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Role of atrial natriuretic factor, cyclic GMP and the renin–aldosterone system in acute volume regulation of healthy human subjects

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Abstract. The role of the atrial natriuretic factor (ANF), its second messenger cyclic guanosine monophosphate (cGMP), and the counteracting renin–aldosterone system in acute volume regulation was investigated in 25 healthy human subjects. Central volume stimulation by 1-h head-out water immersion (WI) into a thermoneutral water-bath increased plasma levels of ANF (mean ± SEM) from 6·0 ± 0·6 to 13·6 ± 2·6 fmol ml^{-1}. This was paralleled by a rise of plasma cGMP levels from 1·9 ± 0·2 to 2·8 ± 0·4 pmol ml^{-1}, and an increase of urinary cGMP excretion from 340 ± 64 to 692 ± 103 pmol min^{-1}. Water immersion reduced plasma aldosterone concentration (PAC) from 13·0 ± 1·7 to 6·5 ± 0·8 ng 100 ml^{-1} and plasma renin activity (PRA) from 5·3 ± 0·9 to 2·4 ± 0·3 ng AI ml^{-1} h^{-1}. Volume stimulation markedly increased diuresis and natriuresis. Whereas the plasma cGMP increase correlated with plasma ANF stimulation, neither ANF nor PRA or PAC correlated with basal or stimulated renal parameters. Water immersion-induced changes in natriuresis and urinary cGMP excretion were correlated. These data suggest a role of ANF and cGMP in acute volume regulation of healthy human subjects.

Keywords. Atrial natriuretic factor, volume regulation, water immersion, cyclic GMP, renin–aldosterone system.

Introduction

The atria have long been attributed an essential role in the regulation of extracellular volume by influencing renal sodium and water handling [1]. However, the hormonal mediators by which the heart modifies renal function have not been satisfactorily defined. With the discovery of the atrial natriuretic factor (ANF), a new agent in the concert of volume regulating systems has to be considered in health and disease states [2, 3]. The peptide is stored in granules of atrial myocytes and released upon atrial distension [4, 5]. There is evidence for a physiological role of ANF [6], which counteracts sodium-retaining principles, such as the renin–aldosterone system [7].

Head-out water immersion (WI) increases central venous and atrial volume by shifting blood from peripheral vessels to the intrathoracic venous bed—thus obviating the necessity of infusing volume expanders that might alter plasma composition [8]. In a preliminary study we had been able to demonstrate that WI stimulates ANF release in man [9] and thus seems to be a useful tool to study the physiological role of ANF in acute volume regulation. Several observations support the contention that cellular actions of ANF are mediated by cyclic guanosine monophosphate (cGMP) [10]. Administration of pharmacological doses of ANF [11], as well as volume stimulation in the animal [12], have been shown to increase plasma concentration and urinary excretion of cGMP. In the present study, the effects of an endogenous ANF release by volume stimulation on cGMP were examined.

The aim of the present study was to investigate the role of ANF and cGMP, as well as its interaction with the renin–aldosterone system, in the renal response to acute volume stimulation by water immersion.

Patients and methods

Twenty-five subjects, 16 men and nine women, aged 19–65 years, were investigated after their informed consent had been obtained. The protocol was approved by the Ethical Committee of the Faculty of Medicine, University of Munich. The subjects showed no evidence of cardiovascular, renal, pulmonary,

Abbreviations: ANF, atrial natriuretic factor; cGMP, cyclic guanosine monophosphate; PRA, plasma renin activity; PAC, plasma aldosterone concentration; cGMPV, urinary excretion of cGMP; UV, urinary flow rate; UNaV, urinary sodium excretion; UKV, urinary potassium excretion; CCr, creatinine clearance; WI, head-out water immersion.

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endocrine or urinary tract diseases. They took no medications, were on a regular diet, containing approximately 150 meq sodium day^{-1}, and were prohibited alcohol, tobacco, tea and coffee the day before and during the experiment. In the morning after complete emptying of the bladder, an intravenous cathether was placed into a forearm vein, subjects were given 400 ml of water orally and they assumed a seated position next to the immersion tank. After 1 h, the subjects were immersed to their neck, maintaining the same seated position, into thermoneutral water ($34{\cdot}5 \pm 0{\cdot}2$°C) for 1 h. This was followed by a 1-h period of sitting outside the tank. Throughout the investigation, 200 ml water h^{-1} were given orally to ensure adequate urine flow. All the urine voided by spontaneous emptying of the bladder, as well as plasma samples, were collected before (baseline), after 1 h WI (immersion) and 1 h subsequent to the end of WI (recovery).

Urine was analysed for sodium and potassium (flame photometry) and creatinine (Jaffe reaction). Plasma renin activity (PRA) was measured by radioimmunoassay after 1-h incubation at 37°C, pH 5·9, as described previously [13]. Plasma aldosterone concentration (PAC) was determined by use of a commercial solid-phase radioimmunoassay (Diagnostic products, U.S.A.). Atrial natriuretic factor was measured in XAD-extracted plasma samples by radioimmunoassay, as described earlier [14]. Briefly, the antibody is mid-molecule- and C-terminal-directed. Cross-reactivity was 70% to rat ANF 99–126, 13% to atriopeptin III, 0·03% to atriopeptins I or II. It did not cross-react with a wide variety of peptides and proteins, including its immunization conjugate (bovine thyreoglobulin). The final titre was 1:120 000 and the assay sensitivity was 0·5 fmol per assay tube. The 50%-binding intercept of the standard curve was 10 fmol. One-millilitre plasma aliquots were extracted by adsorption to pre-rinsed Amberlite XAD-2 adsorbent resin (particle size 0·3–1·0 mm, Serva, Heidelberg, FRG). Recovery of synthetic human ANF 99–126 was approximately 67%. Intra-assay variation was $< 10\%$ ($n = 8$), inter-assay variation was $< 15\%$ ($n = 6$). In 18 subjects baseline, immersion and recovery plasma samples, and in 15 subjects urine samples, were analysed for cGMP by radioimmunoassay according to a method described previously [11].

Clearance of creatinine (CCr) was calculated by the standard formula.

Data are given as means and standard error of the mean. Following a Kolmogorov–Smirnoff test for random distribution, statistical evaluation was done by Wilcoxon's test or by Student's paired *t*-tests; a probability value of $P = 0{\cdot}05$ or less was considered significant. The Pearson correlation coefficient was determined by the usual linear least-squares method.

Results

ANF and cGMP

As shown in Fig. 1, WI significantly increased ANF plasma concentrations from $6{\cdot}0 \pm 0{\cdot}6$ to $13{\cdot}6 \pm 2{\cdot}6$ fmol ml^{-1}. Atrial natriuretic factor increased in all but three subjects; mean stimulation was by $117 \pm 29\%$. In the recovery period, ANF decreased to baseline levels. The stimulation of ANF was paralleled by an increase of plasma cGMP concentration from $1{\cdot}9 \pm 0{\cdot}2$ to $2{\cdot}8 \pm 0{\cdot}4$ pmol ml^{-1}, returning to $2{\cdot}0 \pm 0{\cdot}2$ pmol ml^{-1} in the recovery period. Likewise, urinary cGMP excretion rose from 340 ± 64 (baseline value) to

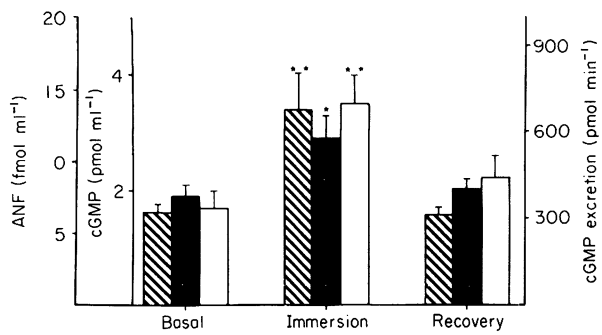

Figure 1. Plasma concentrations of atrial natriuretic factor (▨: ANF) cyclic guanosine monophosphate (■: cGMP) and renal excretion of cGMP (□) before, during and subsequent to head-out water immersion of 25 healthy human subjects. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$, significantly different from baseline level.

Table 1. Renal response to acute volume stimulation by water immersion in 25 healthy human subjects

	Baseline	Immersion	Recovery
Urinary volume ($ml\ min^{-1}$)	$1{\cdot}4 \pm 0{\cdot}2$	$5{\cdot}0 \pm 0{\cdot}6$***	$2{\cdot}8 \pm 0{\cdot}4$*
Urinary sodium excretion ($mmol\ min^{-1}$)	$0{\cdot}16 \pm 0{\cdot}02$	$0{\cdot}30 \pm 0{\cdot}03$***	$0{\cdot}18 \pm 0{\cdot}03$
Urinary potassium excretion ($mmol\ min^{-1}$)	$0{\cdot}07 \pm 0{\cdot}01$	$0{\cdot}14 \pm 0{\cdot}02$***	$0{\cdot}07 \pm 0{\cdot}01$
Creatinine clearance ($ml\ min^{-1}$)	153 ± 26	200 ± 32	117 ± 15

* $P < 0{\cdot}05$, *** $P < 0{\cdot}001$, significantly different from baseline level.

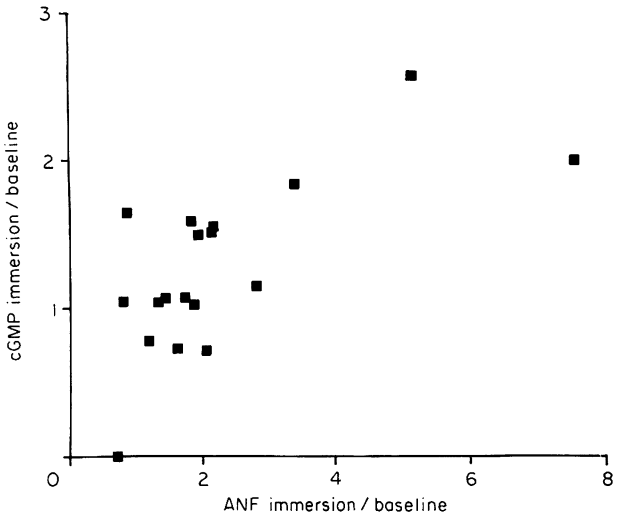

Figure 2. Correlation of immersion-induced stimulation of ANF plasma concentrations with plasma concentrations of cGMP (immersion/baseline ratios); $r = 0{\cdot}68$, $P < 0{\cdot}002$.

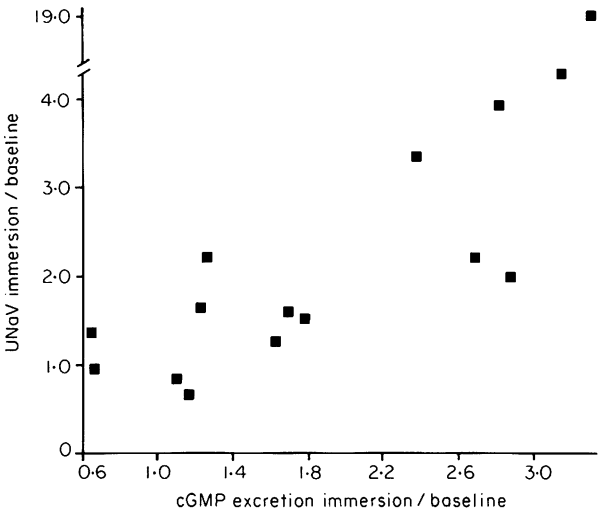

Figure 4. Correlation of immersion-induced stimulation of natriuresis (UNaV) with urinary cGMP excretion (immersion/baseline ratios); $r = 0{\cdot}61$, $P < 0{\cdot}02$.

692 ± 103 pmol min^{-1}, and then returned to 437 ± 79 pmol min^{-1}.

While neither basal nor stimulated values of ANF and cGMP correlated significantly, changes of cGMP were closely correlated with changes of ANF ($r = 0{\cdot}68$, $P < 0{\cdot}002$; Fig. 2).

Renin–aldosterone

The effects of WI on plasma renin activity and plasma aldosterone concentration are shown in Fig. 3. Plasma renin activity decreased from $5{\cdot}3 \pm 0{\cdot}9$ (baseline) to $2{\cdot}4 \pm 0{\cdot}3$ ng ml^{-1} h^{-1}, returning to $3{\cdot}7 \pm 0{\cdot}5$ ng ml^{-1} h^{-1}. Similarly, PAC was suppressed from $13{\cdot}0 \pm 1{\cdot}7$ to $6{\cdot}5 \pm 0{\cdot}8$ ng 100 ml^{-1}, with recovery values of $8{\cdot}1 \pm 1{\cdot}4$ ng 100 ml^{-1}. Basal PAC and PRA values were significantly correlated ($r = 0{\cdot}56$, $P < 0{\cdot}01$) as were the WI-induced changes of both hormones ($r = 0{\cdot}65$, $P < 0{\cdot}002$).

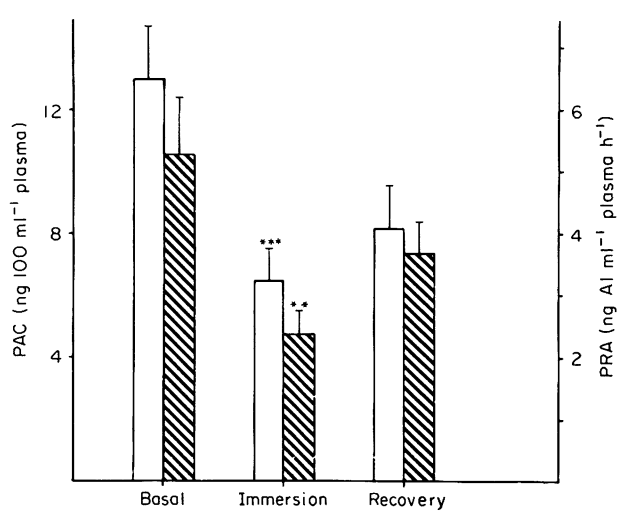

Figure 3. Plasma aldosterone concentration (□: PAC) and plasma renin activity (▨: PRA) before, during and subsequent to immersion. $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$, significantly different from baseline level.

Renal response

Table 1 displays the effects of WI on renal excretion. All but five subjects responded to WI with an increase in sodium excretion. Mean values of sodium excretion were increased two-fold during immersion. Highly significant enhancements by volume stimulation were also observed for urinary flow rate and for potassium excretion. Increases of creatinine clearance ($P > 0{\cdot}1$) did not reach the level of significance.

Relationship of ANF to renin–aldosterone and renal response

Water immersion induced stimulation of ANF as well as suppression of PRA and PAC. However, no relationship between these hormonal changes could be found. Tendencies for negative correlations between basal ($r = -0{\cdot}37$) as well as stimulated ($r = -0{\cdot}30$) values of ANF and corresponding values of PAC did not reach significance ($P > 0{\cdot}1$).

Neither basal nor stimulated natriuresis or diuresis correlated with ANF, PRA or PAC values. Changes of urinary cGMP excretion correlated with the increase of natriuresis ($r = 0{\cdot}61$, $P < 0{\cdot}02$) (Fig. 4).

Discussion

The present study demonstrates that acute central volume stimulation by water immersion induces a

highly significant increase of ANF plasma levels in healthy human subjects. However, large variations of response were observed, with three of 25 subjects exhibiting no stimulation of plasma ANF, despite a suppression of PRA as an indicator of central volume stimulation. In these subjects mean urinary sodium excretion increased less than in the subjects with ANF increase (0·02 vs. 0·16 mmol min^{-1}), possibly suggesting a physiological importance of ANF in WI-induced natriuresis.

Cyclic GMP is being considered a second messenger of cellular ANF action [10]. In this study we investigated cGMP upon endogenous ANF release by volume stimulation. Basal plasma levels of cGMP were not correlated with basal ANF levels. This finding is in accordance with unpublished observations in other subjects (R. Gerzer *et al.*), and might be due to stimulation of guanylate cyclase by substances other than ANF [15–17]. However, as ANF is the only hormonal stimulator of particulate guanylate cyclase described so far [10], corresponding changes of cGMP with ANF stimulation might be expected. Indeed, immersion-induced changes of plasma cGMP levels were closely correlated with changes of plasma ANF levels. These findings demonstrate that in man endogenous stimulation of ANF in the physiological range is accompanied by increases of plasma cGMP, and support the contention that cGMP acts as a second messenger of ANF.

Water immersion prompted significant decreases of PRA and PAC in all but two subjects. These two persons, however, exhibited stimulated ANF plasma levels as well as natriuresis and diuresis, indicating that suppression of the renin–aldosterone system cannot fully account for the renal response to WI. Basal plasma levels of PRA and PAC, as well as changes by volume stimulation, were found to correlate significantly. Administration of ANF in pharmacological doses can reduce renin and aldosterone secretion [18, 19] and decrease their plasma levels [20]. Therefore, in view of WI-induced changes of ANF reciprocal to changes of PRA and PAC, the significance of correlation of these hormonal changes by WI was investigated. However, only trends for negative correlation of basal as well as stimulated values of ANF with the corresponding PAC values were observed. Therefore these data do not provide strong evidence that a physiological increase of ANF suppresses PRA or PAC, although this possibility cannot be excluded.

Water immersion caused a significant increase of natriuresis and diuresis, consistent with the renal response observed by others in this standard model of volume stimulation [21]. However, in five of the 25 subjects, at comparable basal sodium excretion, no increase of natriuresis was induced. Thus, variations of basal natriuresis, possibly reflecting differences in dietary sodium intake, do not seem to have a major influence on the WI-induced renal response. Observations in these five non-responders suggested a role for the ANF system in mediating the renal reaction to WI: mean increase of ANF plasma levels in non-responders was only $4·6 \pm 2·0$ fmol ml^{-1}, compared with a $8·4 \pm 2·8$ fmol ml^{-1} increase in the responding subjects. In three of the non-responders, urinary cGMP excretion was determined. As opposed to a mean increase of cGMPV by 91%, non-responders showed no stimulation of cGMPV. Furthermore, changes of cGMPV varied significantly with changes of natriuresis by immersion. This may support the hypothesis that urinary GMP, and more so its changes, reflect renal action of ANF [21, 22].

Immersion induced an increase of potassium excretion. This phenomenon has been attributed to an increased distal delivery of filtrate and to an increase of urine flow by WI [23]. A kaliuretic effect of ANF, observed after high dose bolus injection in rats [24], might possibly have contributed to the increase of renal potassium excretion. However, several reports indicate that ANF administration in normal man does not significantly affect kaliuresis [20, 25]. In our study, potassium excretion was not significantly correlated with ANF plasma levels. The aforementioned studies in man, as well as this observation, do not support the notion of an ANF effect on kaliuresis. Furthermore, diuresis 1 h after the end of WI was significantly higher than before WI, while ANF concentrations had returned to basal levels. Thus, a role of other mediators of volume regulation, apart from ANF, must be recognized.

From the present data it can be concluded that ANF is released upon acute volume stimulation in healthy subjects, inducing increases of both plasma cGMP levels and urinary cGMP excretion.

Whereas immersion suppresses the sodium-retaining renin–aldosterone system, together with the stimulation of ANF, no correlation of any of these hormones with the renal response was observed. Thus, volume regulation may be influenced by complex interaction of the ANF system with other humoral factors, such as the renin–aldosterone system. Investigation of these hormonal interactions in disease states with impairment of volume regulation might shed further light on the pathophysiological importance of ANF.

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References

1 Gauer OH, Henry JP. Circulatory basis of fluid volume control. Physiol Rev 1963;43:423–81.

2 Arendt RM, Gerbes AL. Atrialer natriuretischer Faktor. Die endokrine Funktion des Herzens. Dtsch med Wochenschr 1986;111:1849–57.
3 Gerbes AL, Arendt RM, Paumgartner G. Editorial review. Atrial natriuretic factor—possible implications in liver disease. J Hepatology 1987;5:123–32.
4 Forssmann WG. Cardiac hormones. Review on the morphology, biochemistry and molecular biology of the endocrine heart. Eur J Clin Invest 1986;16:439–51.
5 Lang RE, Thölken H, Ganten D, Luft FC, Ruskoaho H, Unger T. Atrial natriuretic factor: a circulating hormone stimulated by volume loading. Nature 1985;314:264–5.
6 Naruse M, Obana K, Naruse K *et al.* Antisera to atrial natriuretic factor reduces urinary sodium excretion and increases plasma renin activity in rats. Biochem Biophys Res Commun 1985;132:954–60.
7 Laragh JH. Atrial natriuretic hormone, the renin–aldosterone axis, and blood pressure–electrolyte homeostasis. N Engl J Med 1985;313:1339–40.
8 Epstein M. Renal effects of head-out water immersion in man: implications for an understanding of volume homeostasis. Physiol Rev 1978;58:529–81.
9 Gerbes AL, Arendt RM, Schnizer W *et al.* Regulation of atrial natriuretic factor release in man: effect of water immersion. Klin Wochenschr 1986;64:666–7.
10 Gerzer R, Weil J, Strom T, Müller T. Mechanisms of action of atrial natriuretic factor. Clinical consequences. Klin Wochenschr 1986;64 (suppl VI):21–6.
11 Gerzer R, Witzgall H, Tremblay J, Gutkowska J, Hamet P. Rapid increase in plasma and urine cGMP after bolus injection of atrial natriuretic factor in man. J Clin Endocrinol Metab 1985;61:1217–9.
12 Stasch JP, Hirth C, Kazda S, Wohlfeil S. The elevation of cyclic GMP as a response to acute hypervolemia is blocked by a monoclonal antibody directed against atrial natriuretic peptides. Eur J Pharmacol 1986;129:165–8.
13 Wernze H, Speck HJ, Müller G. Studies on the activity of the renin–angiotensin–aldosterone system in patients with cirrhosis of the liver. Klin Wochenschr 1978;56:389–97.
14 Arendt RM, Gerbes AL, Ritter D, Stangl E. Molecular weight heterogeneity of plasma-ANF in cardiovascular disease. Klin Wochenschr 1986;64 (suppl VI):97–102.
15 Murad F. Clinical studies and applications of cyclic nucleotides. Adv Cyclic Nucleotide Protein Phosphorylation Res 1973;3:355–83.
16 Reiser G, Walter U, Hamprecht B. Bradykinin regulates the level of cyclic GMP in neural cell lines. Brain Res 1984;290:367–71.
17 Kurtz A. Adenosine stimulated guanylate cyclase activity in vascular smooth muscle cells. J Biol Chem 1987;262:6296–300.
18 Chartier L, Schiffrin E, Thibault G, Garcia R. Atrial natriuretic factor inhibits the stimulation of aldosterone secretion by angiotensin II, ACTH and potassium in vitro and angiotensin II-induced steroidogenesis in vivo. Endocrinology 1984;115:2026–8.
19 Goodfriend TL, Elliott ME, Atlas SA. Actions of synthetic atrial natriuretic factor on bovine adrenal zona glomerulosa. Life Sci 1984;35:1675–82.
20 Cuneo RC, Espiner EA, Nicholls MG, Yandle TG, Joyce SL, Gilchrist NI. Renal, hemodynamic and hormonal responses to atrial natriuretic peptide infusions in normal man, and effect of sodium intake. J Clin Endocrinol Metab 1986;63:946–53.
21 Epstein M, Loutzenhiser R, Friedland E, Aceto RM, Camargo MIF, Atlas SA. Relationship of increased plasma atrial natriuretic factor and renal sodium handling during immersion-induced central hypervolemia in normal humans. J Clin Invest 1987;79:738–45.
22 Huang CL, Ives HE, Cogan MG. In vivo evidence that cGMP is the second messenger for atrial natriuretic factor. Proc Natl Acad Sci USA 1986;83:8015–8.
23 Wright FS. Sites and mechanisms of potassium transport along the renal tubule. Kidney Int 1977;11:415–32.
24 Shimizu T, Nakamura M. Renal effect of atrial natriuretic polypeptide: comparison with standard saluretics. Eur J Pharmacol 1986;127:249–59.
25 Weidmann P, Hasler L, Gnädiger MP *et al.* Blood levels and renal effects of atrial natriuretic peptide in normal man. J Clin Invest 1986;77:734–42.

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