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Inhibition of vasopressin secretion when dehydrated rats drink water

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Inhibition of vasopressin secretion when dehydrated rats drink water. Am J Physiol Regul Integr Comp Physiol 289: R1238–R1243, 2005. First published July 14, 2005; doi:10.1152/ajpregu.00182.2005.—The present study determined whether vasopressin (VP) secretion is inhibited by an oropharyngeal signal associated with swallowing fluids when dehydrated rats drink water, as it is when dehydrated dogs are used as experimental subjects (Thrasher, TN, Keil BC, and Ramsay DJ. Am J Physiol Regul Integr Comp Physiol 253: R509–R515, 1987). VP levels in systemic plasma (pVP) fell rapidly when rats drank water after overnight water deprivation. Systemic plasma Na⁺ concentration (pNa) also fell, but that change likely contributed little to the early inhibition of VP secretion. In contrast, consumption of water by dehydrated rats with an open gastric fistula had no effect on pVP, nor did consumption of isotonic saline by dehydrated rats; in neither case was pNa affected by fluid consumption. These findings provide no evidence that the act of drinking inhibits VP secretion in dehydrated rats. Thus some postgastric effect of the ingested water seems to be responsible for the inhibitory signal. These results are consistent with previous suggestions that an early inhibitory stimulus for VP secretion in rats is provided by postgastric visceral osmo- or Na⁺ receptors that sense the composition of the ingested fluid.

In contrast, several years ago we reported that plasma VP levels (pVP) declined rapidly when thirsty rats drank water but not when they drank isotonic saline (11). However, in that experiment, infusion of hypertonic saline was used to elicit thirst, and the stimulus for VP secretion was much more intense than that produced by dehydration in the studies mentioned above. The present investigations reexamined this issue in rats, but this time the animals were made thirsty by water deprivation before being allowed to drink. The main goal was to determine whether VP secretion in dehydrated rats is inhibited because of the act of drinking or because of some postgastric effect, which is related not to the volume but to the composition of the fluid consumed. The results indicated that pVP began to decline well before a bout of water drinking had ended, but it did not diminish either while dehydrated rats consumed 0.15 M NaCl solution or when they drank water but the ingested fluid drained through an open gastric fistula. These latter findings provide no evidence that oropharyngeal signals associated with fluid ingestion inhibit VP secretion in dehydrated rats, but they are consistent with previous suggestions that visceral osmo- or Na⁺ receptors sense the composition of ingested fluid and provide an early inhibitory stimulus for VP secretion in rats (2).

METHODS

Animals. Adult male Sprague-Dawley rats (300–370 g; Harlan Laboratories) were housed singly in stainless-steel cages. The colony room was maintained at a constant temperature (22–23°C) and with a fixed light-dark cycle (lights off from 7:00 PM to 7:00 AM). All rats had >1 wk of ad libitum access to tap water and pelleted chow containing 1% NaCl (diet 90229; Harlan Teklad Diets, Madison, WI) before experiments began. Daily intakes were 30–40 ml of water and 20–25 g of this standard chow. In addition, some rats were given 0.15 M NaCl to drink for 24 h, 5 days before the start of experiments in which they were water deprived, and were then given saline to drink instead of water.

Experimental protocols. One group of dehydrated rats was used to determine the effects of water consumption on VP secretion. In designing this experiment, we considered taking repeated measurements in the same animals. That approach has the advantage of allowing observed values to be compared with other values from the same animal. However, we feared that repeated blood sampling would affect drinking behavior and pVP, and consequently we decided to take single measurements from multiple animals at multiple times. Fortunately, the observed variability between animals was rather small (see below).

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All experimental protocols were reviewed by and received approval from the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Thirty-two rats were given ad libitum access to pulverized food presented in a circular glass dish (2.5 cm in height, 5 cm in diameter) placed on the floor of the cage. After >1 wk, rats were adapted to a 16-h period of water deprivation (5:30 PM to 9:30 AM) for three successive days. On the fourth day, drinking water again was removed at 5:30 PM. At 9:30 AM on the following morning, burettes filled with tap water were placed on the cages, food was removed, and the room lights were dimmed to encourage drinking. Ten rats were killed without being given access to drinking water, whereas the remaining animals were given water to drink. Some of them were allowed to drink until they paused for 10 s, whereas the others drank for variable amounts of time (between 15 and 225 s) before being interrupted by the experimenter. In either case, water intakes (±0.1 ml) were recorded, as was time spent drinking (±1 s). On the terminal day of testing, the water was colored with a dark green food dye (McCormick, Hunt Valley, MD) that allowed the ingested fluid to be readily visible in the intestine

Rats were killed by decapitation within 10 s after the drinking test, and trunk blood was collected in ice-cold heparinized tubes (143 USP sodium heparin; Becton Dickinson, Franklin Lakes, NJ) and kept on ice. The abdomen was opened, and hemostats were placed at the junction of the stomach with the pylorus, at the junction of the stomach with the esophagus, and at the most distal site of visible dye in the small intestine, in that order. This portion of the surgical procedure took <2 min. Each stomach was removed from the carcass, the intestinal distance containing the dye was measured (±1 cm), and the small intestine was removed. The excised tissues were stripped of adhering blood vessels and connective tissue and were placed in separate beakers and covered with Parafilm. The blood was centrifuged (10,000 g for 5 min at 4°C); the plasma was harvested; plasma Na⁺ concentration (pNa) was measured using a sodium-sensitive electrode (±1 meq/l; Synchro EL-ISE model 4410; Beckman Coulter, Brea, CA); and plasma protein concentration was measured (±0.1 g/dl) using a refractometer. Finally, the stomach contents and the segment of small intestine were placed in an oven and dried to constant weight at 60°C for 1–2 days.

The procedures used for measuring VP have been described previously (17). Briefly, duplicate 250-μl plasma samples were extracted using solid-phase columns (Sep-Pak C18 cartridges, 1 ml, 50 mg; Waters, Milford, MA), and VP was measured by radioimmunoassay in aliquots of these extracts. The assay sensitivity was 2.5 pg/ml, and the intra-assay variations were <10%.

A second group of dehydrated rats (n = 22) was used to determine the effect of drinking 0.15 M NaCl instead of water on VP secretion. Procedures identical to those just described were used except that the rats interrupted by the experimenter were allowed to drink saline for different amounts of time (between 30 and 375 s).

A third group of dehydrated rats was used to determine the effect of consuming water or 0.15 M NaCl on VP secretion under circumstances in which the ingested fluid drained from an open gastric fistula. Rats were fitted with indwelling stainless steel gastric fistulas (1.3 cm long, with a 1-cm-diameter flange at each end), using procedures described previously (18), and were subsequently housed singly in polypropylene cages (48 × 25 × 20 cm). Each fistula was plugged with a removable stainless steel screw except during experimental sessions. After 4–7 days of recovery from surgery, rats were acclimated to manipulations of the fistula and to drinking in specially constructed test boxes (13) that permitted drainage of the ingested fluid and collection of it in a calibrated tube (±0.1 ml). Drinking fluid was available in a calibrated burette (±0.1 ml) attached to one end of the cage, but no food was available during the test period. On the test day, rats were treated as described above and given water (n = 8), saline (n = 5), or nothing to drink (n = 5), except that all animals were killed by decapitation after 4 min of drinking. Aliquots of trunk blood plasma were analyzed for Na⁺ and VP concentrations. Green food dye in the drinking fluid allowed confirmation that none of the ingested fluid had entered the small intestine.

In addition to these dehydrated rats, a group of nondeprived rats (n = 9) was killed, and blood samples were taken for determination of control values of plasma Na⁺, protein, and VP.

Calculations. Using data from 13 rats in the third group, we made a comparison between the volume of fluid consumed by dehydrated rats and the volume of fluid that drained from open gastric fistulas while they drank. In addition, 10 other animals were studied using identical procedures, except they were allowed to drink water for varying amounts of time, from 4 to 35 min, and pVP was not measured. A scatterplot of the data from these 23 rats was prepared displaying fluid drainage (on the y-axis, in ml) as a function of fluid intake (on the x-axis, in ml); its trend line (γ = 1.12x + 0.084; r = 0.99, P < 0.001) indicated that an average of ~12.6% more fluid drained from the rats’ stomachs than they had consumed, regardless of whether they drank water or saline. Thus we estimated that 12.6% of fluid drained from food associations in the stomachs of the dehydrated rats was derived from orogastric secretions in response to fluid consumption, whereas the remaining 87.4% was derived from ingested fluid. This additional volume was included in estimating gastric emptying.

Gastric emptying was computed as the difference between the measured fluid intake and the estimated amount of ingested fluid that remained in the stomach and was expressed as a percentage of the intake. To estimate the amount of ingested fluid that remained in the stomach, it was necessary to distinguish that fluid from water already present in the gastric chyme. Accordingly, five other water-deprived rats were trained as above, but on the test day they were denied access to water or saline and were decapitated; their blood, stomachs, and small intestines were removed and treated as described above. A scatterplot of the stomach liquids of individual animals (on the y-axis, in ml) expressed as a function of stomach solids (on the x-axis, in g) produced a trend line (γ = 1.17x + 0.40; r = 0.97, P < 0.001) that was used to correct for the amount of fluid associated with gastric solids in each rat tested. This equation is virtually identical to the one obtained previously in this laboratory using a large group of rats feeding ad libitum (22). Note that ~85% of the dehydrated rats in the present studies had <0.6 g of stomach solids; in those animals, the associated volumes subtracted from measured gastric water were <1.1 ml. Of course, these calculations assumed that food residues present in the stomach at the start of the drinking test, as well as the associated water in the gastric chyme, remained in the stomach during the brief period of testing.

Statistical analysis. Most data are presented as means ± SE. A two-tailed t-test was used to determine the statistical significance of observed differences between groups. When results are presented as scatterplots of data from individual rats, regression lines were computed by the method of least-squares, and correlation coefficients (r) also were computed. A P value of <0.05 was considered to be statistically significant.

RESULTS

When individual intakes were plotted as a function of time spent drinking, it was clear that rats drank water or 0.15 M NaCl at the same steady rate (1.5–2.1 ml/min) after a 16-h period of water deprivation (γ = 1.4388x + 0.7547; n = 44, r = 0.96, P < 0.001). About one-fourth of the animals were killed when they paused from drinking (4–6 min after they began to drink water, 7–10 min after they began to drink saline), whereas the others were interrupted while drinking and then killed.

The pVP values in individual animals were plotted as a function of time from the onset of water ingestion until the rats
were killed. As shown in Fig. 1A, pVP declined linearly when rats consumed water (r = 0.71, P < 0.001). Given the pVP values in deprived rats not allowed access to drinking water (11.7 ± 0.6 pg/ml) and the slope of the regression line (−1.1), it can be computed that pVP decreased by 50% in 5.3 min, at which time it approximated the pVP levels in nondeprived control rats (5.6 ± 0.5 pg/ml). In contrast, ingestion of 0.15 M NaCl by dehydrated rats had no significant effect on pVP (r = 0.26, P = not significant (NS); Fig. 1B).

Dehydrated rats emptied comparable amounts of ingested fluid from their stomachs whether they drank water or saline (51.8 ± 3.4 vs. 55.2 ± 2.7%, respectively). Figure 2 presents a scatterplot of the intestinal distances (past the pylorus) that were colored by the green dye in the drinking fluid as a function of the time rats spent drinking. These two variables were highly correlated with one another (r = 0.86, P < 0.001), and no significant difference was apparent whether rats consumed water or saline. Note that dye was visible in the small intestine soon after the onset of drinking (i.e., by 15 s, when only 0.6 ml of water had been consumed), that it traversed great distances very quickly before slowing (e.g., ~35 cm in 2 min), and it was visible deep in the small intestine by the time rats ceased drinking water (~55 cm in 6 min) or saline (~65 cm in 10 min). Not shown are the similar logarithmic relations between intestinal distance and fluid intake (r = 0.85, P < 0.001) or calculated volume of ingested fluid that emptied into the small intestine (r = 0.87, P < 0.001).

Similarly, pVP values were significantly correlated with pNa values when dehydrated rats drank water (r = 0.53, P < 0.01).
Table 1. Plasma vasopressin levels and sodium concentrations in dehydrated rats with an open gastric fistula while drinking water or 0.15 M NaCl solution

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Drinking Fluid</th>
<th>pVP, pg/ml</th>
<th>pNa, meq/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>None</td>
<td>11.7±0.6</td>
<td>148.3±0.5</td>
</tr>
<tr>
<td>Open fistula</td>
<td>5</td>
<td>None</td>
<td>10.3±0.7</td>
<td>146.2±0.6*</td>
</tr>
<tr>
<td>Open fistula</td>
<td>8</td>
<td>Water</td>
<td>10.9±1.0</td>
<td>145.7±1.0*</td>
</tr>
<tr>
<td>Open fistula</td>
<td>5</td>
<td>Saline</td>
<td>9.9±0.4*</td>
<td>145.0±0.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. No significant differences in plasma vasopressin levels (pVP) or plasma Na⁺ concentrations (pNa) were observed among the 3 groups with gastric fistulas. Control group consisted of dehydrated rats without a gastric fistula and denied access to drinking fluid. *P < 0.05; †P < 0.001 compared with control rats without a gastric fistula.

but not when they drank saline (r = 0.16, P = NS). However, pVP values were not significantly correlated with plasma protein levels (water: r = 0.32, P = NS; saline: r = 0.22, P = NS), which varied little regardless of which fluid was ingested (water: 7.0 ± 0.1 g/dl; saline: 6.9 ± 0.1 g/dl; both P < 0.001 compared with 6.1 ± 0.1 g/dl, the value in nondeprived control animals).

Dehydrated rats with open gastric fistulas usually consumed less fluid in their 4-min tests than 6.5 ml (the average volume ingested in 4 min by the dehydrated rats without gastric fistulas, which was computed from the above equation for the regression line). As shown in Table 1, the pVP values associated with the consumption of water (5.1 ± 0.5 ml) or saline (4.5 ± 0.9 ml) were not significantly different from one another or from the values in rats with gastric fistulas that were denied access to drinking fluid. Similarly, and as expected, the pNa values were comparable in the dehydrated rats with gastric fistulas whether they drank water, saline, or nothing. However, these pNa values were significantly lower than values in dehydrated rats without gastric fistulas and that were denied access to drinking fluid.

DISCUSSION

Compelling evidence suggests that oropharyngeal receptors activated by repetitive swallowing stimulates inhibition of VP secretion when dehydrated dogs drink water (27, 28). Specifically, pVP fell markedly 3–6 min after the onset of water consumption and thirst disappeared as well, yet significant osmotic dilution of plasma was not observed until 12 min after drinking began, and systemic rehydration did not occur for 30 min. Moreover, pVP also diminished rapidly when dogs drank isotonic saline instead of water. Similar results have been reported in studies using sheep or human subjects (3, 7). The present results provide no evidence that the same mechanisms apply when dehydrated rats are allowed to drink. Three important differences between these findings and those of the previous studies should be emphasized. First, pVP did not diminish either when dehydrated rats ingested isotonic saline instead of water or when rats with open gastric fistulas ingested water. Second, osmotic dilution of systemic blood was relatively rapid in rats; it appeared to begin within a few minutes after the onset of water ingestion, and pNa reached normal values soon thereafter. Third, although a reduction in pVP became apparent within a few minutes after the onset of water consumption, drinking continued for additional minutes. Each of these points is considered in turn.

The main goal of these experiments was to determine whether oropharyngeal stimuli inhibit VP secretion when dehydrated rats drink. That hypothesis was evaluated in two ways. In one experiment, pVP values apparently were not affected by fluid consumption when 0.15 M NaCl was substituted for drinking water. These observations extend similar findings in rats made thirsty by marked hypernatremia (11). In another experiment, pVP values were not diminished when water was ingested by dehydrated rats with open gastric fistulas. These results may be contrasted with the rapid decrease in pVP that occurred in similar studies in which dehydrated dogs were used as experimental subjects (28). Thus the present findings do not indicate that the act of drinking inhibits VP secretion in rats as it does in dogs.

In apparent contrast with one of the present observations, a transient decrease in pVP was reported to occur after the consumption of 0.15 M NaCl solution by dehydrated rats (32). Specifically, when drinking was restricted to 30 min daily, a very small (<1 pg/ml) but statistically reliable decrease in pVP was observed after rats had 15 min of access to isotonic saline. However, no significant effects were found after 5 or 30 min of saline ingestion, and closer inspection of the 15-min data set revealed that its statistical significance may have resulted from an unusually low value of pVP in one animal (Engeland WC, personal communication). Be that as it may, it remains possible, although in our opinion unlikely, that transient decreases in VP secretion did occur while the dehydrated rats were drinking saline or while they were drinking water with an open gastric fistula, but they were not detected because of the limitations of an experimental protocol in which single measurements of pVP were made in multiple rats. Further investigations of the apparent species difference in the inhibition of VP secretion by fluid ingestion might involve repeated blood samples from individual rats while they are drinking.

In contrast to these results is the clear inhibition of VP secretion that occurred when dehydrated rats drank water normally. The regression line displayed in Fig. 1A suggests that VP secretion was inhibited within a minute or two after the onset of water consumption. However, inspection of the data indicates that individual values of pVP actually were within the range of control values for 1–2 min after water consumption began, but by 3 min all pVP values had fallen to the bottom of that range or were lower and subsequently declined further. Postmortem examination of the gastrointestinal tracts of these animals indicated that about half of the ingested water emptied from the rats’ stomachs while they were drinking, in confirmation of previous observations (8). This water rapidly moved deep into the small intestine from which it could decrease systemic plasma osmolality both by being absorbed into the circulation and by promoting the diffusion of osmolytes into the intestine. Indeed, the regression line displayed in Fig. 3 indicates that dilution of pNa occurred while the rats drank water.

How is the inhibition of VP secretion mediated? One possibility involves a role for cerebral osmoreceptors, which are well known to inhibit stimulated VP secretion when body fluids become dilute (24). The significant correlation between the decrease in pNa and the decrease in pVP in individual animals appears to support that possibility. However, we be-
lieve that this correlation does not reflect a causal relation, for two reasons. First, Fig. 1A indicates that pVP diminished by 50% in 5.3 min which is similar to the reported half-life of pVP in rats of ~5 min (6). Even if the half-life of VP in rats actually was only 2–3 min and pVP began to fall 2–3 min after drinking started, it seems unlikely that a substantial decrease in VP secretion would begin while pNa values still were elevated and before they had changed by 2%. Furthermore, and more compellingly, in a previous study, pVP was found to fall precipitously when rats drank water under circumstances in which elevated pNa values were not allowed to drop because of a slow infusion of hypertonic NaCl solution (11). Thus a very potent effect of dilute fluids to inhibit stimulated VP secretion in rats can be obtained without noticeable increases in systemic plasma osmolality. Note that the estimated plasma volume deficits of 10–15% in the dehydrated rats, computed from plasma protein values of 6.8–7.1 g/dl (19), probably were too small to have contributed much stimulation of VP secretion (24), and plasma protein did not change as a consequence of drinking; thus it seems likely that this variable was not a significant factor in these considerations.

If cerebral osmoreceptors did not initiate the inhibition of VP secretion when dehydrated rats drank water, then what was responsible for that effect? It is not likely to be gastric distension; for example, previous studies have shown that pVP values were not affected when gastric vagal afferents were stimulated by systemic treatment with cholecystokinin in doses sufficient to increase neurohypophysial oxytocin secretion (29). Together with the present findings, those results suggest that a presystemic signal for inhibiting VP secretion in dehydrated rats is generated when ingested water is detected postgastrically. In this regard, Baertschi and Pence (2) have reported a series of studies suggesting that splanchnic osmoreceptors could mediate this effect in rats. Most persuasive are their observations that gastric water loads inhibit dehydration-induced VP secretion without noticeable dilution of circulating plasma in dehydrated rats; in fact, this effect occurred even when the water load was combined with systemic infusion of hypertonic saline, which prevented a decrease in systemic osmolality. Furthermore, transection of hepatic vagal afferents markedly blunted this inhibitory effect. These and other findings suggested that osmoreceptors in the hepatic portal vein detect the dilution of local blood and send a neural signal to the brain stem that ultimately leads to the inhibition of neurohypophysial VP secretion (2). The present results are consistent with that hypothesis. As such, they complement other evidence that visceral osmoreceptors mediate increased VP secretion and thirst when hypertonic fluids pass through the gastrointestinal tract (5, 12, 20, 22).

Like VP secretion, thirst during water deprivation in rats has been attributed to increased plasma osmolality and decreased plasma volume (15). The dehydrated rats in the present experiment were thirsty at the start of the test; they drank as soon as water was returned to their cages, and they continued to drink at a steady rate for 4–6 min before their intake ceased. These observations may be contrasted with the more rapid inhibition of VP secretion, which evidently has a different basis. Consequently, they support previous findings that the controls of VP secretion and thirst, while often similar, are not identical (23).

In considering the signal that terminates water intake in these rats, it can be estimated from the observed decline in pNa (which fell by 0.8 meq/l per minute; Fig. 3) that 5.3 min were required for the animals to restore basal values of pNa from the elevated levels seen in dehydrated rats not allowed to drink. Similar results have been reported previously (8, 9). Because water intake usually continued without much pause for 4–6 min, it may appear that the rehydration of body fluids as detected by cerebral osmoreceptors mediated the termination of drinking. However, the plasma protein levels of dehydrated rats still were elevated after water consumption ended, which indicates that the hypovolemic component of their thirst persisted. Drinking also stopped when isotonic saline was consumed, even though the pNa values of systemic blood still were elevated. These observations suggest the presence of an inhibitory signal for thirst rather than satiation. Although ongoing studies are still exploring its basis, preliminary findings suggest that the intake of water or 0.15 M NaCl by dehydrated rats is terminated by a signal related not to the composition of the ingested fluid but to its volume, which appears to reflect distension of the stomach and small intestine (Stricker EM and Hoffmann ML, unpublished observations).

In summary, neurohypophyseal VP secretion appeared to be inhibited soon after dehydrated rats began to drink water and before rehydration was complete. Oropharyngeal stimulation associated with the act of drinking likely did not inhibit VP secretion in these animals, because no such effect was apparent either when isotonic saline was consumed instead of water or when water was consumed by dehydrated rats with an open gastric fistula. Similarly, it seems doubtful that cerebral osmoreceptors mediate this inhibitory effect, because VP secretion appeared to cease in rehydrating rats before there was measurable osmotic dilution of systemic blood. On the other hand, the present results are consistent with a previous hypothesis (2) implicating visceral osmoreceptors in this phenomenon, because ingested water emptied from the stomach and reached the small intestine in the same rapid time frame as the inhibition of VP secretion. Additional experiments are needed to further examine this inhibitory effect as well as the termination of water intake, which occurred several minutes after pVP values began to diminish and appears to have a separate basis.

Perspective

One of the main findings in this report is that VP secretion and thirst were not inhibited simultaneously soon after rats began to ingest water. Instead, thirst was terminated coincident with the return of pNa values to normal levels, whereas VP secretion was inhibited more quickly. This finding may be contrasted with the effect of drinking to rapidly inhibit both responses to dehydration in dogs, sheep, monkeys, and humans (1, 3, 4, 16, 28, 31). In considering this species difference, it seems relevant that systemic rehydration is achieved much sooner in rats than in those other animals. Specifically, normal plasma osmolality is not restored by water drinking for 15 min in humans (16), for 30 min in dogs (28), for 40 min in monkeys (31), and for 60 min in sheep (3), whereas it is restored in 6 min in rats. Given the lengthy delay in gastric emptying and osmotic equilibration apparent in those other animals, a clear benefit of an early oropharyngeal signal that terminates water consumption is that it precludes significant overdrinking and
consequent dilutional hyponatremia. Note that the rat is not unique in differing from the other animals in this respect; dehydrated pigs also drink (for 6.6 min on average) until normal plasma osmolality is restored (10).

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