Correlation of Plasma Copeptin and Vasopressin Concentrations in Hypo-, Iso-, and Hyperosmolar States

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Background: Copeptin, the C-terminal moiety of provasopressin, is cosecreted with vasopressin. Copeptin may be a useful parameter to characterize disorders of water homeostasis and can be readily measured in plasma or serum. However, it is unknown to date how circulating copeptin and vasopressin levels correlate at different plasma osmolalites.

Objective: To correlate plasma copeptin with plasma osmolality and vasopressin concentrations in healthy subjects during iso-, hypo-, and hyperosmolar states.

Methods: Plasma osmolalities, copeptin, and vasopressin levels were measured in 20 volunteers at baseline, after an oral water load, and during and after iv infusion of 3% saline. Correlation coefficients were determined between plasma osmolalites and copeptin and vasopressin concentrations, as well as between vasopressin and copeptin concentrations.

Results: Median plasma osmolalities decreased from 290 mOsm/kg (range, 284–302) at baseline to 281 (273–288) mOsm/kg after water load and rose to 301 (298–307) mOsm/kg after hypertonic saline. Median plasma copeptin concentrations decreased from 3.3 (1.1–36.4) pM at baseline to 2.0 (0.9–10.4) pM after water load and increased to 13.6 (3.7–43.3) pM after hypertonic saline. Vasopressin and copeptin concentrations correlated with plasma osmolality (Spearman's rank correlation coefficient 0.49 and 0.77, respectively). There was a close correlation of vasopressin and copeptin concentrations (Spearman's rank correlation coefficient 0.8).

Conclusion: Plasma vasopressin and copeptin correlate strongly over a wide range of osmolalities in healthy individuals. Therefore, the measurement of copeptin, which remains stable for several days, is a useful alternative to vasopressin measurements and will likely facilitate the differential diagnosis of disorders of water metabolism. **(*J Clin Endocrinol Metab* 96: 1046–1052, 2011)**

The antidiuretic hormone, arginine vasopressin (AVP), is a nonapeptide hormone synthesized in the magno- and parvocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. It is stored and secreted into the bloodstream by the posterior pituitary. By increasing water permeability of the apical membrane of renal collecting duct cells, AVP promotes free water reabsorption and is therefore one of the key regulators of the body's water and solute balance (1). A rise in plasma osmolality above ~280 mOsm/kg is the main stimulus for AVP release (2). Nonosmotic stimuli include a decrease of circulating blood volume and low blood pressure (3), as

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-2499 Received October 22, 2010. Accepted January 4, 2011.
First Published Online February 2, 2011

Abbreviations: AVP, Arginine vasopressin; r_S, Spearman's rank correlation coefficient.

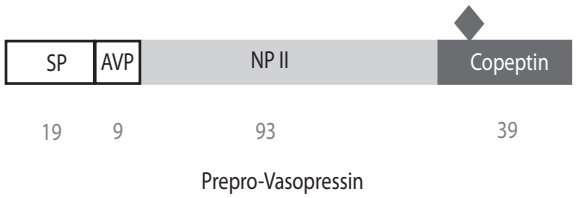

FIG. 1. Schematic structure of the vasopressin prepro-hormone consisting of the signal peptide (SP), the vasopressin hormone (AVP), the carrier protein neurophysin II (NPII), and the glycoprotein copeptin, where the glycan is represented by a *diamond*. The numbers denote the amino acids present in each moiety.

well as nausea, vomiting, pain, various drugs, and insulin-induced hypoglycemia (4).

AVP is synthesized as prepro-hormone and consists of a signal peptide, the AVP and neurophysin II moieties, and a C-terminal peptide of 39 amino acids, termed copeptin, that contains a single N-linked glycosylation site (5, 6) (Fig. 1). In neurosecretory granules, the hormone precursor is proteolytically processed to yield AVP, neurophysin II, and copeptin, which are cosecreted from the posterior pituitary. The plasma half-life of AVP is short (~24 min) (7) and similar to that of copeptin (8, 9). The physiological role of copeptin is unknown.

Determination of plasma AVP concentrations is helpful for the differential diagnosis of disorders involving sodium abnormalities, including the various subtypes of the syndrome of inappropriate antidiuretic hormone secretion and partial forms of both neurohypophyseal and renal diabetes insipidus (10, 11). However, reliable measurement of plasma AVP is challenging and time-consuming, and validated AVP assays are therefore scarce (12). More than 90% of circulating AVP is bound to platelets, resulting in either underestimation or, in case of prolonged storage of unprocessed blood samples at room temperature, falsely elevated AVP levels (13). As a consequence of these technical drawbacks and the paucity of reliable commercially available AVP assays, measurement of circulating AVP levels is not usually part of clinical routine diagnostics.

Unlike AVP, copeptin remains stable *ex vivo* for several days at room temperature in serum or plasma. A sensitive sandwich immunoassay for the detection of copeptin in human serum or plasma has recently been developed (8), offering a potential alternative to available AVP assays. However, as of yet, the assay has mainly been used in the evaluation of copeptin as biomarker (14). Elevated levels of AVP and copeptin have been found in critically ill patients with the systemic inflammatory response syndrome and sepsis (15, 16), in hemorrhagic and septic shock (9), and in trauma patients (17). Copeptin may be prognostically meaningful; high circulating copeptin levels have been found to predict the outcome in advanced heart failure (18, 19), after myocardial infarction (20–22), in community-acquired pneumonia (23), as well as in stroke (24), and may indicate long-term clinical failure after acute exacerbation of chronic obstructive pulmonary disease (25).

Data on the physiological changes of copeptin levels are scarce. A clinical study indicated that circulating copeptin concentrations reflect posterior pituitary integrity in patients undergoing insulin-induced hypoglycemia for evaluation of anterior pituitary function (26). Another study evaluated healthy volunteers in various states of hypo- and hyperosmolality and found that copeptin concentrations correlated well with plasma osmolality (27, 28); however, AVP levels were not reported because of the lack of a reliable assay. Also, no data on urine osmolalities were reported, which is a crucial parameter reflecting AVP action at the target organ. Therefore, important information on copeptin as a surrogate for AVP is still lacking. In particular, no data are available on the correlation between circulating levels of AVP and copeptin. In case of a close correlation of the two parameters, the measurement of copeptin might serve as a surrogate marker for AVP, thereby superseding the problematic AVP assays.

Materials and Methods

Study subjects

The study was performed in 20 healthy volunteers (8 men, 12 women) >18 yr of age. Exclusion criteria included a history or presence of heart failure, liver cirrhosis or chronic alcohol consumption, nephrotic syndrome, renal failure (defined as a calculated creatinine clearance <100 ml/min), anemia (hemoglobin concentration <100 g/liter), uncontrolled hypertension (systolic blood pressure >160 mm Hg, diastolic blood pressure >95 mm Hg), and other severe disease. Subjects with hypo- or hyperthyroidism, hypo- or hypercortisolism, known dipsomania or diabetes insipidus, pregnancy, or lactation were ineligible. All female subjects were investigated during the follicular phase of the menstrual cycle, when the osmotic threshold for AVP release is similar in men and women (29).

Study procedures

The study was approved by the local review board and registered (www.ClinicalTrials.gov number, NCT00696605). Written informed consent was obtained from all study subjects. One week before the test, each subject underwent a clinical and laboratory evaluation, which included a medical history, physical examination, fasting standard blood tests (blood count, creatinine, blood urea nitrogen, glucose, total protein, albumin, and electrolytes), plasma and urine osmolality, TSH (normal values, 0.4 to 4 mU/liter), and cortisol before and after stimulation with 250 μg tetracosactide (Synacthen; Novartis Pharma, Basel, Switzerland) iv (a normal adrenal function was defined as at least one cortisol value >550 nM). Subjects were then scheduled for an oral water load-hypertonic iv saline test (12). For 12 h before the test, they refrained from smoking and drinking caffeinated or alco-

holic beverages but had access to *ad libitum* fluids. Approximately 2 h before the test, they had a light breakfast. The test was performed in recumbent position. Before administering the water load, a separate angiocath was placed in each arm of the subjects for blood draws and for the 3% saline infusion, respectively. All blood samples drawn during the test were centrifuged immediately for 10 min. at 1500 × *g* in a cooled table centrifuge. Plasma was carefully separated from cells using plastic pipettes, and plasma aliquots were rapidly transported on ice to a −20 C freezer, where they were stored for later copeptin and AVP batch analyses. Plasma AVP was measured by RIA as described (12). The coefficient of variation of the assay was 11.9% (low range) to 6.4% (high range). The standard curve was obtained using unlabeled AVP (Ferring Pharmaceuticals, Parsippany, NJ). The curve was very similar to curves obtained with the same stock in earlier assays, confirming adequate labeling of the AVP tracer. Copeptin was measured in a blinded fashion in a single batch with a commercial sandwich immunoluminometric assay (B.R.A.H.M.S LUMItest CT-proAVP, B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany) as described previously (8). Since this initial publication, the assay was modified as follows: The capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137–144 (GPAGAL) of proAVP. This modification improved the sensitivity of the assay. The lower detection limit was 0.4 pM, and the functional assay sensitivity (<20% interassay coefficient of variation) was <1 pM (30). The intraassay coefficient of variation was <10%. In 359 healthy individuals (153 men and 206 women), median copeptin values were 4.2 pmol/liter (range, 1–13.8 pmol/liter; 95% confidence interval, 4.0–4.4 pmol/liter) (8). At all time points, urine and plasma osmolalities were measured immediately after obtaining the samples on an Advanced Instruments 3320 Osmometer by freezing point depression. The intraassay coefficient of variation was <0.7% for osmolalities in the low (300 mOsm/kg), intermediate (500 mOsm/kg), and high (700 mOsm/kg) ranges, respectively. The interassay coefficients of variation were 1.3% for the low, 1% for the intermediate, and 1.6% for the high range, respectively. Electrolytes were measured on a Roche Integra 800 analyzer. As a control, plasma osmolalities were calculated using the formula: osmolality = 2 × [Na] + [Gluc] + [BUN] (all values in mM).

For the water load, subjects drank 20 ml/kg body weight of tap water within ≤30 min. Every 30 min after starting the test, blood and urine samples were collected. Concurrently, blood pressure and heart rate were recorded, and thirst perception was rated on a scale from 1 to 10. These measurements were repeated until urine osmolality had dropped to ≤100 mOsm/kg or until 120 min after beginning of the test, whichever occurred first. Subsequently, administration of 3% saline infusion was started at a rate of 0.1 ml · kg body weight^{-1} · min^{-1}. Every 20 min during the infusion, blood samples were drawn and thirst perception was recorded. The infusion was stopped when plasma osmolality had reached ≥300 mOsm/kg for the first time. Urine samples, if available, were collected and analyzed in parallel to blood. At the end of the infusion, blood and urine were collected. Subjects were then allowed to drink and eat. One and 2 h after the end of the infusion, blood and urine samples were again collected and analyzed.

Statistical analysis

Experimental data from three subjects were excluded from analysis because of technical issues. Thus, complete matched data from 17 individuals were available for analysis. Osmolalities and copeptin concentrations were compared across time points using repeated measures ANOVA. Pairwise *post hoc* comparisons were performed using the paired *t* test. Spearman's rank correlation coefficients were calculated to correlate the following parameters: plasma osmolality and AVP concentration; plasma osmolality and copeptin concentration; plasma AVP and copeptin concentrations; plasma copeptin concentration and urine osmolality; plasma copeptin concentration and thirst perception. Because these correlation coefficients involve repeated measurements in each subject, no *P* values were calculated. To assess temporal correlations of different parameters within subjects, rank correlation coefficients were computed for each pair of parameters and each subject. Confidence limits of their medians were determined in the standard nonparametric way. All tests performed were two-tailed, and statistical significance was defined at a level of 5%.

Results

The baseline characteristics of the 20 subjects participating in the study are shown in Table 1. All had uneventful medical histories and normal findings on physical examination and laboratory evaluation, including thyroid and adrenal function.

Immediately before the water load (time point t-1), median plasma osmolality was 290 mOsm/kg (range, 284–302); plasma AVP 1.84 pM (0.46–15.7); plasma copeptin 3.3 pM (1.1–36.4); and urine osmolality 874 mOsm/kg (219–1141). Figure 2A depicts plasma osmolalities throughout the waterload/hypertonic saline test as box-whisker plots. Median plasma osmolality decreased significantly from 290 mOsm/kg (at time point t-1) to 281 mOsm/kg after water load (range, 273–288). After 3% saline infusion, a peak median osmolality of 301 mOsm/kg (range, 298–307) was reached, a significant increase compared with the values of the previous time points. Changes of plasma copeptin concentrations during the test are shown in Fig. 2B. Median values decreased from 3.3 pM at time point t-1 to 2.0 pM (range, 0.9–10.4) after water load and increased to 13.6 pM (range, 3.7–43.3) after hypertonic saline. Median AVP concentrations changed similarly during the course of the test [data not shown; t-1, 1.84 pM (range, 0.46–15.7); after water load, 1.29 pM (range, 0.46–14.1); after hypertonic saline, 5.07 pM (range, 1.8–46.8)].

TABLE 1. Baseline characteristics of study subjects

Age (yr)	30.3 ± 8.7
Male (n)	8
Female (n)	12
Body mass index (kg/m^2)	21.9 ± 2.88
Plasma [Na] (mM)	138.3 ± 1.72
Plasma osmolality (mOsm/kg)	289.6 ± 6.12
Plasma glucose (mM)	4.8 ± 0.48
Plasma creatinine (μM)	71.8 ± 13.07

Values are given as means ± SD, where appropriate.

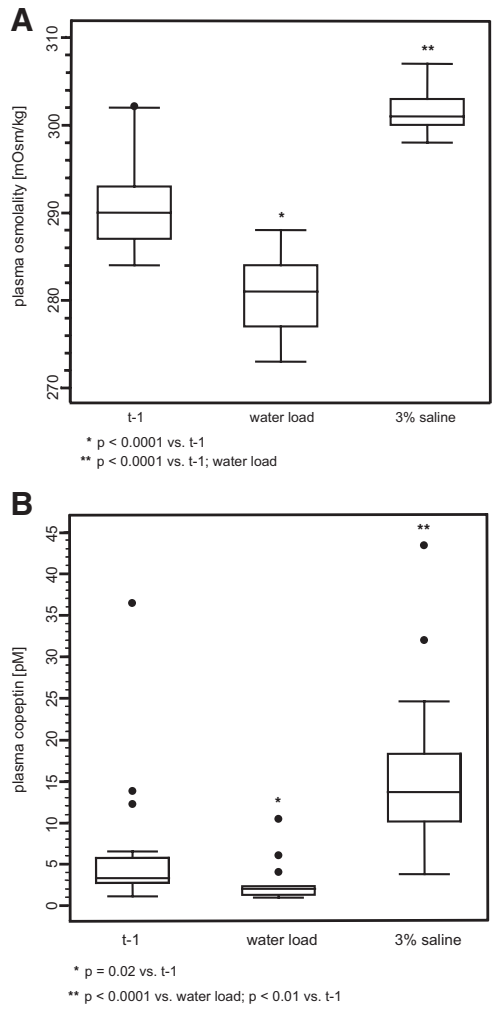

FIG. 2. The distributions of measured plasma osmolalities (A) and plasma copeptin concentrations (B) are shown as box and whisker plots immediately before starting the water load-hypertonic saline test (t-1); after ingestion of 20 ml/kg body weight (water load), and after the infusion of hypertonic saline at 0.1 ml · kg body weight^{-1} · min^{-1} (3% saline), as described in the text. The lower and upper edges of the boxes represent the 25th and 75th percentiles, respectively, whereas the horizontal line inside the box indicates the median. Values whose distance to the box exceeds 1.5 times the interquartile range are displayed as individual points.

We correlated plasma osmolalities of all time points of the test with corresponding copeptin and AVP concentrations. As shown in Fig. 3, plasma AVP and copeptin concentrations at a given osmolality varied widely between individuals, particularly at osmolalities above ~285 mOsm/kg. Nevertheless, the correlations were close [Spearman's rank correlation coefficient (r_S) 0.49 for correlation between osmolality and AVP and 0.77 between osmolality and copeptin, respectively]. Figure 4 shows the corresponding vasopressin and copeptin values of all time points of the test. The parameters are strongly correlated with a r_S of 0.8. The median r_S was significantly larger than 0 ($P < 0.0001$ by the sign test; data not shown). We also analyzed intersubject correla-

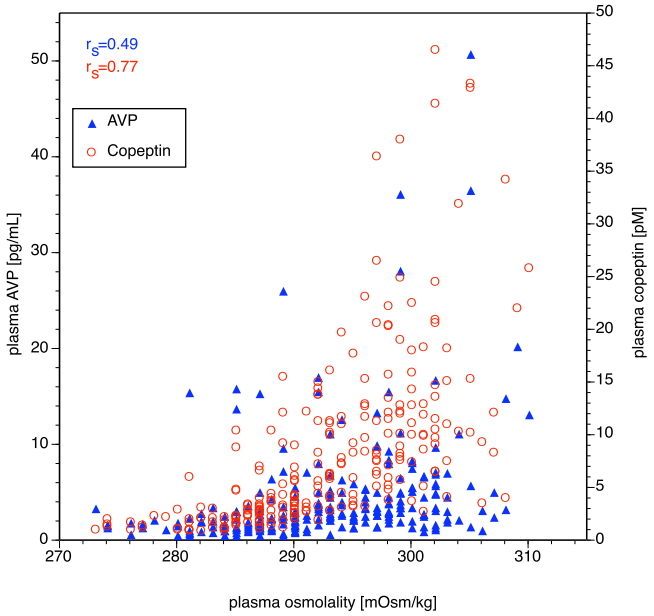

FIG. 3. Plasma AVP and copeptin concentrations measured during the individual water load-hypertonic saline tests are shown as scatter plot. r_S denotes Spearman's rank correlation coefficients.

tions between vasopressin and copeptin across all time points of the water load-hypertonic saline test. The minimal observed r_S was 0.57 ($P = 0.07$; 90 min. after starting the administration of the oral water load), the maximal r_S was 1.0 (observed at 180 min. after starting the 3% saline infusion). In addition, we calculated individual rank correlations between AVP and plasma osmolality as well as copeptin and plasma osmolality. Median r_S for AVP and plasma osmolality was 0.64 (interquartile range, 0.52–

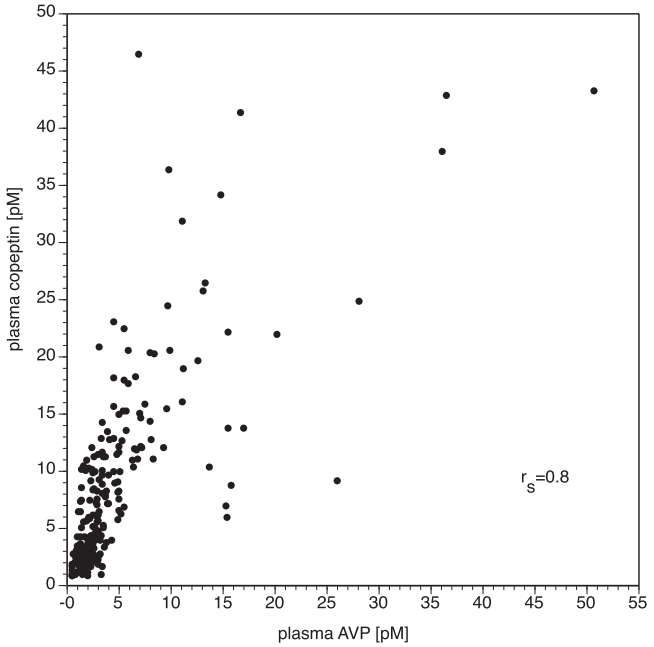

FIG. 4. Scatter plot of all plasma AVP and copeptin concentrations measured during the individual water load-hypertonic saline tests. r_S denotes the Spearman's rank correlation coefficient.

0.79); median r_S for copeptin and plasma osmolality was 0.91 (interquartile range, 0.88–0.95). We correlated plasma copeptin concentrations with urine osmolalities and thirst perception. The Spearman correlation coefficients (r_S) were 0.38 and 0.55, respectively, indicating that circulating copeptin levels reflect the activity of the thirst mechanism as well as the antidiuretic effect of vasopressin at the level of the target organ.

Discussion

Copeptin, the C-terminal glycopeptide domain of provasopressin, is cosecreted with AVP from the posterior pituitary in hyperosmolar states (28) and upon multiple nonosmotic stimuli, such as hypotension, pain, and other nonspecific causes of stress. Circulating copeptin levels are therefore believed to reflect the activity of the neuroendocrine stress axis, and copeptin has increasingly been propagated as prognostically useful biomarker in a variety of acute illnesses (14). In a study with multiple trauma patients, plasma concentrations of copeptin and AVP correlated strongly (17). In addition to its prognostic value, copeptin could serve as diagnostic parameter in the differential diagnosis of hyponatremia. Recently, it has been shown that the ratio of plasma copeptin to urine sodium may be used to differentiate between hyponatremia in the syndrome of inappropriate antidiuresis (ratio <30 pmol/mmol) and hyponatremia attributable to edema-forming states or extrarenal sodium loss (ratio >30 pmol/mmol); furthermore, a suppressed circulating copeptin level (< 3 pM) in the presence of an intact free water clearance (urine osmolality <200 mOsm/kg) may identify patients with primary polydipsia (30). For many years, AVP has been used to differentiate between all types of diabetes insipidus, including partial forms and primary polydipsia (10). However, the reliable measurement of AVP in plasma is time-consuming and technically demanding. Commercially available AVP assays validated for clinical routine are scarce. Thus, the recent development of a copeptin chemoluminescence sandwich immunoassay (8) may constitute a valuable alternative to the AVP RIA (12) when evaluating disorders of water and sodium homeostasis. To establish this, the correlation of circulating copeptin and AVP levels should be known. We therefore measured, for the first time, copeptin and AVP plasma concentrations simultaneously in healthy subjects during isoosmolar as well as hypo- and hyperosmolar conditions induced by a water load or hypertonic saline infusion.

We noted considerable variations of copeptin levels at the start of the tests, most likely representing the lack of a defined steady-state at baseline in terms of hydration and osmoregulation. One study subject showed a maximum value of 36.4 pM, which is above the 99th percentile of 18.9 pM found in a large reference population (31). In this individual, we cannot exclude the presence of a nonosmotic stimulus for AVP/copeptin secretion, although this was clinically not evident.

As expected, both plasma AVP and copeptin concentrations correlated with plasma osmolality (Fig. 3), although in the case of AVP the correlation was less close. There were some instances where measured AVP levels, relative to the plasma osmolalities, were lower than could be expected from published data (Fig. 3). To account for possible technical difficulties with the measurement of plasma osmolalities, we calculated plasma osmolalities and correlated them with the measured osmolalities and the hormone values. We found a close correlation between measured and calculated plasma osmolalities ($r_S = 0.84$). Calculated osmolalitities were somewhat lower than measured values by 4.3 ± 5.3 (mean ± SD) mOsm/kg, but overall, rank correlations (r_S) of AVP and copeptin concentrations with calculated osmolalities (0.45 and 0.72, respectively) were similar to those with measured osmolalities (0.49 and 0.77, respectively). One possible explanation for the relatively low AVP levels found in some individuals is that although the osmotic threshold and sensitivity of AVP secretion are highly reproducible in a given individual, their interindividual variation is quite large (32). Rarely, the osmotic threshold for AVP release may be as high as 290 mOsm/kg or more. Theoretically, we cannot completely exclude that falsely low AVP concentrations may have resulted in some instances from improper handling of the plasma samples in the preanalytical phase, particularly during transport. During the water load-hypertonic saline tests, we took every possible precaution while obtaining the samples. Samples were drawn on ice, centrifuged in a cooled table centrifuge, frozen immediately, and shipped by a courier on dry ice without prior thawing. The complexity and potential methodological drawbacks of the AVP RIA, including potentially long shipping time of samples and the fact that standard reference material for AVP is not available, underscore the need for a reliable substitute for routine clinical practice. The copeptin sandwich immunoluminometric assay offers such an alternative, yielding results to the clinician within hours (8).

Our study has some limitations. The mean age of the studied individuals was ~30 yr (30.3 ± 8.7 yr), therefore our results may not be generalizable to children or to an older population. Also, because we studied healthy individuals, we cannot extend our findings to patients with potentially interfering conditions such as impaired renal function. While the half-life of copeptin in healthy individuals is similar to AVP (as seen by the fast decline during

the water load-hypertonic saline test), it is yet unclear how copeptin is removed from the circulation. Like AVP, copeptin seems to be at least partially cleared via the kidneys, as it is detectable in the urine (N.G. Morgenthaler, unpublished). Hence, the clearance may be impaired in renal disease (16). Furthermore, in acutely ill patients, the secretion of AVP and copeptin may be predominantly driven by nonosmotic stimuli, and plasma concentrations do not reflect osmoregulation (33). In this setting, the role of copeptin in the analysis of electrolyte disturbances needs to be established in further studies.

In summary, the results presented here document a close correlation between plasma AVP and copeptin concentrations across a wide range of plasma osmolalities in healthy individuals. These findings indicate that copeptin can indeed be used as a surrogate for AVP release. This observation has important clinical implications because it suggests that the measurement of copeptin may be a suitable alternative to the technically challenging AVP assay. In the future, establishing the ranges of stimulated copeptin concentrations in patients with complete and partial forms of neurohypophyseal and renal diabetes insipidus, as previously done for AVP (10), are expected to facilitate the correct diagnosis in these patients.

Acknowledgments

We are grateful to the volunteers participating in this study and to Peter Jüni for valuable discussions. We thank Nadine Gerber, Thomas Zysset, and Jean-Pierre Rothen for expert technical assistance.

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This work was supported by an unrestricted gift from David Wiener (to P.K.).

www.ClinicalTrials.gov number: NCT00696605.

Disclosure Summary: N.G.M. is employee of B.R.A.H.M.S. AG, the manufacturer of the Copeptin assay used in this study. The other authors have nothing to declare.

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