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Antidiuretic hormone infusion reduces taurine and NaCl-induced hypernatremia in the rat*

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Summary. Rats drinking taurine and hypertonic saline (T + S) develop severe hypernatremia, but rats drinking either T or S alone do not. One hypothesis for this disruption of homeostasis is that the T + S combination interferes with the actions of antidiuretic hormone (ADH). Rats drinking T + S developed severe hypernatremia (170 mmol/L) by day 8 when infused with distilled water by osmotic minipumps, but maintained plasma sodium below 150 mmol/L when infused with ADH. Cumulative water balance in T + S drinkers receiving ADH was consistently higher than in those not receiving ADH. However the ratio of cumulative sodium balance to cumulative water balance suggests little uniform advantage to rats receiving ADH nor does comparison of urine osmolality in the two groups. Precisely how ADH administration reduces hypernatremia in T + S drinking rats remains unclear, but the hypothesis that T + S interferes with the action of ADH in its regulation of extracellular fluid volume and osmolality remains viable.

Keywords: Amino acids – Taurine – Hypernatremia – Antidiuretic hormone – Salt and water balance

Introduction

Ingestion of taurine (2-aminoethanesulfonic acid) in combination with hypertonic saline has been shown to induce severe hypernatremia (>160 mmol/L) in rats (Dlouha and Krecek, 1986; McBroom et al., 1989; McBroom et al., 1990; McBroom and Davidson, 1996). Ingestion of taurine alone has no effect and ingestion of hypertonic saline has only a modest and transient effect on plasma sodium levels (P_{Na}). Our previous studies also have

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shown that the development of hypernatremia is accompanied by an inability of rats to concentrate their urine (i.e., to retain free water) sufficiently to maintain a normal plasma osmolality.

Most reports of taurine action concern its diverse regulatory actions in many tissues, particularly when conditions deviate from normal (van Gelder, 1983). For example, oral ingestion of taurine exerts an antihypertensive effect in DOCA-salt rats (Fujita and Sato, 1988), possibly via an action at the hypothalamic level (Fujita et al., 1986). However, in normal rats drinking the taurine + saline solution, the presence of taurine seems to compromise the normal extracellular fluid volume and/or osmolality regulating mechanisms which operate in rats drinking the saline alone. This is of interest as it is usually assumed that taurine has negligible toxicity (Huxtable, 1992). Indeed all actions of taurine so far described, apart from this induction of hypernatremia, appear to help maintain function in unstable situations, a property that has been called enantiostasis (Mangum and Towle, 1977).

The present study of hypernatremia induced by taurine + saline ingestion incorporates infusion of arginine vasopressin (aVP = antidiuretic hormone) from subcutaneously implanted osmotic minipumps. These experiments were designed to test whether such hypernatremia can be minimized by administration of aVP.

Materials and methods

Animals, diet and drinking regimens

Locally bred adult (>150 g) male Wistar rats were housed under controlled conditions in metabolism cages in an animal holding room and received *ad libitum* standard (0.2% Na w/w) rat chow throughout all experiments. Also provided *ad libitum* to each group was one of the following drinking regimens: tap water control (C); 0.1 M taurine (T); 1.8% NaCl (S); or 0.1 M taurine +1.8% NaCl (T + S). For all groups n = 6.

Experimental protocol

The animal holding room, where metabolism cages were kept and sample collections were taken, was temperature controlled at 25°C with a 12 h : 12 h light : dark cycle. Each rat was placed into an individual metabolism cage on day −2 to allow for stabilization prior to provision of the assigned drinking regimen on day 0. All rats had osmotic minipumps (Alzet mini-osmotic pump, model 2001) implanted subcutaneously in the back of the neck on day 0. These had a delivery rate of 1.0 μL/hour and were filled (200 μL capacity) with either distilled water vehicle, or with distilled water containing 1 mg arginine vasopressin (aVP) per 10 ml. Ether anesthesia was used both for subcutaneous implantation of the pumps and for killing the rats at the termination of the experiments.

Measurements were made as described below, beginning on day −2, and experiments were continued until final sample collections were completed on the morning of day 8. Only data collected from day 0 onward are reported here. The experimental duration was based on earlier findings (McBroom and Davidson, 1995; McBroom and Davidson, 1996) that T + S predictably produced hypernatremia midway into this period and that control groups infused with aVP (Tap Water with aVP) produced an antidiuresis which peaked by day 2 and began to decline around day 6 (McBroom and Davidson, 1997). Measurements were made between 0900h and 1000h. Body weights were determined daily and tail-tip blood samples from which plasma sodium concentration (P_{Na}) and osmolality

(P_{osm}) were determined were taken on alternate days from day −2. Food and solution consumption, urine volume (UV), osmolality (U_{osm}) and sodium concentration (U_{Na}) were measured daily from day −1. Variables calculated daily using these data were: sodium balance; cumulative sodium balance (Cum Na); "visible" water balance (i.e., volume of solution consumed − UV); and cumulative water balance (Cum H_2O).

It should be noted that the so-called visible water balance is determined by subtracting only urine volume from total fluid volume consumed. Thus, even in the control group the result is a positive value and, consequently, Cum H_2O appears to increase throughout the experiment in all groups. U_{Na} and P_{Na} were determined by flame emission spectrophotometry and U_{osm} and P_{osm} were measured by vapor pressure osmometry.

Statistical analyses

All values reported are mean ± SEM. Statistical tests used were (Glantz, 1992): one-way repeated measures analyses of variance (ANOVAs) for within regimens over the 8-day experimental period, with the nonparametric alternative of Friedman's repeated measures ANOVA on ranks used when the normality test failed. If the ANOVA indicated the presence of statistically significant differences, a suitable multiple comparison test (Tukey or Dunnett) was used to compare mean values from day to day within the group. Two-way ANOVAs were used to test for significant differences among regimens over the course of the experiment, and when appropriate, were followed by a Tukey test.

Results

Figure 1 shows that rats drinking a solution containing 0.1 M taurine and 1.8% NaCl and infused with distilled water (T + S without aVP) had a significantly elevated P_{Na} by day 2, and severe hypernatremia (>160 mmol/L) by day 8. One animal in this group died (on day 5). This is a very similar result to those

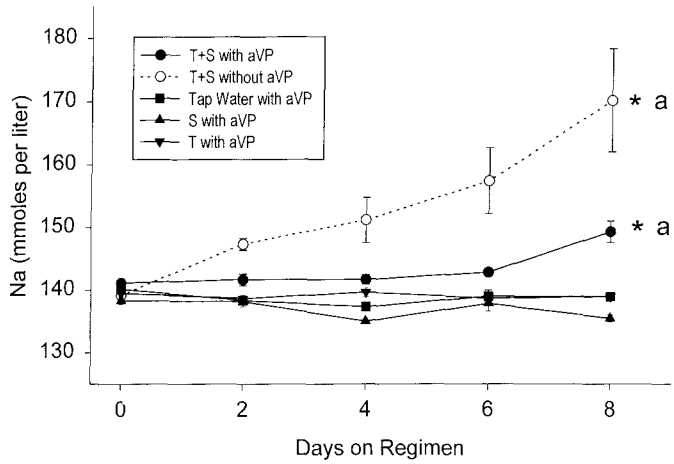

Fig. 1. Plasma sodium concentration in rats drinking the regimens indicated while infused from subcutaneously implanted osmotic minipumps containing either 0.02 mg of aVP in 200 μL of distilled water (with aVP) or distilled water alone (without aVP). All values are means ± SEM (n = 6 for each group). Statistically significant ($P < 0.05$) results of two-way ANOVAs are indicated as follows: *Regimen is different from tap water control over the 8-day period; *a* regimen is different from all other treatment regimens over the 8-day period

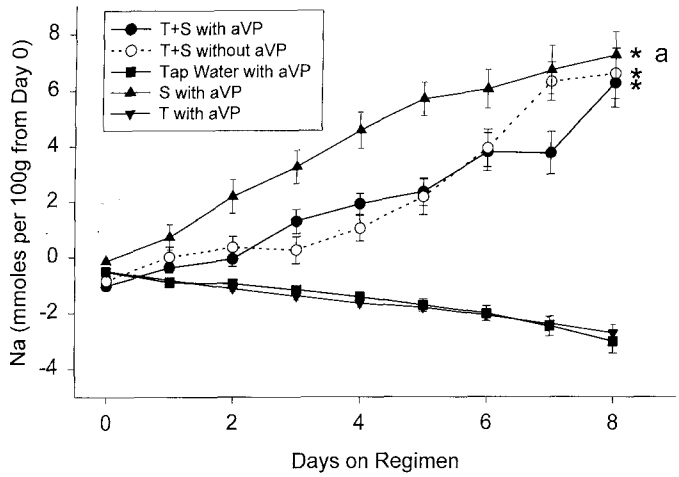

Fig. 2. Cumulative sodium balance in rats drinking the regimens indicated while infused from subcutaneously implanted osmotic minipumps containing either 0.02 mg of aVP in 200 μL of distilled water (with aVP) or distilled water alone (without aVP). All values are means ± SEM (n = 6 for each group). Statistically significant ($P < 0.05$) results of two-way ANOVAs are indicated as follows: *Regimen is different from tap water control over the 8-day period; *a* regimen is different from all other treatment regimens over the 8-day period

of our previous reports (McBroom and Davidson, 1995; McBroom and Davidson, 1996) on rats drinking T + S only. Rats drinking S with aVP, T with aVP, or tap water with aVP showed no significant alterations in P_{Na} throughout the 8 days of the experiment. By contrast, in the T + S with aVP group, P_{Na} remained below 145 mmol/L through day 6. Only on day 8 did P_{Na} rise significantly, but still remained below 150 mmol/L. No deaths occurred other than the one mentioned above in the T + S without aVP group.

Cumulative sodium balance (Cum Na) declined gradually but steadily in C with aVP and T with aVP groups (Fig. 2). All groups drinking saline showed a significant and rapid rise in Cum Na. However there was no significant difference between the T + S with aVP group and the T + S without aVP group. The S with aVP group had a significantly greater and more rapid rise in Cum Na than all other groups.

Cumulative water balance (Cum H_2O) showed much less divergence among the groups (Fig. 3). Cum H_2O in the T + S group did not differ significantly from the tap water control group. The T with aVP group had a consistently and significantly higher Cum H_2O than all other groups.

The daily ratios of Cum Na/Cum H_2O depicted in Fig. 4 show little overall difference between rats drinking T + S with aVP and rats drinking T + S without aVP. The group showing the most rapid rise in Cum Na/Cum H_2O is the one drinking S with aVP, which is consistent with their Cum Na pattern (Fig. 2). However, by day 8 there is no significant difference between this and the T + S with aVP or the T + S without aVP groups.

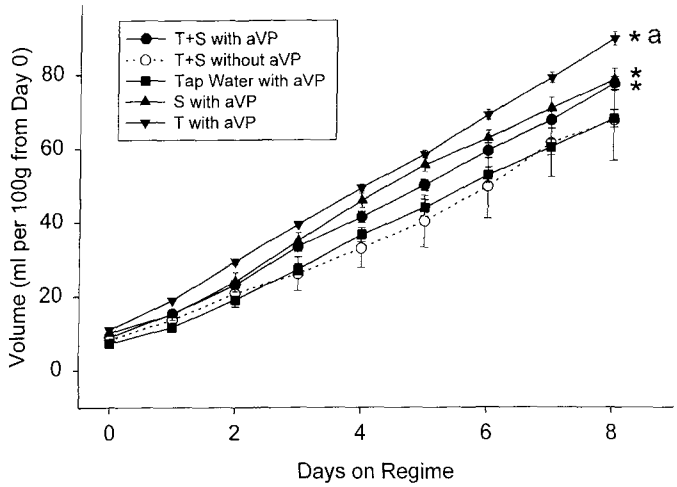

Fig. 3. Cumulative water balance in rats drinking the regimens indicated while infused from subcutaneously implanted osmotic minipumps containing either 0.02 mg of aVP in 200 μL of distilled water (with aVP) or distilled water alone (without aVP). All values are means ± SEM (n = 6 for each group). Statistically significant ($P < 0.05$) results of two-way ANOVAs are indicated as follows: *Regimen is different from tap water control over the 8-day period; *a* regimen is different from all other treatment regimens over the 8-day period

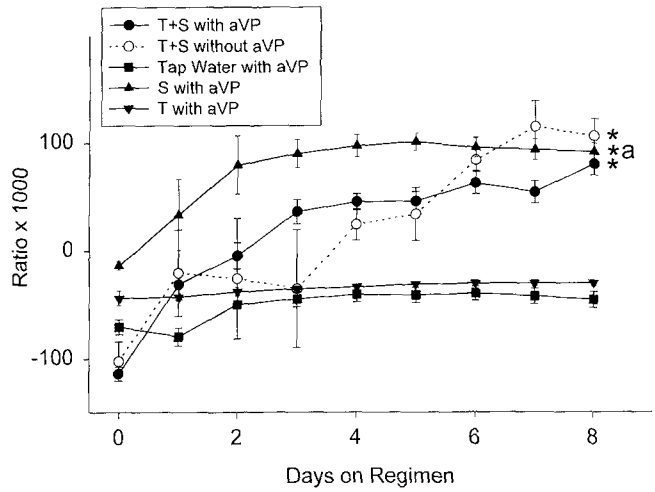

Fig. 4. Cumulative sodium balance/cumulative water balance ×1,000 in rats drinking the regimens indicated while infused from subcutaneously implanted osmotic minipumps containing either 0.02 mg of aVP in 200 μL of distilled water (with aVP) or distilled water alone (without aVP). All values are means ± SEM (n = 6 for each group). Statistically significant ($P < 0.05$) results of two-way ANOVAs are indicated as follows: *Regimen is different from tap water control over the 8-day period; *a* regimen is different from all other treatment regimens over the 8-day period

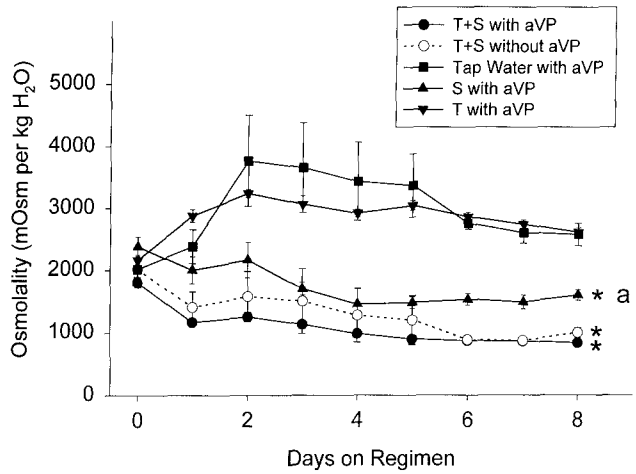

Fig. 5. Urine osmolality in rats drinking the regimens indicated while infused from subcutaneously implanted osmotic minipumps containing either 0.02 mg of aVP in 200 μL of distilled water (with aVP) or distilled water alone (without aVP). All values are means ± SEM (n = 6 for each group). Statistically significant ($P < 0.05$) results of two-way ANOVAs are indicated as follows: *Regimen is different from tap water control over the 8-day period; *a* regimen is different from all other treatment regimens over the 8-day period

Figure 5 shows that the tap water control and T with aVP groups increase their urine osmolality steadily from day 0. The antidiuresis in these two groups appears to peak on day 2 and remains significantly higher than that in the other three groups through day 8. While rats drinking S with aVP are producing a diuresis, their urine remains significantly more concentrated than rats drinking T + S with or without aVP.

Figure 6 shows that tap water control, S with aVP and T with aVP groups all have significant gains in body weight by day 8 compared to day 0. This is in contrast to both T + S without aVP and T + S with aVP groups which have significant losses of body weight. Furthermore, rats drinking T + S without aVP lose significantly more weight from day 4 through day 8 than do those drinking T + S with aVP.

Discussion

Many putative central regulatory actions have been ascribed to taurine (Wright et al., 1986). These include physiological roles as a hypothalamic neurotransmitter (Hanretta and Lombardini, 1987) regulating neuroendocrine release (Scheibel et al., 1984; Price et al., 1978; Collu et al., 1978), as well as in thermoregulation (Carla et al., 1981), blood pressure control (Singewald et al., 1993) and cerebral osmoregulation (Trachtman et al., 1988). Taurine may also act peripherally to modulate blood pressure (Fujita and Sato, 1988) and in cellular osmoregulation (Atlas et al., 1984).

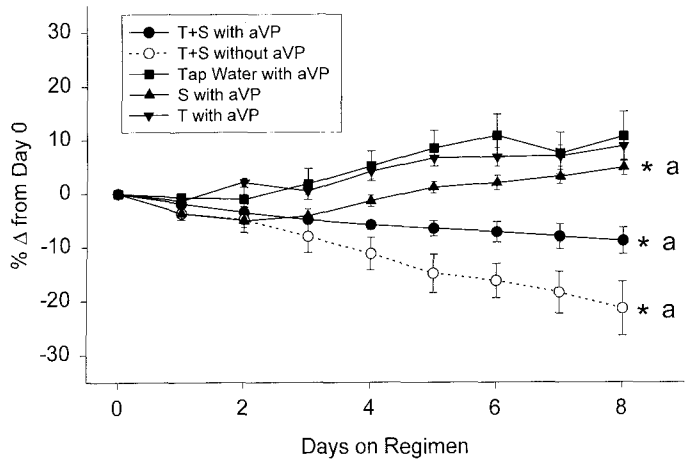

Fig. 6. Body weight changes (as % from day 0 body weight) in rats drinking the regimens indicated while infused from subcutaneously implanted osmotic minipumps containing either 0.02 mg of aVP in 200 μL of distilled water (with aVP) or distilled water alone (without aVP). All values are means ± SEM (n = 6 for each group). Statistically significant ($P < 0.05$) results of two-way ANOVAs are indicated as follows: *Regimen is different from tap water control over the 8-day period; *a* regimen is different from all other treatment regimens over the 8-day period

It has been generally accepted that taurine acts to conserve normal function, so the discovery that it causes lethal disruption of an important homeostatic mechanisms was entirely unexpected. It has long been known that excessive taurine administration can have untoward effects (Schmidt et al., 1918). However, the discovery that ingestion of an innocuous (when taken by itself) amount of taurine ingested together with hypertonic saline produces a lethal hypernatremia (mean $P_{Na} > 160$ mmol/L) was surprising (McBroom et al., 1989; McBroom and Davidson, 1996).

The present study has confirmed that rats drinking T + S develop severe hypernatremia by day 8 of that regimen. However, rats drinking T + S and infused with aVP from a subcutaneously implanted osmotic minipump develop no significant hypernatremia (i.e., less than 145 mmol/L) until day 8, when P_{Na} rose slightly but was still less than 150 mmol/L (Fig. 1). It is perhaps relevant to note that the antidiuretic effect of infused aVP was falling off by day 6 (Fig. 5). This is consistent with the fact that the minipump used in this study is designed to deliver its contents over a period of approximately 7 days. The small rise in P_{Na} on day 8 may reflect the end of a period of protection against hypernatremia conferred by infusion of aVP.

The beneficial effect of this protective action is clearly seen in Fig. 6. Rats drinking T + S without aVP steadily lose body weight. One rat in this group had died by day 8 and unpublished data from our laboratory have shown that over a longer time period the lethal effects of hypernatremia will extend to all members of the group. However, with infusion of aVP, not only is severe hypernatremia avoided, but body weight loss is significantly reduced.

It should be noted that there is an apparent incongruity in Fig. 5, viz., rats drinking tap water with aVP have a high U_{osm} while those drinking concentrated solutions of S or T + S with aVP have a low U_{osm}. This is consistent, however, with the reduction of renal concentrating (or diluting) ability which accompanies a high solute excretion rate (de Wardener and del Greco, 1955). In the present study, rats drinking tap water with aVP exhibit a modest solution consumption, a frank antidiuresis (urine output 2–3 ml/100 g/24 h) and a high U_{osm}. By contrast, those drinking S with aVP have solution consumption 2–3 times higher than water drinkers (T + S with or without aVP 3–5 times higher) and urine output 7–16 ml/100 g/24 h (T + S with or without aVP 15–55 ml/100 g/24 h) and a low U_{osm}. In groups drinking hypertonic solutions, urine sodium contributes much more to the total urine osmolality than it does in water drinkers. However, this additional sodium is not sufficient to maintain osmolality in the face of the diuretic response resulting from the additional volume load.

Thus, at this point, the nature of the advantage conferred by aVP administration upon rats drinking T + S remains unclear. The daily ratios of Cum Na/Cum H_2O (Fig. 4) show little uniform advantage to the T + S with aVP group compared to the T + S without aVP group. Nevertheless, the protective action of aVP infusion against severe hypernatremia, which we have demonstrated in this report, appears to support the hypothesis that drinking T + S somehow interferes with the role of ADH in extracellular osmolality and volume regulation.

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