Impaired Osmoregulation at High Altitude

Studies on Mt Everest

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• **Osmoregulation was studied in 13 mountaineers who had experienced long-term exposure to high altitude on Mt Everest. Serum osmolality rose from 290±1 mOsm/kg to 295±2 mOsm/kg at 5,400 m and finally to 302±4 mOsm/kg at 6,300 m after a mean of 26.5 days above 5,400 m. Despite this degree of osmoconcentration, plasma arginine-vasopressin concentration remained unchanged: 1.1±0.1 μU/mL at sea level, 0.8±0.1 μU/mL at 5,400 m, and 0.9±0.1 μU/mL at 6,300 m. Urinary vasopressin excretion was also similar at all three altitudes. We conclude that prolonged exposure to high altitude may result in persistent impairment of osmoregulation, caused in part by an inappropriate arginine-vasopressin response to hyperosmolality.**

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AT HIGH altitude, humans experience a loss of body water associated with decreased voluntary fluid intake and usually increased urine output.[1-7] The pathophysiology of this phenomenon is unclear, but it may be of importance to the health of high-altitude sojourners. Between 3,000 and 5,500 m, diuresis and weight loss may be indicative of successful acclimatization[3,4]; their absence has been associated with severe acute mountain sickness.[8-10] Such effects are often transient, but persistent negative water balance has been documented for up to 28 days at 4,300 m.[1]

Above 5,500 m humans do not acclimatize, and permanent residence is not possible.[11] Many authors have suggested that dehydration may contribute to the physical deterioration observed there,[11-13] but few data concerning osmoregulation in such settings are available. In particular, it is not known if data derived from short-term human or animal studies at moderate altitudes accurately reflect the effects of chronic exposure to more extreme elevations.

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We now report observations on osmoregulation at sea level, 5,400 m, and 6,300 m. With increasing altitude there was a progressive rise in serum osmolality that failed to elicit an appropriate increase in the plasma concentration of arginine vasopressin. These observations document the potential hazard of dehydration for moutaineers, and suggest the presence of a chronic alteration of hypothalamic osmoregulatory mechanisms at very high altitude.

METHODS

Studies were performed in 13 healthy men as part of the 1981 American Medical Research Expedition to Everest. Subjects were mountaineers with previous experience above 6,000 m. They were tested at sea level two months before the expedition and then restudied after seven to nine consecutive days (mean±SE, 7.3±0.2) at 5,400 m and seven to 17 consecutive days (10.6±1.1) at 6,300 m. The mean total stay at altitudes greater than 5,400 m at the time of final testing was 26.5±1.6 days. Diuretics were not taken by any subject during the study.

At 7 PM on the night before testing, subjects voided and began a 12-hour urine collection and an overnight fast. For reasons of safety at high altitude, water was permitted ad libitum during the fast. To assure comparable data, water was also permitted at sea level. At 7 AM urine volume was measured and aliquots of urine were frozen. A 50-mL sample of blood was then collected into a plastic syringe. Five milliliters of blood was immediately transferred to a glass test tube containing 10.5 mg edetate disodium and 1,000 units of aprotinin. After centrifugation, the plasma was separated and rapidly frozen. The remaining blood was centrifuged and the serum frozen within an hour of collection.

Blood samples at high altitude were collected in a heated hut. Subjects were warm, free of nausea, and normotensive when tested. All specimens were kept frozen at −17 °C in the field and at −40 °C in the laboratory until the time of assay. When transported, all samples were kept frozen on dry ice. The plasma specimens were briefly thawed and refrozen once before assay for arginine vasopressin. For each assay, all samples were run simultaneously. Conditions did not permit measurement of food or water intake during the study.

Urine concentrations of sodium, chloride, potassium, calcium, inorganic phosphate, and creatinine were measured by autoanalyzer, as were serum concentrations of sodium, chloride, potassium, total CO_2, creatinine, calcium, and phosphate. Serum osmolality was measured with a vapor-pressure osmometer. Radioimmunoassay of arginine vasopressin in plasma[14] and urine[15] was performed in the laboratory of Delbert Fisher, MD, at the University of California at Los Angeles. In this assay, approximately 30% of activity is lost during frozen storage. Statistical procedures included one-way analyses of variance for comparisons among all altitudes and paired Student's *t* tests, where appropriate, for the comparison of means at two altitudes.

RESULTS

The serum osmolality and concentrations of electrolytes, total CO_2, creatinine, and arginine vasopressin are given in Table 1. At sea level, all values were within normal limits. At 5,400 m, the serum concentration of chloride increased beyond the upper limit of normal, and total CO_2 fell to below the lower limit of normal. There was some suggestion of osmoconcentration in that the serum osmolality rose to the upper limit of normal and was significantly higher than at sea level.

Table 1.—Effect of High Altitude on Serum Osmolality and Electrolytes and Plasma Arginine Vasopressin*

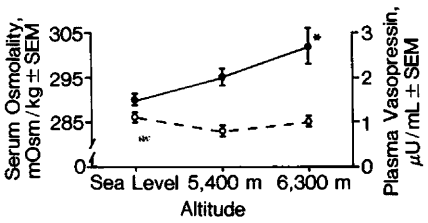
	Normal Range	Altitudes: Sea Level	5,400 m	6,300 m
Osmolality, mOsm/kg	280-295	290±1	295±2†	302±4‡§
Sodium, mEq/L	**135-148**	**143±0.4**	**143±1.3**	**148±1.6†‖**
Chloride, mEq/L	98-106	106±0.6	109±1.4	114±1.0‡‖
Potassium, mEq/L	**3.5-5.3**	**4.4±0.1 (N=12)**	**4.7±0.2 (N=12)**	**4.9±0.2† (N=12)**
Calcium, mg/dL	8.5-10.5	9.4±0.1	9.6±0.2	10.2±0.2‡‖
Phosphate, mg/dL	**2.6-4.8**	**3.3±0.1**	**3.5±0.1**	**3.6±0.1†**
Total CO_2, mEq/L	22-26	23.8±0.4	21.0±0.5‡	18.1±0.7‡§
Arginine vasopressin, μU/mL	. . .	1.1±0.1	0.8±0.1†	0.9±0.1
Creatinine, mg/dL	0.6-1.2	0.9±0.1	1.1±0.1	1.1±0.1†

*All values are the mean ± SEM of 13 subjects except where indicated.
†$P<.05$ *v* sea level.
‡$P<.01$ *v* sea level.
§$P<.05$ *v* 5,400 m.
‖$P<.01$ *v* 5,400 m.

Table 2.—Effect of High Altitude on Urine Volume, Osmolar Clearance, Creatinine Clearance, and Arginine-Vasopressin Excretion*

	Altitudes: Sea Level	5,400 m	6,300 m
Volume, mL/12 hr	599±62	1,076±126†	1,144±141†
Creatinine clearance, mL/min	104±8 (N=12)	90±8 (N=12)	101±9 (N=12)
Arginine-vasopressin excretion, mU/12 hr	6.7±1.0	6.5±0.7	5.9±1.1
Osmolar clearance, mL/min	2.10±0.15	1.92±0.13	2.65±0.23

*All values are the mean ± SEM of 13 measurements except where indicated.
†$P<.01$ *v* sea level.



Serum osmolality (solid line) and plasma arginine-vasopressin concentrations (dashed line) at sea level, 5,400 m, and 6,300 m. Each value represents mean ± SEM of 13 subjects. Osmolality at 6,300 m (indicated by asterisk) is significantly greater than at 5,400 m ($P<.05$) and sea level ($P<.01$). Osmolality at 5,400 m is also significantly greater than at sea level ($P<.05$). Normal range for serum osmolality is 280 to 295 mOsm/kg. Mean arginine-vasopressin level after overnight dehydration is reported to be 7.2 μU/mL using this assay.[14]

At 6,300 m, serum osmolality exceeded the upper limit of normal and was significantly greater than at 5,400 m or at sea level. The serum concentrations of sodium, chloride, and calcium were all significantly greater than at 5,400 m or at sea level. The serum concentrations of potassium, phosphate, and creatinine were all significantly greater than at sea level. The serum total CO_2 concentration at 6,300 m was significantly lower than at 5,400 m or sea level.

In contrast, the plasma concentration of arginine vasopressin was similar at all three altitudes. The values are typical of those obtained in hydrated normal persons at sea level.[14] The relationship between serum osmolality and the plasma concentration of arginine vasopressin is shown in the Figure.

Data derived from the urine are given in Table 2. The mean 12-hour urinary outputs at 5,400 and 6,300 m were similar, and both were significantly greater than at sea level. Osmolar clearance, creatinine clearance, and the urinary excretion rate of arginine vasopressin were similar at all altitudes.

COMMENT

This study demonstrates that long-term exposure to high altitude may result in significant serum hypertonicity that fails to elicit the appropriate release of arginine vasopressin. These observations differ substantively from many previous human studies with regard to both solute concentration and circulating levels of arginine vasopressin.

Galster and Morrison[16] observed little change in serum electrolyte concentrations after brief exposure to altitudes up to 6,200 m. Several other studies have reported that the serum sodium concentration changes very little during short periods of time at moderately high altitudes.[2,5,6]

Brahmachari et al[17] noted no change in plasma vasopressin concentrations during the first four days of exposure to 3,500 m, but found an 80% increase thereafter. Hackett et al[18] observed that plasma arginine-vasopressin concentration at 4,243 m was increased in trekkers with pulmonary edema when compared with trekkers without edema. Serum-solute concentrations were not reported in either study. Harber et al[3] found no consistent changes in urinary arginine vasopressin during ascent from 2,000 to 3,500 m. Claybaugh et al[19] reported a reduction in the concentration of arginine vasopressin after one hour of exposure to mild but not to severe hypoxia in a decompression chamber. Other chamber studies have reported increases in plasma arginine-vasopressin concentrations at high altitude.[6,20]

The present data suggest that previous investigators have reported transient changes that do not reflect the steady-state conditions achieved in subjects exposed to very high altitude for a long period of time.

The failure of the plasma concentration of arginine vasopressin to rise in the face of progressive dehydration provides evidence of hypothalamic-posterior pituitary dysfunction in the subjects tested at 6,300 m. Previous studies employing this assay have shown that serum arginine-vasopressin levels average 7.2 μU/mL after overnight dehydration at sea level, compared with 1.4 μU/mL after rehydration.[14] A similar or greater increment in arginine-vasopressin concentration would clearly be expected in the hyperosmolar subjects at 6,300 m, because the usual threshold for release in humans is about 280 mOsm/kg, with a range of 276 to 291 mOsm/kg.[21] The data on plasma arginine-vasopressin concentration in these subjects were corroborated by observing that the 12-hour urinary

arginine-vasopressin secretory rate also failed to increase at high altitude. Urinary vasopressin provides an index of vasopressin secretory rates integrated over time.[15] Both the plasma and the urinary data indicate an inappropriate response to the osmoconcentration found at 6,300 m. The cause of this altered response is not clear, but it could result from changes in osmoreceptor sensitivity or in the synthesis or release of arginine vasopressin. The effect could be mediated by an opiate peptide.[22]

It is of interest to note that one of the few animal studies to document an inappropriate diuresis and increased serum osmolality at a high altitude made observations similar to those reported here.[23] In that study, Jones et al[23] described an inappropriately reduced or unchanged arginine-vasopressin release in rats exposed to a simulated altitude of 5,450 m.

In the present study, water intake was not measured, but we would argue that it was likely to have been inappropriately low. In keeping with mountaineering practice, subjects were repeatedly encouraged to maintain high fluid intakes. Nevertheless, their dipsogenic response at 6,300 m was insufficient to prevent a rise in serum osmolality. In addition, the investigators did not observe the subjective complaints of thirst that would normally be anticipated with a serum osmolality of 302 mOsm/kg. This situation contrasts sharply to that observed clinically in patients with diabetes insipidus. Such patients generally maintain a normal or near normal serum osmolality, but at the expense of clinically obvious polyuria and polydipsia. A derangement in thirst was, in fact, the primary disturbance Jones et al[23] observed in their rats exposed to simulated high altitude. The mechanism may reside at the level of the osmotic-sensing mechanism itself.[24] We speculate that a similar derangement in thirst may have occurred in our subjects. Given the neuroanatomic proximity of structures regulating both thirst and arginine-vasopressin release, it is possible that a single neurological derangement could explain the impairment of osmoregulation at very high altitude.

Our results disclosed no significant alteration of creatinine clearance at any altitude, indicating that an increased glomerular filtration rate probably did not contribute to the loss of free water. This is supported by the fact that osmolar clearance also was similar at all altitudes. The fact that the same circulating level of arginine vasopressin was associated with a lesser urinary solute concentration at 6,300 m raises the possibility of end-organ resistance to the hormone at high altitudes. Studies in hypoxic dogs, however, have failed to demonstrate renal resistance to the effects of vasopressin.[25]

The present study demonstrates a defect in osmoregulatory mechanisms at high altitudes. In a setting where strenuous activity and hyperventilation predispose to high insensible fluid losses, a free-water diuresis occurred in the presence of a serum osmolality (302 mOsm/kg) substantially greater than the upper limit of normal. An inappropriately low plasma concentration of arginine vasopressin may have contributed to this defect. Additional studies are needed to examine those factors that control osmoreceptor sensitivity, the synthesis and release of arginine vasopressin, and the action of exogenous vasopressin on the nephron at high altitude. It would also be desirable to study a more representative group of subjects than mountaineers preselected for tolerance to high altitude. Such studies could lead to information and, possibly, therapeutics that might enhance the health and safety of sojourners to high altitude.

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References

1. Consolazio CF, Matoush LO, Johnson HL, et al: Protein and water balances of young adults during prolonged exposure to high altitude (4,300 meters). *Am J Clin Nutr* 1968;21:154-161.

2. Janoski AH, Whitten BK, Shields JL, et al: Electrolyte patterns and regulation in man during acute exposure to high altitude. *Fed Proc* 1969;28:1185-1189.

3. Harber MJ, Williams JD, Morton JJ: Antidiuretic hormone excretion at high altitude. *Aviat Space Environ Med* 1981;52:38-40.

4. Krzywicki HJ, Consolazio CF, Johnson HL, et al: Water metabolism in humans during acute high altitude exposure. *J Appl Physiol* 1971; 30:806-809.

5. Frayser R, Rennie ID, Gray GW, et al: Hormonal and electrolyte response to exposure to 17,500 ft. *J Appl Physiol* 1975;38:636-642.

6. Claybaugh JR, Wade CE, Sato AK, et al: Antidiuretic hormone responses to eucapnic and hypocapnic hypoxia in humans. *J Appl Physiol* 1982;53:815-823.

7. Hannon JP, Chinn KSK, Shields JL: Alterations in serum and extracellular electrolytes during high altitude exposure. *J Appl Physiol* 1971;31:266-273.

8. Singh I, Khanna PK, Srivastava MC, et al: Acute mountain sickness. *N Engl J Med* 1969; 280:175-184.

9. Richalet J-P, Rathat C, Keromes A, et al: Plasma volume, body weight, and acute mountain sickness. *Lancet* 1983;1:525.

10. Singh I, Malhotra MS, Khanna PK, et al: Changes in plasma cortisol, blood antidiuretic hormone and urinary catecholamines in high altitude pulmonary oedema. *Int J Biometeorol* 1974;18:211-221.

11. Heath D, Williams DR: *Man at High Altitude.* London, Churchill Livingstone, 1977, pp 247-256.

12. Pugh LGCE: Physiological and medical aspects of the Himalayan Scientific and Mountaineering Expedition 1960-1961. *Br Med J* 1962; 2:621-627.

13. Hultgren HN: High altitude medical problems, in Sutton JR, Jones NL, Houston CS (eds): *Hypoxia: Man at Altitude.* New York, Thieme-Stratton Inc, 1982, pp 161-167.

14. Skowsky WR, Rosenbloom AA, Fisher DA: Radioimmunoassay of arginine vasopressin in serum: Development and application. *J Clin Endocrinol Metabol* 1974;38:278-287.

15. Tausch A, Stegner H, Leake RD, et al: Radioimmunoassay of arginine vasopressin in urine: Development and application. *J Clin Endocrinol Metabol* 1983;57:777-781.

16. Galster WA, Morrison PR: Effects of high altitude on components of blood and urine in mountaineers. *Int J Biometeorol* 1974;18:23-32.

17. Brahmachari HD, Malhotra MS, Ramachandran K, et al: Progressive changes in plasma cortisol, antidiuretic hormone, and urinary volume of normal lowlanders during short stay at high altitude. *Indian J Exp Biol* 1973;11:454-455.

18. Hackett PH, Forsling ML, Milledge J, et al: Release of vasopressin in man at altitude. *Horm Metab Res* 1978;10:571.

19. Claybaugh JR, Hansen JE, Wozniak DB: Response of antidiuretic hormone to mild and severe hypoxia in man. *J Endocrinol* 1978; 77:157-160.

20. Heyes MP, Farber MO, Manfredi F, et al: Acute effects of hypoxia on renal and endocrine function in normal humans. *Am J Physiol* 1982;243:R265-R270.

21. Robertson GL: The regulation of vasopressin function in health and disease. *Recent Prog Horm Res* 1977;33:333-385.

22. Grossman A, Besser GM, Milles JJ, et al: Inhibition of vasopressin release in man by an opiate peptide. *Lancet* 1980;2:1108-1110.

23. Jones RM, LaRochelle FT Jr, Tenney SM: Role of arginine vasopressin on fluid and electrolyte balance in rats exposed to high altitude. *Am J Physiol* 1981;240:R182-R186.

24. Jones RM, Terhaard CT, Zullo J, et al: Mechanism of reduced water intake in rats at high altitude. *Am J Physiol* 1981;240:R187-R191.

25. Anderson RJ, Pluss RG, Berns AS, et al: Mechanism of effect of hypoxia on renal water excretion. *J Clin Invest* 1978;62:767-777.