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Renal Adrenomedullin and High Altitude Diuresis

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Summary

Previous investigations revealed that most of the fluid regulating hormones showed no consistent relationship to the hypoxic diuretic response (HDR). In this study we examined if adrenomedullin (AM), a hypoxia-mediated diuretic/natriuretic peptide is connected to HDR. Thirty-three persons were examined at low altitude (LA), on the third exposure day at 3440 m (medium altitude, MA) and on the fourteenth day at 5050 m (high altitude, HA). Nocturnal diuresis rose from 460 ml [interquartile range 302 ml] at LA to 560 [660] ml at MA to 1015 [750] ml at HA ($p<0.005$). Sodium excretion was similar at LA and MA (41.8 [27.0] vs. 41.4 [28.4] mM) and increased to 80.2 [29.1] mM at HA ($p<0.005$). Urinary AM excretion was 7.9 [3.9] at LA, 7.5 [5.7] pM at MA, and increased to 10.5 [5.1] pM ($p<0.05$) at HA. Urinary AM excretion was correlated to diuresis ($r=0.72$, $p<0.005$) and sodium excretion ($r=0.57$, $p<0.005$). Plasma AM concentration rose from 16.4 [3.1] to 18.8 [4.9] pM/l at MA ($p<0.005$) and to 18.3 [4.3] pM/l at HA ($p<0.005$). Plasma AM concentration and urinary AM excretion were not correlated, neither were plasma AM concentration and diuresis or natriuresis. Our data suggest the involvement of increased renal AM production in the pathophysiology of high altitude fluid and sodium loss.

Key words

Adrenomedullin • High altitude • Hypoxic diuretic response • Volume regulation • Adaptation

Introduction

In a laboratory environment, hypoxic conditions, equivalent to a 25-50 % reduction of inspired oxygen, cause a 'hypoxic diuretic response' (HDR) within 1-2 days of exposure (Honig 1989). HDR occurs with a considerable delay since 13 h hypoxia under controlled laboratory conditions were shown to be insufficient to produce differences in urine output between simulated altitude (2800 m) and sea level (Greenleaf *et al.* 2001). Data on the onset of HDR at the real altitude have not been published yet.

As a result of HDR, total body water is reduced, plasma volume decreases and hemoglobin values rise because renal sodium reabsorption is inhibited, despite low water and sodium intake (Honig 1989). Hypoxia itself appears to be the main stimulus of HDR, as isolated hypoxic perfusion of the carotid body also causes hypoxic diuresis and natriuresis by inhibition of renal tubular sodium reabsorption.

Because HDR persists even after renal denervation, it is likely that some humoral factor is involved in the renal water and sodium excretion, but the role of particular volume-regulating hormones in

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mediating HDR is still contentious. Circulatory levels of atrial natriuretic peptide, antidiuretic hormone, renin, aldosterone and urodilatin seem to be poorly correlated to diuresis or natriuresis (Bärtsch *et al.* 1991, Swenson *et al.* 1995, Hildebrandt *et al.* 2000), whereas endothelin-1 and epinephrine might be involved in the etiology of HDR (Hildebrandt *et al.* 2000).

Adrenomedullin (AM) is a vasodilating and diuretic/natriuretic peptide that is expressed by a variety of tissues, mainly endothelial and smooth muscle cells. It spills over into the circulation, where its plasma concentration can be quantified (Kitamura *et al.* 1993, Entzerroth *et al.* 1995, Samson *et al.* 1995). Plasma AM levels are elevated with exercise and orthostasis (Tanaka *et al.* 1995, Rössler *et al.* 1999). Hypoxia is known to be one of the strongest stimulators for transcription of AM mRNA and for AM release from human endothelial cells (Nakayama *et al.* 1999, Hofbauer *et al.* 2000), in part mediated by the so-called hypoxia-inducible factor-1 (HIF-1) (Cormier-Regard *et al.* 1998).

Two previous studies dealing with the acute hypoxic effect on plasma AM levels produced contradictory results (Toepfer *et al.* 1998, Hasbak *et al.* 2002). Plasma AM concentration and urinary AM excretion during long-lasting high altitude (HA) sojourn have not yet been looked into.

The primary goal of this study was to determine if AM is involved in the regulation of HDR during a long-term exposure to hypoxia. Furthermore, we present evidence that the diuretic/natriuretic effect may mainly be mediated by locally produced renal AM rather than by systemic effects of circulating AM.

Methods

Expedition

The 'Silver Pyramid 2002' project was an interdisciplinary high altitude research expedition, performed in the Khumbu Himal/Nepal throughout 4 weeks during the spring of 2002. At Kathmandu, the subjects were assigned to either the "trekking team" (TT, 17 subjects, 8 females, aged 19-65 years) or the "climbing team" (CT, 16 subjects, 4 females, aged 23-63 years) and they flew to Lukla (2800 m) with CT preceding TT by one day. Until medium altitude (MA) was reached, the daily altitude profile and the sleeping altitude were the same in both groups. Thereafter, TT hiked along the Gokyo valley, the highest overnight altitude was 4750 m. The CT group attempted to climb

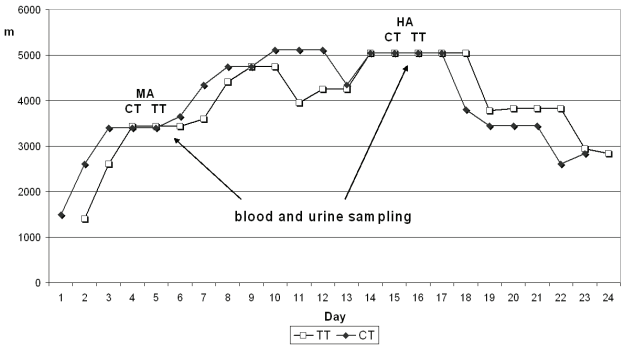

Fig. 1. Overnight altitude profiles of the "climbing team" (CT) and the "trekking team" (TT).

the Imja Tse (also called Island peak, 6189 m) before reaching the "Silver Pyramid", the base camp was located at 5150 m (Fig. 1). There was a daily moderate physical exertion of 6-8 h, the elevation profile was also moderate. The investigation started 36 h after reaching MA/HA. The previous day was used as a relaxation period, without altitude change or any major physical effort. Both teams enjoyed stable weather conditions.

All group members reached MA. At day 8, five members of TT had to return because of increasing symptoms of acute mountain sickness (AMS), so they were not examined at HA. Thirteen of the CT group tried to climb the summit of Imja Tse, three stayed in the base camp because of mild to moderate AMS symptoms, all sixteen CT members reached HA.

Experimental procedure

Our protocol was approved by the University of Graz Ethics Committee. 33 subjects (21 males, 12 females, age 19-65 years, height 160-186 cm, body weight 52-91 kg, BMI 20.0-28.7) underwent standard medical, physical and mental examination, were fully informed about possible risks and the experimental procedure, and gave their informed consent.

A baseline examination was performed at low altitude (LA, Herxheim, Germany, 150 m) 6 weeks before starting the climb. Between baseline examination and expedition, none of the subjects had a high altitude sojourn. During the field study in Nepal, each subject underwent two examinations, one during the adaptation on the third day of exposure to MA (Namche Bazar, 3440 m) and another after two weeks acclimatization to HA at the so-called "Silver Pyramid" (Italian-Nepalesian research center Ev-K2-CNR, Lobuche, 5050 m). Subjects were continuously monitored for AMS by expedition doctors, pulse-oxymetry and the individual physical and

psychological stress was also verified daily.

On days 3 and 14, antecubal venous blood samples were taken in EDTA coated tubes before breakfast between 6:30 and 7:30 h from all subjects in a sitting position after a ≥ 15 min resting period. Samples were immediately spun, plasma stored in Trasylol (aprotinin, 500 kallikrein inhibition units per ml) prechilled tubes and kept frozen (at –20 °C during the expedition, then at –80 °C until measurement). At HA, blood samples were also drawn from seven HA-accustomed Sherpas. As stable conditions were anticipated during overnight sleeping periods due to the absence of any physical exertion, no fluid intake and narrow range of ambient temperature, and because the full volume of urine samples could not be stored, urine was collected between 22:00 h. the day before blood sampling and 7:00 h. Urine volumes were determined, an aliquot taken and stored at –20 °C. Proper functioning of the mobile deep-freezer was permanently controlled by using a minimum-maximum thermometer.

Logistics had to be kept at a minimum level. Throughout the whole trip, food intake was not standardized and fluid intake was allowed *ad libitum*. Food consisted of usual Sherpa meals with 250-350 mM daily sodium intake, equal to European standards. No food additives were given. Any medication of the subjects was monitored by the expedition doctors, and none of the subjects took any diuretics at MA or HA or the preceding day.

Laboratory procedures

Plasma and urinary AM concentrations were measured (Ohta *et al.* 1999) using the radioimmunoassay from Shionogi (Osaka, Japan). AM is sandwiched between biotinylated antibody specific to the intramolecular ring structure and ^{125}I-labeled antibody specific to the C-terminal part of human AM. The mixture is reacted with biotin antibody coated beads. The antibody does not cross-react with CGRP, proadrenomedullin N-terminal 20 peptide (PAMP), neuropeptide Y, or amylin. After 20 h incubation at 4 °C, the beads are washed to remove the unbound antibody, and the remaining radioactivity is gamma counted. AM concentrations are expressed as AM-like immuno-reactivity; the minimal detectable concentration for this assay was 0.5 pM/l. The same kit has already been used in determining urinary AM concentrations (Nishikimi *et al.* 2001), and a prior extraction procedure is not necessary for measurement of urinary AM concentration (Dötsch *et al.* 1998).

Urinary and plasma sodium was determined with an electron-sensitive device (AVL 988-4, AVL, Graz, Austria), total plasma proteins and urinary creatinine concentrations were quantified with an automatized analyzer (Cobas Mira, Roche Inc., Switzerland). Urine and plasma osmolalities were measured with a freezing point depression osmometer (Fisk One-Ten, Fiske Associates, Uxbridge, MA). Hematocrit was determined at LA by calculation of red blood cell volume and by microcentrifugation at MA and HA, respectively.

Data analysis

A two-tailed Wilcoxon matched pairs signed ranks test was used to analyze the differences between the paired measurements for each subject. The null hypothesis was rejected if $p<0.05$. Data analysis was performed using the prism software set (version 4.03, Graphpad Software, Inc). Data are presented as median [interquartile range] unless otherwise stated.

Results

Fluid and sodium loss, urinary osmolality and urinary creatinine excretion are summarized in Table 1, whereas plasma osmolality, plasma protein and sodium data are shown in Table 2. There was a significant water loss during the ascent, mirrored by hemoconcentration and body weight reduction from 74.2 [13.2] to 69.9 [9.5] kg (n.s.). Compared to LA, total plasma proteins as a marker of hemoconcentration were increased in both teams during the whole sojourn. Nocturnal diuresis was significantly enhanced in both teams at HA. Overnight urinary osmolality decreased at MA and HA (Table 1). Urinary creatinine excretion decreased as well, but not proportionally to the increase in diuresis. Urinary sodium excretion was unchanged at MA, but increased significantly at HA compared to LA (Table 1). As expected, urinary Na^+ concentration and urinary osmolality were correlated ($r=0.88$, $p<0.005$).

Plasma Na^+ concentration and plasma osmolality were within the normal range in TT and CT (Table 2). Urinary AM excretion showed no obvious changes between LA and MA, but there was a significant increase at HA (Table 3). Plasma AM levels before HA were 16.4 [3.1] pM/l in both teams (TT 15.9 [3.0], CT 16.7 [3.1]), they increased at MA and remained elevated at HA (Table 3). This pattern was preserved even when hemoconcentration was taken into account.

Table 1. Nocturnal 9-h diuresis and natriuresis, urinary osmolality and urinary creatinine excretion in the members of CT, in the subjects of TT, who reached HA and who failed (TT-AMS), as well as in all subjects combined.

		Diuresis (ml/9h)	Natriuresis (mM/9h)	Urinary omolality (mosm/kg)	Urinary creatinine excretion (mg/9h)
	LA	460 [302-630]	41.8 [34.1-61.1]	647 [413-840]	860 [666-1041]
Combined	*MA*	560 [360-1010]*	41.4 [30.6-59.0]	236 [147-440]**	630 [456-751]**
(n = 28)	*HA*	1015 [645-1395]**,##	80.2 [65.1-94.2]**,##	264 [183-312]**	663 [524-864]**
	LA	490 [368-655]	48.7 [34.3-76.2]	612 [407-840]	921 [709-1073]
Climbing Team	*MA*	510 [358-823]	42.4 [38.5-59.4]	304 [150-453]**	689 [563-867]**
(CT, n = 16)	*HA*	810 [600-1195]**,##	80.1 [61.4-105.4]*,##	283 [223-410]**	744 [567-935]*
	LA	405 [273-623]	38.5 [32.1-49.9]	647 [497-786]	720 [558-942]
Trekking Team	*MA*	580 [418-1055]*	32.7 [29.5-54.8]	216 [116-289]**	500 [435-638]*
(TT, n = 12)	*HA*	1215 [895-1443]**,#	80.2 [70.9-89.4]**,#	208 [143-285]**	598 [506-722]*,#
TT-AMS	*LA*	290 [220-310]	36.2 [33.8-48.1]	740 [731-878]	612 [581-616]
(n = 5)	*MA*	380 [300-480]	25.8 [24.6-35.9]	323 [197-561]*	528 [449-542]*

Data are presented as median [25th and 75th percentile, respectively]. * p<0.05 and ** p<0.005 compared to LA, # p<0.05 and ## p<0.005 HA compared to MA.

Table 2. Total plasma proteins, plasma sodium concentration and plasma osmolality in the members of CT, in the subjects of TT, who reached HA and who failed (TT-AMS), as well as in all subjects combined.

		Total plasma proteins (g/l)	Plasma Na^+ concentration (mM/l)	Plasma omolality (mosm/kg)
	LA	66.8 [64.1–70.9]	145.2 [143.6-146.8]	306 [302-310]
Combined	*MA*	69.4 [66.9-71.2]*	146.6 [143.7-147.3]	294 [288-304]*
(n = 28)	*HA*	71.8 [69.1-74.0]**,#	145.6 [142.6-147.1]	289 [287-292] *,#
	LA	69.2 [66.6-72.2]	144.6 [142.8-147.2]	304 [300-305]
Climbing Team	*MA*	69.7 [66.7-71.6]	145.5 [141.8-149.4]	293 [287-302]*
(CT, n = 16)	*HA*	72.0 [70.3-73.5]	145.4 [142.2-148.8]	289 [287-293] *,#
	LA	64.4 [64.0-66.6]	145.5 [144.2-146.5]	309 [308-315]
Trekking Team	*MA*	68.6 [67.2-70.7]**	145.2 [144.1-147.1]	293 [291-295]*
(TT, n = 12)	*HA*	71.0 [68.0-74.4]**,#	145.4 [145.1-146.7]	288 [287-290] *,#
TT-AMS	*LA*	68.6 [64.0-69.1]	144.3 [143.9-144.5]	304 [299-317]
(n = 5)	*MA*	67.3 [64.8-71.6]	145.7 [145.4-146.3]	291 [288-297]*

Data are presented as median [25th and 75th percentile, respectively]. * p<0.05 and ** p<0.005 compared to LA, # p<0.05 and ## p<0.005 HA compared to MA.

Urinary AM excretion was significantly related to the amount of diuresis and natriuresis, and negatively correlated to urinary osmolality (Fig. 2). There was no correlation between plasma AM levels and diuresis and/or natriuresis as well as between plasma AM levels and urinary AM excretion (Fig. 3).

Persons reaching HA did not show any significant difference in either plasma AM levels or

Table 3. Urinary adrenomedullin excretion and plasma adrenomedullin concentration in the members of CT (n=16), in the subjects of TT, who reached HA and who failed (TT-AMS), and all subjects combined. HA natives (Sherpa) had higher plasma adrenomedullin levels.

		Urinary AM excretion (pM/9h)	Plasma AM concentration (pM/l)
	LA	7.9 [6.0-9.9]	16.4 [15.0-18.1]
Combined	*MA*	7.5 [4.5-10.2]	18.8 [17.1-22.0]**
(n=28)	*HA*	10.5 [7.5-12.6]**,##	18.3 [17.4-21.7]**
Climbing	*LA*	9.0 [7.5-10.4]	16.7 [14.8-17.9]
Team	*MA*	7.5 [5.2-9.4]*	19.0 [17.6-22.0]**
(CT, n=16)	*HA*	9.5 [7.2-14.0]##	19.5 [18.0-22.7]**
Trekking	*LA*	6.9 [4.9-7.8]	15.9 [15.1-18.1]
Team	*MA*	7.5 [3.9-10.6]	18.0 [16.5-20.7]*
(TT; n=12)	*HA*	10.8 [9.2-11.4]**,#	18.0 [16.4-18.8]*
TT-AMS	*LA*	6.1 [5.4-6.4]	15.7 [15.6-17.4]
(n=5)	*MA*	5.8 [4.6-7.1]	23.4 [20.3-27.1]*
Sherpa	*HA*		23.4 [22.1-24.2]

Data are presented as median [25th and 75th percentile, respectively]. * p<0.05 and ** p<0.005 compared to LA, # p<0.05 and ## p<0.005 HA compared to MA.

urinary AM excretion, diuresis or natriuresis at MA compared to those who developed AMS and consequently had to return to the base camp.

Discussion

We observed increased urinary adrenomedullin concentrations at high altitude, despite reduced glomerular filtration. Adrenomedullin excretion and high altitude diuresis/natriuresis were correlated, but not to circulating adrenomedullin levels or the duration of high altitude exposure. Increased urinary excretion of AM suggests its renal origin.

Available data on the hormonal control of sodium and water balance at HA are rather contradictory. After several days of exposure to HA, insensible fluid loss, increased sodium excretion and reduced salt-water intake lead to a decrease of total body water by 1-3 liters, with commensurate hemoconcentration (Krzywicki *et al.* 1971, Jain *et al.* 1980). Renal sodium and water excretion also rises transiently with acute hypoxemia (Koller *et al.*

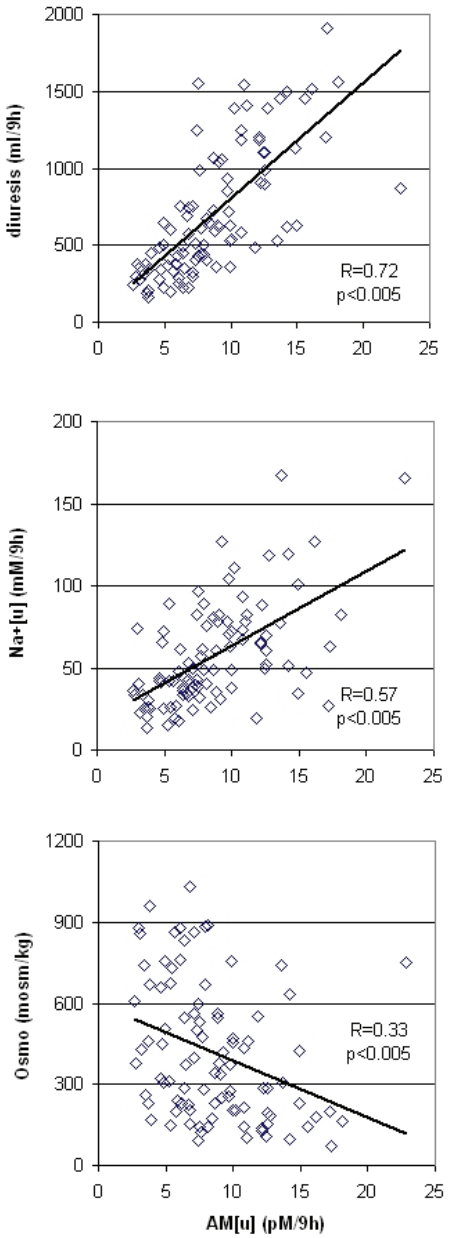

Fig. 2. Nocturnal diuresis, natriuresis (Na^+[u]) and urinary osmolality (Osmo) as a function of absolute renal AM excretion (AM[u]) (n=94).

1991, Olsen *et al.* 1992, Hildebrandt *et al.* 2000). Since this effect persists after renal denervation, an unknown humoral link is likely to exist. In recent field studies as well as under laboratory hypoxic conditions, there was some evidence for an influence of ET-1 and catecholamines on HDR, but no significant correlations between other plasma hormones (vasopressin, aldosterone, urodilatin, ANP) and diuresis/natriuresis were found (Bärtsch *et al.* 1991, Swenson *et al.* 1995, Hildebrandt *et al.* 2000). These results are consistent with earlier studies on the renin-angiotensin-aldosterone

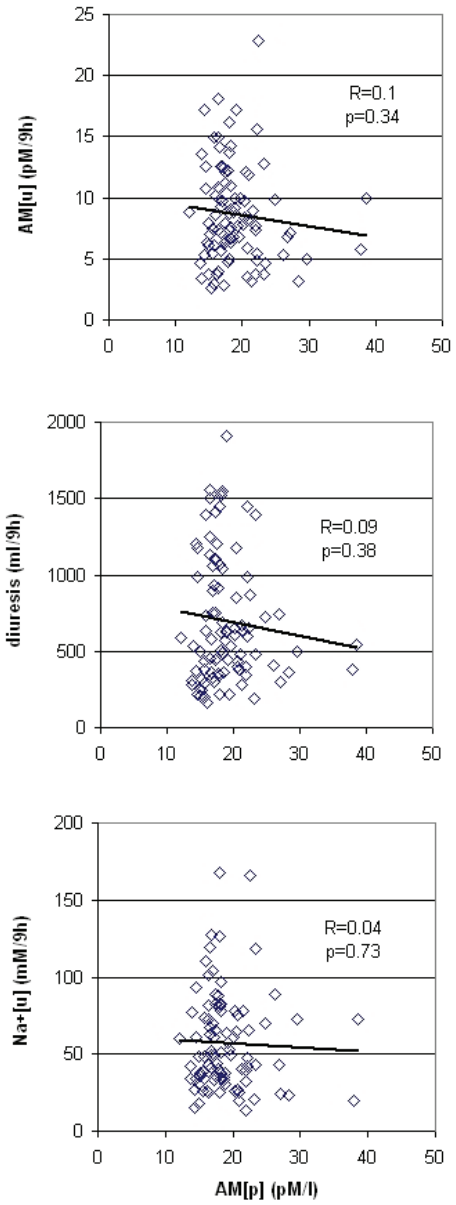

Fig. 3. Urinary AM excretion (AM[u]), nocturnal diuresis and natriuresis (Na^+[u]) are not correlated to plasma AM levels (AM[p]).

system with HA (Ramirez *et al.* 1988, Zaccaria *et al.* 1998). Chronic hypobaric hypoxemia elevates the set point of osmolality-driven vasopressin release. This causes hypovolemia and hyperosmolality, and blunts the natriuretic response to hypertonic volume expansion (Bestle *et al.* 2002).

It is important to note that the magnitude of hypoxia-related diuresis and natriuresis does not correlate with changes in circulating aldosterone, renin, ANP, and vasopressin (Swenson *et al.* 1995). This led us to focus on the link between fluid-electrolyte balance at HA and adrenomedullin with its vasodilatory, diuretic and natriuretic effects. Our data suggest, for the first time, a link between HDR and renal AM excretion *in vivo*.

Hypoxia belongs to the strongest stimuli to release AM from human endothelial cells (Hofbauer *et al.* 2000). The kidneys are particularly sensitive to hypoxia, and AM production is increased under hypoxic conditions both in renal parenchymal cells as well as in vascular cell cultures (Nagata *et al.* 1999). This may cause a protective effect against renal hypoxic injury caused by hypoxia-mediated increased ET-1 and decreased NO production. Urinary concentration of AM exceeds its plasma level, suggesting that the kidney is a major site of AM production (Sato *et al.* 1995). Numerous studies have indicated urinary AM excretion to be mainly driven by renal synthesis (Sato *et al.* 1995, Jougasaki *et al.* 1995, Nagata *et al.* 1999). Receptor autoradiography revealed specific binding sites for AM in renal arteries and glomeruli (Hjelmquist *et al.* 1997). However, an apparent correlation between plasma and urinary AM has not yet been found. An important local role in the regulation of water balance and sodium excretion seems very likely (Jougasaki *et al.* 1995, Samson 1999). AM decreases vasopressin and aldosterone (Taylor and Samson 2002), thereby raising renal blood flow, diuresis and natriuresis. Additionally, AM inhibits renal sympathetic nerve activity and increases renin release in a paracrine fashion (Jensen *et al.* 1997).

Urinary excretion of any substance usually is related to creatinine output. However, as shown earlier and confirmed by our data, creatinine excretion is reduced at HA. Decreased glomerular filtration rate (GFR), probably caused by increased renal sympathetic activity, might explain this effect (Bestle *et al.* 2002). Consequently, urinary creatinine concentration is not valid as a dilution marker in HDR.

Limitations

This is an observational study. We report data with partly weak correlations because they represent a first indication that the diuretic and natriuretic effect of AM might be mediated by locally produced renal AM rather than by systemic action of circulating AM. This fits well with the suggestion that AM acts as a paracrine/autocrine rather than an endocrine factor. Additionally, the fact that circulating AM seems to be unrelated to diuresis and natriuresis supports this conclusion. Furthermore, increased sodium excretion together with unchanged plasma sodium levels might be

explained with an osmotically inactive sodium stored in the tissue compartment (Titze *et al*. 2002, Gerzer and Heer 2005).

Furthermore, this the first report demonstrating the time course of plasma AM levels during a long-term HA sojourn. The elevation of plasma AM levels in all subjects at MA conceivably mirrors a general acclimatization effect. Interestingly, the increased plasma AM levels of HA sojourners are similar to those seen in high altitude natives.

In conclusion, renal adrenomedullin might be a "missing link" within the fluid regulatory adaptive factors at high altitude, possibly driving the hypoxic diuretic response in concert with the usual volume regulating hormones. The interaction of adrenomedullin with other fluid regulating hormones during long-lasting high altitude exposure will be discussed in a subsequent article.

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References

BÄRTSCH P, PFLÜGER N, AUDETAT M, SHAW S, WEIDMANN P, VOCK P, VETTER W, RENNIE D, OELZ O: Effects of slow ascend to 4559 m on fluid homeostasis. *Aviat Space Environ Med* **62**: 105-110, 1991.

BESTLE MH, OLSEN NV, POULSEN TD, ROACH R, FOGH-ANDERSEN N, BIE P: Prolonged hypobaric hypoxemia attenuates vasopressin secretion and renal response to osmostimulation in men. *J Appl Physiol* **92**: 1911-1922, 2002.

CORMIER-REGARD S, NGUYEN SV, CLAYCOMB WC: Adrenomedullin gene expression is developmentally regulated and induced by hypoxia in rat ventricular cardiac myocytes. *J Biol Chem* **273**: 1787-1796, 1998.

DÖTSCH J, HÄNZE J, KNÜFER V, STEISS JO, DITTRICH K, SEIDEL A, RASCHER W: Increased urinary adrenomedullin excretion in children with urinary-tract infection. *Nephrol Dial Transplant* **13**: 1686-1689, 1998.

ENTZERROTH M, DOODS HN, WIELAND HA, WIENEN W: Adrenomedullin mediates vasodilation via CGRP-1 receptors. *Life Sci* **56**: 259-269, 1995.

GERZER R, HEER M: Regulation of body fluid and salt homeostasis – from observations in space to new concepts on Earth. *Curr Pharm Biotechnol* **6**: 299-304, 2005.

GREENLEAF JE, HINGHOFER-SZALKAY H, RÖSSLER A, FARRELL PA, LOOMIS JL, FEDELE MJ, WEST J, COWELL BS: Plasma sodium-osmotic dissociation and hormonal interaction with drinking-induced hypervolaemia at 2800 m altitude. *Aviat Space Environ Med* **72**: 522-528, 2001.

HASBAK P, LUNDBY C, OLSEN NV, SCHIFTER S, KANSTRUP IL: Calcitonin gene-related peptide and adrenomedullin release in humans: effects of exercise and hypoxia. *Regul Pept* **108**: 89-95, 2002.

HILDEBRANDT W, OTTENBACHER A, SCHUSTER M, SWENSON ER, BÄRTSCH P: Diuretic effect of hypoxia, hypocapnia, and hyperpnea in humans: relation to hormones and O_2 chemosensitivity. *J Appl Physiol* **88**: 599-610, 2000.

HJELMQUIST H, KEIL R, MATHAI M, HUBSCHLE T, GERSTBERGER R: Vasodilation and glomerular binding of adrenomedullin in rabbit kidney are not CGRP receptor mediated. *Am J Physiol* **273**: R716-R724, 1997.

HOFBAUER KH, JENSEN BL, KURTZ A, SANDNER P: Tissue hypoxygenation activates the adrenomedullin system in vivo. *Am J Physiol* **278**: R513-R519, 2000.

HONIG A: Peripheral arterial chemoreceptors and the reflex control of sodium and water homeostasis. *Am J Physiol* **257**: R1282-R1302, 1989.

JAIN SC, BARDHAN J, SWAMY YV, KRISHNA B, NAYAR HS: Body fluid compartements in humans during acute high-altitude exposure. *Aviat Space Environ Med* **51**: 234-236, 1980.

JENSEN BL, KRAMER BK, KURTZ A: Adrenomedullin stimulates renin release and renin mRNA in juxtaglomerular granular cells. *Hypertension* **29**: 1148-1155, 1997.

JOUGASAKI M, WEI CM, AARHUS LL, HEUBLEIN DM, SANDBERG SM, BURNETT JC Jr: Renal localization and action of adrenomedullin: a natriuretic peptide. *Am J Physiol* **268**: F657-F663, 1995.

KITAMURA K, KANGAWA K, KAWAMOTO M, ICHIKI Y, NAKAMURA K, MATSUO H, ETO T: Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* **192**: 553-560, 1993.

KOLLER EA, BUHRER A, FELDER L, SCHOPEN M, VALLOTTON MB: Altitude diuresis: endocrine and renal responses to acute hypoxia of acclimatized and non-acclimatized subjects. *Eur J Appl Physiol* **62**: 228-234, 1991.

KRZYWICKI HJ, CONSOLAZIO CF, JOHNSON HL, NIELSEN WC Jr, BARNHART RA: Water metabolism in humans during high altitude exposure (4300 m). *J Appl Physiol* **30**: 806-809, 1971.

NAGATA D, HIRATA Y, SUZUKI E, KAKOKI M, HAYAKAWA H, GOTO A, ISHIMITSU T, MINAMINO N, ONO Y, KANGAWA K, MATSUO H, OMATA M: Hypoxia-induced adrenomedullin production in the kidney. *Kidney Int* **55**: 1259-1267, 1999.

NAKAYAMA M, TAKAHASHI K, MURAKAMI O, SHIRATO K, SHIBAHARA S: Induction of adrenomedullin by hypoxia in cultured human coronary artery endothelial cells. *Peptides* **20**: 769-772, 1999.

NISHIKIMI T, HORIO T, KOHMOTO Y, YOSHIHARA F, NAGAYA N, INENAGA T, SAITO M, TERANISHI M, NAKAMURA M, OHRUI M, KAWANO Y, MATSUO H, ISHIMITSU T, TAKISHITA S, MATSUOKA H, KANGAWA K: Molecular forms of plasma and urinary adrenomedullin in normal, essential hypertension and chronic renal failure. *J Hypertens* **19**: 765-773, 2001.

OHTA H, TSUJI T, ASAI S, SASAKURA K, TERAOKA H, KITAMURA K, KANGAWA K: One-step direct assay for mature-type adrenomedullin with monoclonal antibodies. *Clin Chem* **45**: 244-251, 1999.

OLSEN NV, KANSTRUP IL, RICHALET JP, HANSEN JM, PLAZEN G, GALEN FX: Effects of acute hypoxia on renal and endocrine function at rest and during graded exercise in hydrated subjects. *J Appl Physiol* **73**: 2036-2043, 1992.

RAMIREZ G, BITTLE PA, HAMMOND M, AYERS CW, DIETZ J, COLICE GL: Regulation of aldosterone secretion during hypoxemia at sea level and moderately high altitude. *J Clin Endocrinol Metab* **67**: 1162-1165, 1988.

RÖSSLER A, LÁSZLÓ Z, HADITSCH B, HINGHOFER-SZALKAY HG: Effect of postural changes on adrenomedullin plasma levels in humans. *Hypertension* **34**: 1147-1151, 1999.

SAMSON WK: Adrenomedullin and the control of fluid and electrolyte homeostasis. *Annu Rev Physiol* **61**: 363-389, 1999.

SAMSON W, MURPHY T, SCHELL D: A novel vasoactive peptide, adrenomedullin, inhibits pituitary adrenocorticotropin release. *Endocrinology* **136**: 2349-2352, 1995.

SATO K, HIRATA Y, IMAI T, IWASHINA M, MARUMO F: Characterization of immunoreactive adrenomedullin in human plasma and urine. *Life Sci* **57**: 189-194, 1995.

SWENSON ER, DUNCAN TB, GOLDBERG SV, RAMIREZ G, AHMAD S, SCHOENE RB: Diuretic effect of acute hypoxia in humans: relationship to hypoxic ventilatory responsiveness and renal hormones. *J Appl Physiol* **78**: 377-383, 1995.

TANAKA M, KITAMURA K, ISHIZAKA Y, ISHIYAMA Y, KATO J, KANGAWA K, ETO T: Plasma adrenomedullin in various diseases and exercise-induced change in healthy subjects. *Intern Med* **34**: 728-733, 1995.

TAYLOR MM, SAMSON WK: Adrenomedullin and the integrative physiology of fluid and electrolyte balance. *Microsc Res Tech* **57**: 105-109, 2002.

TITZE J, MAILLET A, LANG R, GUNGA HC, JOHANNES B, GAUQUELIN-KOCH G, KIHM E, LARINA I, GHARIB C, KIRSCH KA: Long-term sodium balance in humans in a terrestrial space station simulation study. *Am J Kidney Dis* **40**: 508-516, 2002.

TOEPFER M, HARTMANN G, SCHLOSSHAUER M, HARTMANN H, TSCHÖP M, FISCHER R, HUBER RM: Adrenomedullin: a player at high altitude? *Chest* **113**: 1428, 1998.

ZACCARIA M, ROCCO S, NOVENTA D, VARNIER M, OPOCHER G: Sodium regulating hormones at high altitude: basal and post-exercise levels. *J Clin Endocrinol Metab* **83**: 570-574, 1998.

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