Release of Kaliuretic Peptide During Immersion-Induced Central Hypervolemia in Healthy Humans (43872)

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Abstract. **Kaliuretic peptide, a new peptide hormone consisting of amino acids 79–98 of the 126 amino acid atrial natriuretic factor (ANF) prohormone, is synthesized in the heart and is a potent stimulator of potassium excretion. The mechanism(s) controlling the release of kaliuretic peptide heretofore has not been defined. Because water immersion to the neck provides an acute central volume expansion identical to that produced by 2 liters of saline but without the plasma compositional change, immersion to the neck (NI) was utilized to assess kaliuretic peptide responses to acute central blood volume expansion in seven seated sodium-replete normal subjects. Since atrial natriuretic factor (ANF; amino acids 99–126 of the prohormone) originates from the amino acids adjacent to kaliuretic peptide in the ANF prohormone but is proteolytically cleaved from the rest of the prohormone before release, measurement of ANF was incorporated into this study to determine if there are differences with respect to release of these two portions of the ANF prohormone. Both kaliuretic peptide and ANF increased promptly with NI, with ANF peaking at 1 hr of immersion, whereas kaliuretic peptide peaked at the 3rd hr of immersion. With cessation of immersion, ANF decreased to preimmersion levels within 0.5 hr while kaliuretic peptide was still significantly ($P < 0.05$) elevated at 1 hr postimmersion. These findings indicate that kaliuretic peptide and ANF are released simultaneously but that kaliuretic peptide peak circulating concentration and its return to preimmersion values are prolonged compared with ANF. These last findings suggest a slower clearance from the circulation for kaliuretic peptide. The diuretic peak response to NI corresponded in a temporal manner to the peak circulating concentration of kaliuretic peptide, suggesting a possible physiologic role for kaliuretic peptide in modulating volume homeostasis in humans.** [P.S.E.B.M. 1995, Vol 209]

Kaliuretic peptide is a new peptide hormone consisting of amino acids 79–98 of the 126 amino acid atrial natriuretic factor (ANF) prohormone (Fig. 1) (1–3). This peptide has the strongest potassium excreting properties of all the atrial natriuretic peptides in animals (2) and humans (3, 4). In addition to stimulating potassium excretion, kaliuretic peptide has blood pressure-lowering and diuretic properties (2–5). Recently, kaliuretic peptide was demonstrated to circulate in healthy humans (4, 6). This peptide originates from the 98 amino acid N terminus of ANF prohormone by proteolytic processing to a peptide consisting of amino acids 68–98 and then with further processing pro ANF 79–98 is formed as outlined in Figure 1.

Previous studies from our laboratory have demonstrated that head-out water immersion produces a prompt, marked, and sustained central hypervolemia without the necessity of infusing exogenous volume expanders and thus altering plasma composition (7–

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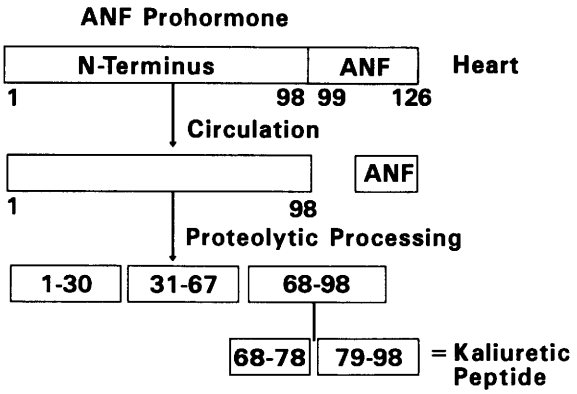

Figure 1. Origination of kaliuretic peptide from atrial natriuretic factor prohormone. The 126 amino acid atrial natriuretic factor prohormone (pro-ANF) is stored within granules in myocytes within the heart. Shortly before release into the circulation, this prohormone is cleaved by protease(s) into a 98 amino acid N terminus and a 28 amino acid C terminus (i.e., ANF) both of which circulate. The 98 amino acid N terminus is further proteolytically processed in the circulation to three peptides consisting of amino acids 1–30, 31–67, and 68–98. The peptide consisting of amino acids 68–98 has its N-terminal amino acids proteologically removed in the circulation to form a peptide consisting of amino acids 79–98 of this prohormone. This peptide is kaliuretic peptide.

13). Water immersion is a well-defined model for reproducibly producing a marked and sustained stimulation of release of atrial natriuretic factor (ANF; C-terminus of prohormone) (14–17) and the N terminus of the ANF prohormone in healthy human subjects (18, 19). Although kaliuretic peptide is known to circulate (4, 6), there has been no previous investigation determining the stimuli responsible for its release. The present study examines the time course and magnitude of response in healthy human volunteers of kaliuretic peptide in comparison with atrial natriuretic factor (amino acids 99–126 of the prohormone) in response to acute central volume expansion. Since atrial natriuretic factor originates from the amino acids adjacent to kaliuretic peptide in the ANF prohormone but is proteolytically cleaved from the rest of the prohormone before release (1, 20), the present study allows one to determine if there are differences with respect to release of these two portions of the ANF prohormone.

Materials and Methods

Subjects. Seven male volunteers between the ages of 20 and 35 years (average, 28 ± 4 years) were investigated during head-out water immersion. For time control an additional seven healthy male subjects (mean age 27 ± 5 years) sat quietly outside the immersion tank for a corresponding 5-hr period of investigation. All had a negative history of hypertension, cardiovascular disease, and diabetes. Clinically apparent renal disease was excluded in all subjects by documenting the presence of a normal urine sediment and creatinine clearance, and the absence of proteinuria. The use of alcohol, tobacco, tea, coffee, and all medications was prohibited for at least 24 hr before and during each of the studies. The experimental protocols were similar and were carried out as follows.

Following 10 hr of overnight fluid restriction, each subject was instructed to sit quietly. At 0800 hr, after voiding and completely emptying his bladder, the subject once again sat down. Immediately after the subjects had voided, an 18-gauge, 1.5-inch Teflon catheter with a flash chamber and an accompanying Teflon stylet (Critikon, Tampa, FL) was inserted into a forearm vein, permitting sequential sampling of blood without the use of an anticoagulant or an iv infusion. Venous blood was drawn using a prechilled 10-ml polystyrene disposable syringe. This sample was then immediately injected into 5 ml ethylenediaminetetraacetic acid (EDTA) tubes. EDTA was utilized to prevent protease breakdown of any peptides that might be present. After each sample was obtained, a sterile stylet was inserted into the catheter. After a 60-min prestudy period, the immersion subjects sat quietly in the study tank immersed in water to the neck for 3 hr (0900–1200 hr); this was followed by a 1-hr recovery period of quiet sitting outside the tank. In order to establish an appropriate time control, an additional seven healthy male subjects were studied during an identical 5-hr period while seated in chairs outside the immersion tank.

Blood samples (2 ml) were obtained before, during, and after the study for sodium, potassium, osmolality, and creatinine determinations. Samples (0.5 ml of plasma) for immunoreactive ANF, and immunoreactive pro-ANF 79–98 were obtained every 30 min during the prestudy period, at 15, 30, 60, 120, and 180 min of immersion, and at 15, 30, and 60 min of the recovery period. The plasma was separated with a refrigerated centrifuge and flash-frozen with dry ice and acetone, and stored at −76°C until radioimmunoassay evaluation. Each subject was requested to void spontaneously at hourly intervals during the studies. To void during the immersion period, the subjects stood briefly on a platform in the immersion tank after collection of blood. To maintain adequate urine flow, an initial waterload of 400 ml was administered, and subsequently 200 ml of water were ingested hourly. Sodium, potassium, osmolality, and creatinine were measured in all urine samples.

Immersion was carried out in a waterproof tank described in detail previously (7–13). A constant water temperature of 34.5 ± 0.5°C was maintained by two heat exchangers, detailed previously (7–13).

Radioimmunoassays to measure kaliuretic peptide and atrial natriuretic factor (ANF) were devised to

amino acids 79–98 and 99–126 of the 126 amino acid atrial natriuretic factor prohormone as described previously by our laboratory (4–6). Both the [^{125}I]-labeled and unlabeled synthetic human forms of kaliuretic peptide and atrial natriuretic factor utilized in this investigation were synthesized by Penninsula Laboratories, Inc. (Belmont, CA). For each radioimmunoassay, 200 μl plasma was first extracted with 100% ethanol (1:2 dilution of plasma with absolute ethanol), which was added for 30 min at 4°C. After 30 min at 4°C the samples were centrifuged at 3000*g* for 15 min, and the supernatants were taken to dryness (at 50°C) with low flow nitrogen. Then, the samples were reconstituted in 100 μl of 0.1 *M* phosphate buffer (pH 7.4) containing 0.05 *M* NaCl, 0.01% bovine serum albumin, 0.1% Triton X100, and 0.01% NaN_3. To the redissolved sample, 100 μl (0.03 mg) rabbit IgG plus 100 ml of the respective antisera were added and incubated for 24 hr. Then, 100 μl [^{125}I]-labeled peptides (10,000 cpm) were added, mixed, and incubated for 18 hr at 4°C. The precipitation of the antibody-bound tracer was accomplished by adding 100 μl goat anti-rabbit globulin after the above 18-hr period and incubating this mixture for 2 hr at room temperature. Each tube was then centrifuged at 3000*g* for 20 minutes. The supernatant was aspirated and the pellet counted in a gamma counter. All determinations were performed in triplicate. The intra-assay coefficient of variation for kaliuretic peptide and ANF radioimmunoassays were 5.5%, and 5.7%, respectively. Kaliuretic peptide and ANF's interassay variation were 7.6% and 6.9%, respectively.

Recovery was examined by adding synthetic unlabeled kaliuretic peptide and ANF at 100, 200, and 500 pg/ml to pooled plasma. Recovery of kaliuretic peptide was 86.8% ± 9.6%, while ANF was 92% ± 11%. The respective IC_{50} values were 47 and 11 fmols/tube, while the lowest detectable concentrations were 5 and 1.4 fmols/tube for the kaliuretic peptide and ANF radioimmunoassays, respectively. Serial dilution of pooled plasma has revealed excellent parallelism of standards and unknowns in these assays (4–6, 21). The kaliuretic peptide radioimmunoassay was evaluated against the other portions of the ANF prohormone, i.e., amino acids (a.a.) 1–30, 31–67, and 99–126 of the 126 a.a. prohormone and there is no cross-reactivity with any of the other peptide hormones derived from the ANF prohormone and kaliuretic peptide (i.e., a.a. 79–98 of this prohormone as one observes in Fig. 2). Likewise, ANF does not cross react with kaliuretic peptide or any other portion of the ANF prohormone (4, 6).

To determine the molecular forms immunologically recognized in plasma of these individuals by the kaliuretic peptide assay, 50 ml of plasma (i.e., approximately 80 ml of blood) pooled from the healthy

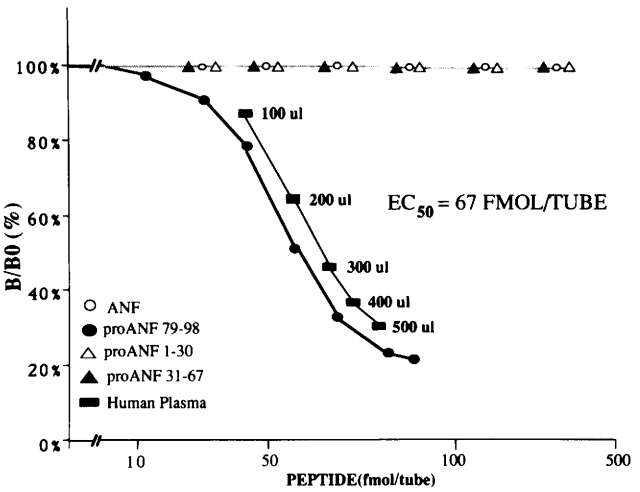

Figure 2. Typical standard curve for kaliuretic peptide radioimmunoassay with dilution curves of ANF, pro-ANF 1–30, pro-ANF 31–67, and plasma extracts from healthy human subjects. There was less than 0.5% cross-reactivity with pro-ANF 1–30, pro-ANF 31–67, or ANF with kaliuretic peptide (i.e., pro-ANF 79–98). Plasma immunoreactivity paralleled this radioimmunoassay curve as demonstrated with 100, 200, 300, 400, and 500 μl of normal human plasma.

subjects before immersion and at 30 min of immersion was extracted with 100 ml of ethanol (1:2 dilution), dried, and subjected to high-performance gel permeation chromatography (HP-GPC). The extracted plasma was resuspended in 100 μl of HP-GPC column mobile phase (10 m*M* trifluoroacetic acid containing 0.3 *M* sodium chloride and 30% acetonitrile) for HP-GPC assay as described previously (6, 17). These 100-μl samples were applied to a TSK-GEL G2000SW column (7.5 × 600 mm equipped with a guard column, 7.5 × 75 mm [Toyo Soda, Tokyo, Japan]) and eluted isocratically with HP-GPC column mobile phase at flow rate of 0.3 ml/min. Fractions (0.3 ml) were collected, dried, and then assayed for kaliuretic peptide and ANF by their respective RIAs described above. Blue dextran (2,000,000 mol wt) and p-aminohippuric acid (216 mol wt) were used to determine the void and total volumes of the column. To calibrate the column: carbonic anhydrase (29,000 mol wt), myoglobin (16,900 mol wt), cytochrome C (12,384 mol wt), vasoactive intestinal peptide (3300 mol wt), and (try^1)-somatostatin (1730 mol wt) were utilized. The elution positions of kaliuretic peptide and ANF were determined using [^{125}I]-labeled and unlabeled synthetic human forms of these peptides. Recoveries of these labeled peptides were as follows: 77% for ANF, 76% for kaliuretic peptide. High-performance gel permeation chromatography was repeated three times for this evaluation.

Permission for the study was obtained from each subject after a detailed description of the procedure and potential complications. The protocol was approved by the Human Experimentation Committees of

the University of Miami School of Medicine and the Miami Veterans Administration Medical Center and was in compliance with the principles set forth in the Declaration of Helsinki. No complications occurred.

Statistical Analysis. In the presentation of the data, mean values are followed by the standard error of the mean as an index of dispersion. Data were evaluated statistically by ANOVA. Difference with $P < 0.05$ (95% confidence limits) were considered significant.

Results

Water immersion markedly increased the simultaneous release of kaliuretic peptide and atrial natriuretic factor (Fig. 3). Cross-reactivity evaluation (Fig. 2) resolved that these 2 radioimmunoassays do not recognize each other (i.e., the kaliuretic peptide assay does not recognize ANF and vice versa for the ANF radioimmunoassay) indicating that two separate and distinct peptides were being released with immersion. As depicted in Figure 3, the circulating concentrations of kaliuretic peptide and ANF were remarkably stable when sampled at 30-min intervals during the preimmersion hour with the mean values for kaliuretic peptide being 67 ± 3, 66 ± 2, and 69 ± 3 pmol/liter while the mean circulating concentrations of ANF of 17 ± 1, 18 ± 1, and 18 ± 1 pmol/liter, were likewise very stable during the 30-min preincubation intervals.

In response to immersion, both kaliuretic peptide and ANF began to increase promptly in the circulation being apparent at the first time period (15 min) after immersion (Fig. 3). The mean circulating concentration of ANF was maximal at 1 hr of immersion (31 ± 2 pmol/liter) with its circulating concentration being not significantly different at 2 and 3 hr of immersion (30 ± 3 and 30 ± 4 pmol/liter). Kaliuretic peptide, on the other hand, doubled in the circulation after 1 hr of immersion (133 ± 5 pmol/liter) and continued to increase during immersion, attaining its maximal concentration (173 ± 6 pmol/liter) at the 3rd hr of immersion. The mean circulating levels of kaliuretic peptide and ANF were significantly higher at every time point of water immersion compared with their preimmersion values ($P < 0.05$). There was no increase in either kaliuretic peptide or ANF during the same time period in seven seated healthy volunteers who were not immersed, as can be seen in Table I.

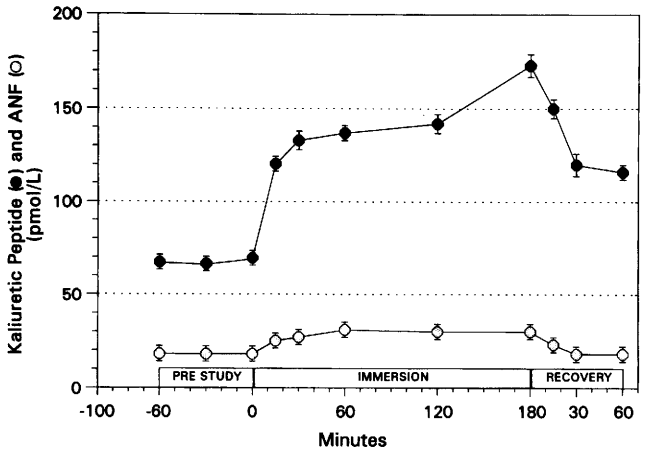

Figure 3. Water immersion to the neck stimulates the releases of both kaliuretic peptide (●) and atrial natriuretic factor (ANF) (○). Both kaliuretic peptide and ANF increased promptly with the onset of water immersion. Although the plasma concentration of both peptides declined with cessation of immersion, there was a temporal dissociation: ANF levels decreased promptly to preimmersion levels, whereas kaliuretic peptide levels remained elevated at 1 hr as compared with preimmersion levels. Results are the mean ± SEM.

Cessation of water immersion resulted in a prompt decrease in the circulating concentrations of kaliuretic peptide and ANF (Fig. 3). Within 30 min, the circulating concentration of ANF was not statistically different from the prestudy levels when evaluated by ANOVA. In contrast, kaliuretic peptide remained elevated in the circulation 1 hr after cessation of immersion compared with its preimmersion concentration ($P < 0.05$) even though kaliuretic peptide had also begun to decrease immediately after stopping the 3 hr of immersion (Fig. 3).

The circulating form(s) of kaliuretic peptide in these healthy human subjects was determined by high-performance gel permeation chromatography (HP-GPC) both before (Fig. 4) and during immersion (Fig. 5). Human synthetic kaliuretic peptide eluted in 0.3 ml fractions 76–81 with fraction 78 having the predominant peak when evaluated by HP-GPC as depicted in Figure 4 and 5. Determination of the molecular forms in human plasma recognized by the kaliuretic peptide radioimmunoassay before and during immersion revealed that this assay recognized kaliuretic peptide as

Table I. Mean Circulating Concentration of Kaliuretic Peptide and Atrial Natriuretic Factor (ANF) in Seven Seated Healthy Nonimmersed Volunteers Evaluated at the Same Time Periods as the Immersed Volunteers

Time (min)	Kaliuretic Peptide (pmol/liter)	ANF (pmol/liter)
−60	65 ± 3[a]	18 ± 1[a]
−30	68 ± 2	17 ± 2
0	66 ± 3	19 ± 2
15	67 ± 4	18 ± 2
30	64 ± 3	17 ± 1
60	68 ± 4	19 ± 2
120	65 ± 3	16 ± 2
180	64 ± 2	17 ± 1
195	64 ± 4	18 ± 3
210	66 ± 2	17 ± 3
240	68 ± 3	19 ± 2

[a] The values obtained over the 5-hr study period did not vary significantly when evaluated by analysis of variance (ANOVA).

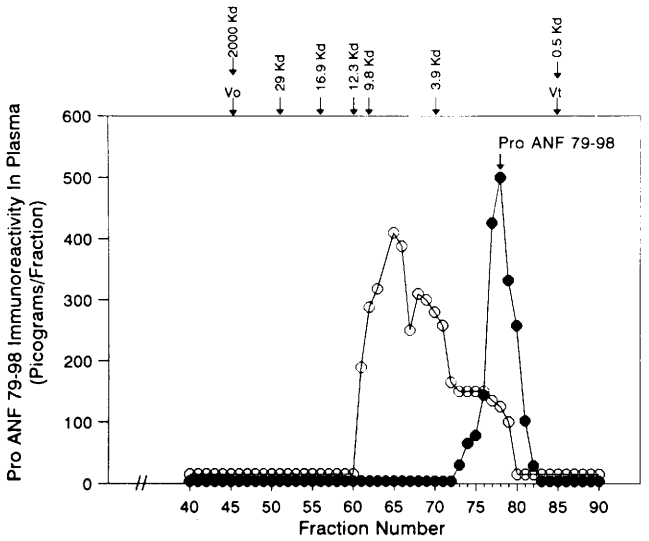

Figure 4. High-performance gel permeation chromatography of (A) pure synthetic human sequence of kaliuretic peptide (i.e., pro-ANF 79–98; closed circles), (B) [^{125}I]-labeled kaliuretic peptide (arrow), and (C) evaluation of plasma obtained before immersion (open circles). Pure synthetic kaliuretic peptide eluted in 0.3 ml fractions 76–81 with the peak in fraction 78. [^{125}I]-labeled kaliuretic peptide was similar with its peak in fraction 79. The elution of kaliuretic peptide from plasma was in a peak where the human synthetic form of kaliuretic peptide elutes. In addition, two other peaks are observed consistent with (i) pro-ANF 1–98 and (ii) pro-ANF 68–98 based upon their molecular weights. To define the molecular weight of the peaks, the column was calibrated with the following molecular weight markers: Carbonic anhydrase (29,000 mol wt), myoglobin 1 (16,900 mol wt), cytochrome c (12,384 mol wt), vasoactive intestinal peptide (3300 mol wt), and try-somatostatin (1700 mol wt). Blue dextran (2,000,000 mol wt) and p-aminohippuric acid (216 mol wt) were used to determine the void (V_0) and total (V_t) volumes of the column. V_0 = void volume; V_t = total volume collected. Each fraction = 0.3 ml.

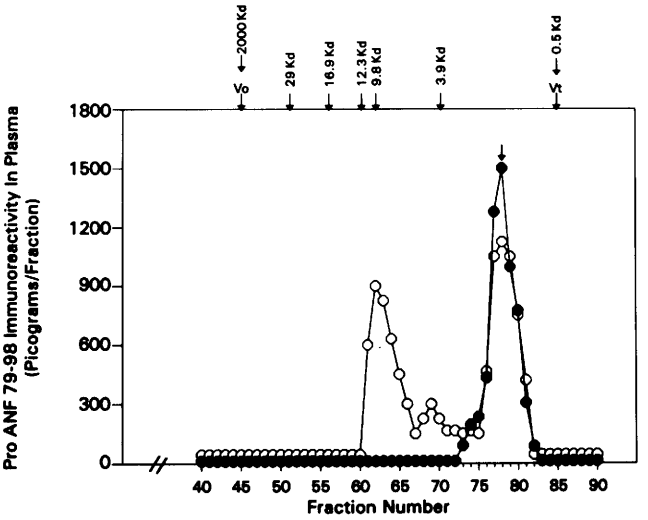

Figure 5. High-performance gel permeation chromatography evaluation of plasma obtained after 30 min of head-out water immersion. Pure human sequence of kaliuretic peptide (enclosed circles) eluted in 0.3 ml fractures 76–81 with peak in fraction 78 (arrow). The elution of kaliuretic peptide (i.e., pro-ANF 79–98, open circles) from plasma obtained after 30 min of immersion revealed that the amount of kaliuretic peptide had increased 5-fold ($P < 0.01$) compared with preimmersion values when evaluated by analysis of variance (ANOVA). At this time point, two other peaks are also noted consistent with (i) pro-ANF 1–98 and (ii) pro-ANF 68–98, based upon their molecular weights. Molecular weight markers are the same as in Figure 4. It is important to note when comparing the two figures that the concentration on the vertical axis are 3-fold greater in Figure 5 than in Figure 4.

a distinct circulating peptide proteolytically cleaved from pro-ANF 68–98 (2nd eluted peak Fig. 4 and 5). This assay also recognized a 9800-mol wt peptide consistent with the 98 amino acid N terminus of the ANF prohormone without the C-terminus (i.e., ANF) attached to it (Fig. 4 and 5). After immersion the amount of immunoreactivity increased under the kaliuretic peptide peak indicating that this peptide definitely increases with head out of water immersion in healthy human subjects (Fig. 5). The amount of immunoreactivity increased in the proANF 1–98 and proANF 68–98 elution peaks after 30 min of immersion but not to the extent that kaliuretic peptide did (Fig. 5). When the amount of immunoreactivity in the kaliuretic peptide peak was quantilated before and during immersion, its concentration had increased 5-fold during immersion.

Discussion

The possible participation of cardiac atria in the control of extracellular fluid volume has been known for many years (9, 22). It is well recognized that mammalian atria have mechanoreceptors that are sensitive to stretch or distensibility induced by volume changes (22, 23). The present studies demonstrate that central hypervolemia induced by head-out water immersion provokes a prompt and sustained increase in both kaliuretic peptide and atrial natriuretic factor in healthy human subjects. In view of the compelling evidence that the effects of water immersion are mediated by increases in central volume (8, 22), the present findings suggest that a volume-mediated increase in atrial stretch is one mechanism subserving the release of both kaliuretic peptide and atrial natriuretic factor.

The data obtained with the HP-GPC evaluation of the kaliuretic peptide assay would suggest that the N terminus of the ANF prohormone (i.e., amino acids 1–98 of the 126 amino acid prohormone) is proteolytically cleaved to pro-ANF 68–98, which is further processed to form kaliuretic peptide (i.e., amino acids 79–98 of the ANF prohormone) in the circulation. The present investigation also suggests that this processing occurs fairly soon after release since even at an early time point (i.e., 30 min) after immersion began, immunoreactivity of kaliuretic peptide was increased in the circulation and in a greater proportion than the increase of the whole N terminus of the ANF prohormone and pro-ANF 68–98 as determined by high-performance gel permeation chromatography. This would suggest that in addition to the increased release

of the N terminus of the ANF prohormone that there was also increased processing of the 98 a.a. N terminus of this prohormone as the product of this processing (i.e., kaliuretic peptide) was increasing to a greater extent than the whole N terminus of this prohormone.

The renal response to immersion of these same seven subjects has been published previously (16). With immersion, urine flow increased 3-fold and natriuresis increased 2-fold (16). Since kaliuretic peptide has no significant natriuretic properties (3, 4), its increase in the circulation with immersion did not contribute to the natriuresis that was observed. As detailed in a recent review (10), it is apparent that the natriuresis of immersion is complex and attributable to the participation of several hormonal and/or neural effectors, acting in concert. This natriuresis appears secondary to suppression of the renin-angiotensin-aldosterone system, suppression of the renal sympathetic nervous outflow, augmentation of renal vasodilatory prostaglandins, and to atrial natriuretic factor and two other natriuretic hormones from the N terminus of the 126 amino acid ANF prohormone consisting of amino acids 1–30 (i.e., long-acting natriuretic peptide) and amino acids 31–67 (i.e., vessel dilator) (18).

In contrast, the diuresis observed with immersion may be attributable in part to kaliuretic peptide, which has previously been reported to possess potent diuretic properties (3, 4). The diuresis in these subjects was maximal at the 3rd hour of immersion (16), while ANF's concentration was maximal at the 1st hour of immersion. Kaliuretic peptide, on the other hand, was maximal in the circulation at the 3rd hour of immersion. Since kaliuretic peptide circulated at a 3-fold higher concentration than atrial natriuretic factor in these healthy humans subjects and had its peak in the circulation at the same time as the peak diuresis (16), this may reflect kaliuretic peptide's contribution to the immersion-induced diuresis.

In this investigation, we have demonstrated that the kaliuretic peptide peaked later than ANF during acute volume expansion induced by head-out water immersion. One might wonder why, if both ends of the prohormone are being released simultaneously, does kaliuretic peptide peak later. The answer to this, we believe, may be its longer circulating half-life, with the peak at the 3rd hr of immersion versus 1 hr of immersion for ANF reflecting its slower clearance from the circulation. The high-performance gel permeation chromatography evaluation of what the kaliuretic peptide assay immunologically recognized in the plasma of these subjects revealed that in addition to kaliuretic stimulator the 98 amino acid N terminus of the ANF prohormone (i.e., pro-ANF 1–98) and pro-ANF 68–98 are recognized. Pro-ANF 1–98 has a half-life 15-fold longer than that of ANF (24).

The temporal dissociation between ANF and kaliuretic peptide during the recovery hour supports the interpretation that kaliuretic peptide has a longer half-life than ANF. With cessation of immersion, ANF concentration after 0.5 hr was not significantly different from its preimmersion value. In contrast, kaliuretic peptide's concentration continued to exceed preimmersion levels ($P < 0.05$ compared with preimmersion values), suggesting that kaliuretic peptide's half-life is also longer than ANF's. Previous studies in which kaliuretic peptide, ANF, pro-ANF 1–30, and pro-ANF 31–67 were infused into healthy human subjects and their half-lives were monitored has revealed that kaliuretic peptide and the other peptides derived from the N terminus of the ANF prohormone have prolonged half-lives with respect to ANF (5). The longer half-life of kaliuretic peptide compared with ANF suggests that clearance from the circulation is the most probable reason that, when immersion ceases, ANF returns to normal within an hour, while kaliuretic peptide is still significantly elevated at 1 hr postimmersion.

This formulation is consistent with previous observations with rapid-paced heart rates (i.e., another stimulus to the release of the N terminus and the C terminus of the ANF prohormone) (25). With ventricular cardiac pacing at heart rates of 125 bpm and above, both the C terminus and the N terminus of the prohormone are released; but, with cessation of pacing, the C terminus (ANF) returns to prepacing levels within 30 min, while the N terminus is still elevated at 2 hr postpacing, although steadily declining from the time the pacing was stopped (25). Thus, in both experimental models: (i) pacing and (ii) in water immersion-induced central hypervolemia, the prolonged elevation with cessation of stimuli of the N terminus from which kaliuretic peptide originates reflects its longer half-life in the circulation.

In summary, we have demonstrated that kaliuretic peptide is released simultaneously with ANF secondary to acute central volume expansion elicited by water immersion to the neck. Kaliuretic peptide's peak circulating concentration and its return to preimmersion values are prolonged compared with ANF, suggesting a slower clearance from the circulation for kaliuretic stimulator. The diuretic peak response to water immersion corresponded in a timewise fashion to the peak circulating concentration of kaliuretic peptide, suggesting a possible physiologic role for kaliuretic peptide in modulating volume homeostasis in humans.

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