Dehydration-induced vasopressin secretion in humans: involvement of the histaminergic system

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Kjær, Andreas, Ulrich Knigge, Henrik Jørgensen, and Jørgen Warberg. Dehydration-induced vasopressin secretion in humans: involvement of the histaminergic system. Am J Physiol Endocrinol Metab 279: E1305–E1310, 2000.—In rats, the hypothalamic neurotransmitter histamine participates in regulation of vasopressin secretion and seems to be of physiological importance, because blockade of the histaminergic system reduces dehydration-induced vasopressin secretion. We investigated whether histamine is also involved in regulation of vasopressin secretion during dehydration in humans. We found that 40 h of dehydration gradually increased plasma osmolality by 10 mosmol/kg and induced a fourfold increase in vasopressin levels. Pretreatment with the H2-receptor antagonists cimetidine or ranitidine significantly reduced the dehydration-induced increase in vasopressin levels ~40% after 34 and 37 h of dehydration, whereas this was not the case with the H1-receptor antagonist mepyramine. Dehydration reduced aldosterone secretion by ~50%. This effect of dehydration was reduced by both H1- and H2-receptor blockade after 16 and/or 34 h of dehydration. We conclude that vasopressin secretion in response to dehydration in humans is under the regulatory influence of histamine and that the effect seems to be mediated via H2-receptors. In addition, the regulation of aldosterone secretion during dehydration also seems to involve the histaminergic system via H1 and H2 receptors.

histamine H1 receptor; histamine H2 receptor

DEHYDRATION IS A POTENT physiological stimulus for arginine-vasopressin (AVP) secretion. It is believed that dehydration via induction of hyperosmolality activates osmoreceptors and subsequently causes magnocellular AVP neurons to release AVP from the posterior pituitary gland (1, 18, 22). The exact mechanism by which fluctuation in osmolality influences AVP neurons is still not fully understood, but it is known that direct osmoreception by magnocellular neurons accounts for only part of the regulation (12, 21–23). Thus other neurotransmitters and neuropeptides seem to be involved in the regulation (21–23).

Recently, we and others have suggested that histamine (HA), which acts as a hypothalamic neurotransmitter (20), is an important regulator of vasopressin secretion in rats (6). This suggestion is supported by the findings that histaminergic compounds stimulate vasopressin secretion, induce c-fos expression in vasopressinergic neurons, and increase vasopressin synthesis, as indicated by higher mRNA levels (7, 9). Furthermore, the physiological importance of HA in rats is indicated by the finding that blockade of the central histaminergic system reduces dehydration-induced AVP secretion and that dehydration increases hypothalamic HA turnover as well as the activity (mRNA) of the HA synthesis enzyme histamine decarboxylase (7, 9). The compounds used in our rat experiments were all drugs widely used against allergy (H1-receptor antagonists) and gastric acid secretion (H2-receptor antagonists). Because the drugs are widely used, have minor and reversible side effects, and are in general well tolerated, we wanted by the present investigation to extend to humans our studies of a possible histaminergic involvement in dehydration-induced AVP secretion.

The aims of the study were 1) to develop and characterize a dehydration model and 2) to study the effect of HA receptor antagonists on dehydration-induced AVP secretion in humans.

MATERIALS AND METHODS

Subjects

Ten healthy nonsmoking male volunteers were used. They were aged 23–44 yr and weighed 60–90 kg. Oral and written consent was obtained, and all experiments were performed in accordance with the Helsinki II declaration and were approved by the local scientific ethics committee of Copenhagen and Frederiksberg (permission no. KP 01–296/95).

Compounds

The compounds used were the HA H1-receptor antagonist mepyramine (Mepyramine “DAK”, Nycomed DAK, Copenhagen, Denmark) and the HA H2-receptor antagonists cimeti-dine (Acnil, GEA, Frederiksberg, Denmark) or ranitidine (Kuracid, GEA). Calcium lactate tablets (500 mg, Nycomed DAK) were used as control medication (placebo).

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Experimental Protocol

Design. A double-blind crossover study was performed, where all subjects received all four treatments (placebo, H₁ antagonist or the two H₂ antagonists) in random order.

Pharmacological treatment. All subjects received HA-receptor antagonists or placebo throughout the dehydration period. The drugs were given per os four times a day at 0730, 1300, 1800, and 2330. The doses used were: mepyramine 500 mg/day, cimetidine 1,600 mg/day, and ranitidine 600 mg/day. The doses correspond to twice the standard dosage (cimetidine and ranitidine) or twice the maximum recommended dose (mepyramine). The doses were chosen as a compromise between being safe and being as high as possible to ensure sufficient concentrations in the brain (not measured).

 Vasopressin stimulation. To stimulate AVP secretion, the subjects abstained from consumption of water for 40 h. Throughout dehydration, standardized meals were ingested with a calorie content equivalent to the normal intake of the subjects. The meals were supplemented with 2 g (34 mmol) of sodium chloride to further increase plasma osmolality.

Protocol. On day 1, at 0830, the normohydrated subjects emptied their urinary bladders, and they were weighed, seated, and had a venous line placed in a cubital vein. After a resting period of 45 min (seated) and measurement of blood pressure and heart rate, two baseline blood samples were drawn, separated by 10 min. At 2330, the subjects again emptied their urinary bladders and started the dehydration period of 40 h.

On day 2, at 0930 (10 h of dehydration) and 1530 (16 h of dehydration), the subjects had two blood samples drawn, separated by 10 min. Before blood sampling, the subjects emptied their bladders (urine was kept for further analysis), they were weighed and seated for at least 45 min, and blood pressure and heart rate were measured.

On day 3, the procedures described above were repeated at 0930 (34 h of dehydration), 1230 (37 h of dehydration), and 1530 (40 h of dehydration).

Analysis. Blood and plasma samples were analyzed for hematocrit, hemoglobin, osmolality, protein, sodium, potassium, AVP, atrial natriuretic peptide (ANP), aldosterone, and plasma renin activity (PRA). Urine samples were analyzed for volume, osmolality, sodium, potassium, and AVP.

Hematocrit, Hemoglobin, Protein, Osmolality, Sodium, and Potassium

Hematocrit was measured directly on microhematocrit tubes after centrifugation. Hemoglobin was measured by a photometric method using a commercial kit according to the instructions of the manufacturer (Merektest 3317, E. Merck, Darmstadt, Germany). Plasma protein was measured by refractometry using a refractometer (Delta Refractometer, Bellingham and Stanley, Kent, UK). Osmolality was measured in triplicate by freezing-point depression (Advanced Microsorrometer 3MO, Advanced Instruments, Needham Heights, MA). Plasma sodium and potassium were measured electrochemically using a sodium- or potassium-selective electrode (KNA2, Radiometer, Copenhagen, Denmark).

AVP, ANP, Aldosterone, and PRA

AVP was measured by RIA of plasma extracted by means of C₁₈ Sep-Pak cartridges according to a previously described procedure (8, 11). Synthetic AVP (mol wt 1,083; Peninsula Laboratories, Belmont, CA) served as reference preparation. The least detectable quantity was 0.1–0.3 pmol/l plasma, and the intra- and interassay coefficients of variation were 8 and 12%, respectively.

ANP was measured by RIA of plasma extracted by means of C₁₈ Sep-Pak cartridges according to a previously described procedure (19). Synthetic ANP (Peninsula Laboratories) served as reference preparation. The least detectable quantity was 1 pmol/l, and the intra- and interassay coefficients of variation were 4 and 5%, respectively.

Aldosterone was measured by RIA of unextracted plasma using a commercial kit according to the instructions of the manufacturer (Coat-A-Count, DPC, Los Angeles, CA). The least detectable quantity was 44 pmol/l, and the intra- and interassay coefficients of variation were 6 and 7%, respectively.

Determination of PRA was made by RIA of generated and antibody-trapped angiotensin I according to a previously described procedure (16). Synthetic angiotensin I (Bio-Schwartz), which was tested against Research Standard A (Institute for Medical Research, Holy Hill, London, UK) served as reference preparation. The intra- and interassay coefficients of variation were 3.2 and 3.6%, respectively.

Statistical Analysis

Data are presented as means ± SE. Comparisons over time and between treatment groups were performed as one-way analyses of variance for repeated measures followed by the least significant difference post hoc procedure for multiple comparisons where appropriate. P < 0.05 was considered significant.

RESULTS

Effect of Dehydration on Water and Salt Balance in Placebo-Treated Control Subjects

Dehydration gradually increased plasma osmolality from 286.7 ± 0.8 at 0 h to 291.8 ± 0.6 mosmol/kg at 16 h and to 296.8 ± 0.4 at 40 h (Fig. 1; P < 0.01). Dehydration for 10 h had no effect on plasma osmolality. Plasma sodium rose from a baseline level of 140.6 ± 0.3 to 143.1 ± 0.2 mmol/l at 16 h and to 145.6 ± 0.3 at 40 h (Fig. 1; P < 0.01). Plasma potassium was lower throughout dehydration. The baseline level of potassium was 4.34 ± 0.07 (37–40 h, P < 0.01) with the nadir of 4.06 ± 0.04 was observed after 10 h of dehydration (Fig. 1; P < 0.01). Hematocrit (baseline, 0.45 ± 0.01), hemoglobin (baseline, 8.2 ± 0.2 mmol/l), and plasma protein (baseline, 87.2 ± 1.4 g/l) were all unaffected by dehydration (data not shown).

Forty hours of dehydration decreased diuresis from 0.90 ± 0.11 ml/min (0–10 h) to 0.56 ± 0.07 (P < 0.01) and increased urine osmolality from 597 ± 80 mosmol/kg (0–10 h) to 1,120 ± 25 (37–40 h, P < 0.01), leaving the rate of solute excretion relatively constant from 0.54 (0–10 h) to 0.63 mosM/min (37–40 h). An inverse correlation was found between diuresis (D) and urine osmolality (U osmol; r = −0.51, P < 0.01) with the regression line: U osmol = 1,291 − 500 × D, predicting a theoretical maximal concentration of urine of 1,290 (1,120–1,460, 95% confidence interval) mosmol/kg. Urine sodium increased from 70 ± 11 (0–10 h) to 237 ± 11 mmol/l (37–40 h, P < 0.01), urine potassium...
increased from 36 ± 5 (0–10 h) to 119 ± 10 mmol/l (37–40 h, P < 0.01), and urine AVP increased from 24 ± 4 (0–10 h) to 746 ± 153 pmol/l (37–40 h, P < 0.01). Dehydration had no influence on blood pressure (baseline, 123 ± 4/72 ± 3 mmHg) or heart rate (baseline, 67 ± 3; data not shown).

**Effect of Dehydration on Hormone Secretion in Placebo-Treated Control Subjects**

Dehydration for 40 h gradually increased plasma AVP levels to more than fourfold baseline levels (Fig. 2; P < 0.01). The plasma AVP levels correlated with plasma osmolality (r = 0.34, P < 0.01). The level of aldosterone fell to almost one-half the baseline level after 16 h of dehydration and stayed at that level for the rest of the test period (Fig. 3; P < 0.01). PRA (baseline, 1.7 ± 0.3 ng·ml⁻¹·h⁻¹) and ANP (baseline, 4.6 ± 0.6 pmol/l) were unaffected by dehydration (data not shown).

**Effect of Selective Histamine H₁- or H₂-Receptor Blockade on Dehydration-Induced Hormone Secretion and Excretion**

The H₂-receptor antagonists cimetidine and ranitidine reduced dehydration-induced AVP secretion by ~40% at 34 and 37 h (Fig. 2; P < 0.05). In contrast, the H₁-receptor antagonist mepyramine did not influence AVP secretion (Fig. 2). HA receptor blockade had no influence on urine concentration of AVP (data not shown). Dehydration-induced inhibition of aldosterone secretion was reduced by the H₁- and the H₂-receptor antagonists after 16 and/or 34 h (Fig. 3; P < 0.05 or P < 0.01). HA receptor blockade did not influence secretion of ANP or PRA, which were not affected by dehydration (data not shown). HA receptor blockade had no effect on plasma osmolality, plasma sodium, plasma potassium, diuresis, or urine osmolality (data not shown).

**DISCUSSION**

Dehydration for 40 h increased plasma osmolality and sodium. Because plasma osmolality is the major regulator of AVP secretion, it was expected that AVP would increase during dehydration. There was a correlation between osmolality and AVP levels in our study. The increase in osmolality and AVP in response to dehydration was comparable with what was found in rats (7).

Blockade of HA H₂ receptors throughout dehydration reduced the AVP secretion significantly. H₁-receptor blockade by mepyramine did not significantly reduce AVP secretion (P = 0.05). However, with regard to the latter, it should be noted that the risk of type II error, i.e., the risk of overlooking a true difference, is ~30% in our study. The effect of HA receptor blockade was seen after 34 and 37 h of dehydration but not after 40 h, indicating that other mechanisms take over when dehydration has persisted for a certain time. We have shown that, taken together, H₂-receptor blockade reduces dehydration-induced AVP secretion. It could be argued that differences in AVP levels may be due to differences in clearance of AVP rather than in secretion. However, we found no differences in diuresis or urine concentrations of AVP between treatment groups, ruling this possibility out. On the other hand, it should be noted that, because cholinergic neurons are
known to be involved in regulation of vasopressin secretion (21) and mepyramine possesses anticholinergic activity (3), we cannot totally rule out the effect (non-significant) of mepyramine being in part mediated via its anticholinergic properties.

How and where is the effect of HA in dehydration-induced vasopressin secretion exerted? First, it should be noted that the histamine receptor blockade had no effect on the degree of hyperosmolality obtained, i.e., the effect of HA blockade resulted in lower AVP secretion at the same degree of hyperosmolality. Direct osmoreception by magnocellular neurons is thought to be ascribed to mechanosensitive channels (14) and is therefore unlikely to be influenced by HA. Thus we believe that, most likely, HA is one of several transmitter systems that project to magnocellular AVP neurons in the paraventricular nucleus (PVN) and supraoptic nuclei (SON), thereby regulating release of AVP. This idea is anatomically supported by the existence in rats of histaminergic fibers projecting to the PVN and SON from the posterior hypothalamus, where histaminergic perikarya are exclusively located (5, 15). Furthermore, H₁ and H₂ receptors have been demonstrated in the hypothalamus, including the PVN.
and SON of rats (2, 20) and in the human hypothalamus (13, 24). Finally, dehydration activates the histaminergic system in rats, as indicated by the increased hypothalamic content of HA and its metabolite tele-methylhistamine (7) as well as by increased levels in the posterior hypothalamus of the HA synthesis enzyme histidine decarboxylase (9).

We have previously demonstrated in rats that blockade of the histaminergic system by inhibition of HA synthesis or blockade of H1 and H2 receptors decreased dehydration-induced AVP secretion. With respect to the H2-receptor effect, we were able, in the present study, to reproduce the inhibitory effect in humans. However, with respect to the H1-receptor effect, this could not be done. One possible explanation for this difference might be the dosage and route of administration. In the animal experiments, the HA receptor antagonists were administered centrally (intracerebroventricular), i.e., close to the expected site of action in the hypothalamus. In the present human experiment, the HA receptor antagonists were administered systematically (per os). This may have led to much lower concentrations in the probable target region, namely the hypothalamus. Although cimetidine and ranitidine do not readily pass the blood-brain barrier (BBB) (3), we have, nevertheless, in previous rat experiments, obtained centrally mediated effects by systemically administered (intraperitoneally) cimetidine and ranitidine (10). However, we cannot rule out that the effect could be exerted outside the BBB. Therefore, the somewhat lower effect observed in humans compared with rats is probably a matter of dosage, although we cannot rule out the importance of HA in regulation of dehydration-induced AVP secretion being different in humans and rats.

The only other hormone of those measured that changed during dehydration was aldosterone. The regulation of aldosterone is complex (17) and closely interrelated with regulation of salt and water balance. A possible explanation for the decrease in aldosterone levels throughout dehydration may be that the decrease observed in plasma potassium concentration inhibits aldosterone secretion, an effect believed to be exerted directly at the level of adrenocortical cells (4). What favors this idea is that we found a significant correlation between potassium and aldosterone ($r = 0.32, P < 0.01$). Other possible mechanisms could be via the renin-angiotensin system or ACTH. However, because we measured both PRA and ACTH and both were unaffected by dehydration, these mechanisms are unlikely. Whatever the mechanism, it was reduced by blockade of H1 and H2 receptors. Therefore, it seems that dehydration-induced inhibition of aldosterone is influenced by histamine acting on H1 and H2 receptors. How histamine is involved in this is not clear, but no differences were found between potassium levels in the different treatment groups throughout dehydration, i.e., the effect of antihistamines seems to be a change in response to a given potassium level.

In summary, we found that dehydration-induced AVP secretion in humans seems to be mediated, in part, via histamine and that this effect is mediated via H2 receptors. In addition, we found that the decrease in aldosterone levels throughout dehydration also seems to involve the histaminergic system acting via H1 and H2 receptors.

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