline, and tubed/Pitressin rats is presented in Tables 1 and 2.

As expected, the water-loaded rats showed marked hemodilution. When compared with deprived rats, the water content per kilogram serum was elevated in both the tubed/saline and tubed/Pitressin groups (P < .06, .05, respectively), and significant decreases in the serum concentrations of sodium (both P's < .001) and chloride (both P's < .001) were also found. Tubed/Pitressin rats showed a significant decrease in serum protein (P < .05) as well. These changes indicate an increased plasma volume.

When compared with deprived rats, the water content per kilogram muscle was also elevated in both tubed/saline and tubed/Pitressin rats (both P's < .001). In addition, the amount of chloride per kilogram dried muscle was significantly increased (both P's < .05) and the amount of potassium was decreased (both P's < .05). These changes suggest that the extracellular portion of the muscle was increased. From the above data, and the assumption that 81% of all muscle chloride is in the extracellular phase, the relative proportion of extracellular chloride per kilogram muscle was also calculated (Table 2) and found expanded in both tubed/saline and tubed/Pitressin rats (both P's < .05) was confirmed.

Intracellular fluid volume was also calculated (Table 2) and found expanded in both tubed/saline and tubed/Pitressin rats (P < .01, .001, respectively).

Thus, 90 min after 5% body-wt stomach loads of water in rats, significant increases in their intravascular, interstitial, and intracellular fluid volumes could be
observed. In general, tubed/Pitressin rats showed similar but more pronounced effects than tubed/saline animals, as would be expected from the greater water retention resulting from the inhibited diuresis.

**Group II**

Water consumption and urine excretion. The volumes of water consumed and urine excreted by rats injected with Formalin, polyethylene glycol, or the vehicle solutions are summarized in Table 3.

The increased water consumption by Formalin and PG rats was significant at the .001 level, when compared with either their previous intakes or the intakes of rats injected with the vehicle. In addition, the water intake of Formalin rats was significantly larger than the intake of PG rats (P < .001).

The decreased urine volumes of Formalin and PG rats were comparable, but were respectively significant at the .01 and .001 levels when compared with their previous urine outputs, and at the .02 and .001 levels when compared with the volumes excreted by rats injected with the vehicles. In addition, the urine of Formalin and PG rats showed significant decreases in mean sodium ion concentration (both P's < .001) and significant increases in mean potassium ion concentration (both P's < .01). This suggests an increased secretion of aldosterone, in response to contracted intravascular space (3).

Shifts in body fluids and electrolytes: Formalin rats. The data obtained from the analyses of the serum and muscle of nine Formalin rats are summarized in Tables 1 and 2.

**Body-fluid compartments.** When compared to deprived rats, Formalin rats showed a decreased intravascular volume but increased intracellular and interstitial fluid volumes. A pronounced increase in the mean hematocrit (P < .001) indicated a considerable decrease in the intravascular fluid. The marked decrease in the mean serum protein concentration (P < .001), resulting in the significant increases in water content per kilogram serum (P < .001), also indicated a loss of serum solutes. The magnitude of these changes indicate a loss of protein-rich plasma fluid rather than a simple dilution of the fluid (group I). This is also suggested by the normal serum chloride concentration in Formalin rats, in contrast to its significant reduction following water loading.

The increased water content per kilogram muscle (P < .02) and the unchanged proportion of the cellular and extracellular phases of the tissue suggest that both intracellular and interstitial fluid volumes were increased. The former was confirmed by direct calculation (P < .001).

**Mechanism of action.** The gross swelling of the abdominal wall following subcutaneous injection of Formalin indicates the presence of considerable fluid in the area. A portion of this fluid apparently comes from an accelerated loss of both plasma fluid and plasma protein through damaged local capillaries, as suggested by the above serum changes and the high concentration of protein (4.0-4.2 g/100 ml) found in the edema fluid. The water content of the edematous tissue averaged 80.3%, and from comparison with the 67.3% in comparable samples from deprived rats it was estimated that 10-12 ml of edema fluid was accumulated. Together with an estimated 8 ml of fluid lost to the muscles (due in part to the lowered oncotic pressure of the blood caused by the serum protein loss), this volume is in great excess of the initial plasma volume of the rats. Examination of the renal and extrarenal losses and the water content of the gastrointestinal tract and peritoneal cavity, and consideration of the volume of solution injected, still left 11-13 ml of fluid unaccounted for. This fluid probably came from the local necrotic tissue itself and from an increased production of metabolic water caused by the inflammation (28).

The decrease in serum sodium concentration (P < .001) and the increase in the mean potassium content per kilogram dried muscle (P < .10), as compared with deprived rats, suggests an exchange of intracellular potassium for extracellular sodium and a breakdown of the sodium-potassium pump of the injured cells (due to the disruption of the cellular proteins by Formalin) which has been reported in other studies of tissue trauma (4, 13).

The loss of chloride into injured cells is balanced by an increased shift of chloride out of the red blood cells (21), thereby maintaining serum chloride at normal levels. Coupled with the decrease in serum sodium, this necessitates a decrease in some other serum anion. The loss of protein into the edematous tissue accounts for some of this imbalance; a decrease in bicarbonate ion is contraindicated, however, by an elevated blood CO2 (26.2 mm/liter) and a normal pH (7.43).

**Shifts in body fluids and electrolytes: PG rats.** The data from the analyses of serum and muscle of nine PG rats are summarized in Tables 1 and 2.

**Body-fluid compartments.** When compared with deprived rats, PG rats showed a decreased intravascular fluid volume but an unaltered intracellular volume. The increased mean hematocrit (P < .001) suggests the loss of plasma, and the decreased water content (P < .001) and increased protein concentration (P < .01) of the serum specify the loss as a protein-free filtrate. A biuret test gave a mean serum protein of 6.73 g/100 ml in three PG rats, approximating the 6.96 g/100 ml reading by the above serum changes and the high concentration of protein (4.0-4.2 g/100 ml) found in the edema fluid.

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of the refractive index method and thereby confirming an actual increase in serum protein concentration rather than a systemic absorption of the colloid.

The calculated decrease in extracellular space of muscle indicates a loss of interstitial fluid, as does the decreased water content of the whole muscle in the absence of changes in the intracellular compartment. These changes lack statistical reliability, however.

**MECHANISM OF ACTION.** The gross swelling of the abdominal wall following subcutaneous injection of polyethylene glycol solution superficially resembled the edema produced by Formalin, although it was somewhat larger because of the greater volume of injected material. The mean water content of the edematous tissue was 79.7%, and an estimated 11–12 ml of fluid were accumulated from body sources. These values are comparable to those found in Formalin rats. The sum of the estimated loss of fluid from plasma and muscle, added to the volume conserved by the decreased renal and extrarenal losses, still left 4–5 ml of fluid unaccounted for. As before, this balance probably represents water produced by a general metabolic increase (28).

The injections of polyethylene glycol apparently caused little direct cellular destruction, since the electrolyte concentrations in the serum and muscle were unchanged. Thus, in contrast to the complex changes following Formalin treatment, the accumulation of edema fluid in rats injected with polyethylene glycol seems largely the result of a direct oncotic withdrawal of isoosmotic plasma fluid into the injected area.

The increased serum protein concentration in PG rats increased the absorption of interstitial fluid into the blood and thereby helped to re-expand the plasma volume. In Formalin rats, on the other hand, fluid moved in the opposite direction, as cells absorbed the hypoosmotic ECF. This difference in fluid shifts is reflected by the lower hematocrit in PG rats (P < .01), despite the comparable losses of body fluids and edema formation.

**DISCUSSION**

**Group I**

Early reports had found that thirst in man was temporarily augmented following prolonged periods of voluntary polydipsia (34, 33). A simple overhydration of bodily fluids does not seem probable in these cases, however. On the contrary, their salt appetite and the increased freezing-point depression of their serum instead suggest that the water flushing had left them in a salt-depleted or dehydrated state, or both, in which one or both fluid compartments had been contracted. Continuously administered water has been observed to lead to a negative salt and water balance in man (41).

The present results indicate that the water intubation did not increase thirst, but decreased it. This finding agrees with other studies in which acute forcing of fluids did not lead to increased drinking (10, 11, 16, 19). In none of these earlier studies, however, were the effects of the water excess on the intracellular and extracellular compartments measured. In the present study, the mean increase in cellular water content was 1.4% in the tubed/saline rats and 2.2% in the tubed/Pi rexin animals. The estimated increase accompanying salt depletion and thirst in other studies (5, 35) was approximately 1.2–2.1%. If these changes in the cellular volume of muscle tissue parallel changes in the volume of the osmoreceptor cells, then it is apparent that the osmoreceptor expansion did not cause drinking under the present conditions of increased ECF volume. This result does not support the notion that osmoreceptor expansion mediates thirst or plays a significant role in the drinking observed following salt depletion (6, 20).

It is unlikely that the animals in the present experiment were thirsty but did not drink due to discomfort or incapacitation caused by the water excess, the tubing, or the stomach distention, since they immediately began to eat, and then drink, when returned to their home cages. Furthermore, other rats receiving a sham intubation in which no water was delivered showed no inhibition of the drinking response. Finally, the possible aversive properties of the initial stomach distention would not be expected to last longer than 1 hr (27), and thus should not inhibit drinking during the entire 3 hr of observation.

Like salt depletion, insulin has been reported to cause a movement of extracellular water into brain cells (47) and to elicit thirst (30). However, the presence of large deposits of chloride in the neuroglia (22) necessitates a re-evaluation of these findings, since the determinations of the fluid compartments of the brain had assumed that tissue chloride was exclusively extracellular. Even if insulin does in fact facilitate the movement of extracellular water into cells, the contracted ECF volume might still be the factor underlying thirst. This hypothesis was supported when Novin (30) found that insulin does not reduce the thirst of 8-hr water-deprived rats but instead increases it. The present experiment argues against the possibility that the single large dose of insulin used by Novin elicited thirst by overexpanding the osmoreceptors.

In sum, these results indicate that cellular expansion under conditions of general body hydration does not lead to thirst, and suggest that thirst may only accompany cellular hydration when, as in salt depletion, ECF volume is decreased.

**Group II**

These results demonstrate that significant increases in water intake and decreases in urine output follow the sequestration of ECF caused by subcutaneous injection of Formalin or polyethylene glycol solution. The oliguria following either treatment may be due to the secretion of ADH (23) or to decreased renal plasma flow (7) following intravascular fluid loss. The drinking seems also to be related to the plasma loss, and not to osmoreceptor changes. In Formalin rats, ICF volume increases were
comparable to those produced in hyperhydrated or salt-depleted animals, although it now seems evident that this expansion is not directly related to thirst. In PG rats, the following arguments suggest that no changes occurred in the cellular volume of the osmoreceptors. First, there was no osmotic basis for causing them, since no changes were found in the osmolality (12) or the electrolyte concentration of the ECF. In addition, there was no change in the calculated ICF volume of muscle cells; thus, if hypothalamic osmoreceptors respond to osmotic forces as muscle cells do (42, 43), then they should also have remained unchanged in volume and consequently not have played a part in the mediation of thirst under these conditions. In addition, the lower water intake of PG rats as compared to Formalin rats is consistent with the hypothesis that thirst is proportional to, and caused by, intravascular fluid reduction. (Estimates of the reduction in plasma volume, based on changes in plasma protein concentration or hematocrit, are 8-18% in PG rats and 25-40% in Formalin rats.) This notion received additional support when increased thirst and plasma loss, to levels comparable to that in Formalin rats, were obtained by increasing the concentration of polyethylene glycol solution injected (30).

The estimated plasma losses in the present experiment are comparable to those reported in other studies in which drinking followed intravascular fluid volume reduction (8, 12, 20, 31). On the other hand, they are also comparable to fluid losses in hemorrhage studies in which no drinking was observed (19, 34). In the latter studies, however, the subjects were only observed for a few hours; in contrast, all but one (91) of the studies in which increased drinking was observed after ECF volume losses were of a longer duration. Perhaps, like the initial salt-depletion work in which no drinking was observed (9), a sufficient time must be allowed for the debilitating effects of acute anemia or shock, or both, to be overcome and thereby permit drinking.

It cannot be determined whether the thirst sensations produced by ECF volume depletion are identical with those resulting from osmoreceptor dehydration. A number of authors have noted the inability of water (in contrast to sodium chloride) to relieve the thirst of salt-depleted subjects, and McCance (25) has suggested that an aberration in their sense of taste arising from the hyponatremia (a salt appetite?) was mistakenly interpreted as a need for water. Since subcutaneous Formalin injections produce hyponatremia and elicit a salt appetite in rats (46), it is therefore possible that the water drinking observed in the present experiment had such cause. On the other hand, this explanation could not account for the thirst of PG rats, since treatment with polyethylene glycol causes neither hyponatremia nor salt appetite (38).

Conclusions

In light of these findings, it would seem appropriate to summarize and briefly re-evaluate the conditions under which thirst is known to appear. It is well known that thirst occurs when the effective osmotic pressure of the ECF is increased, as after simple dehydration or hypertonic salt infusion. Presumably, this is due to the decreased size of the osmoreceptors, which mediates the thirst reflex and causes the organism to drink. When the effective osmotic pressure is decreased, on the other hand, thirst only seems to appear when intravascular fluid volume is also decreased, as after Formalin injection or intraperitoneal glucose dialysis, but not after hypervolemia. This volume decrease has also been emphasized in accounting for the thirst following food intake (15), hyperoncotic colloid injection (12), hemorrhage (8, 12, 31), diarrhea (37), and the accumulation of ascites in hepatic cirrhosis (29). Since it is the only known aspect of fluid and electrolyte balance correlated with increased water intake in each of these conditions, it seems probable that it is another factor important in stimulating thirst.

The mediation of thirst produced by intravascular fluid volume reduction might be through special volume or pressure receptors. Such receptors have already been hypothesized and assumed important in this regard as well as in the renal regulation of body fluid volume, and several reviews of this topic have appeared (14, 36, 45). Renal compensation following the acute loss of intravascular fluid is particularly well documented, whether the loss was produced by acute hemorrhage, ip glucose dialysis, or by subcutaneous injection of Formalin or polyethylene glycol. It seems reasonable to suspect that a similar volume preservation is involved in the thirst produced by these procedures.

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