Copeptin concentrations during psychological stress: the PsyCo study

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Abstract

Objective: The prognostic/diagnostic biomarker copeptin, an arginine vasopressin surrogate, reflects physical stress. Whether copeptin concentration increases upon psychological stress is unknown. We investigated psychological stress effects on copeptin secretion in healthy volunteers and patients with central diabetes insipidus (DI).

Design: A prospective observational study was conducted to study the relation between copeptin concentration and psychological stress.

Methods: A total of 20 healthy adults (ten female) and eight patients with central DI (four female) underwent the Trier Social Stress Test including, in order, 30-min waiting period, 10-min anticipation period, 10-min test period and 40-min recovery. Serum copeptin and cortisol concentrations and self-rated stress component feelings were determined in the pre-/post-anticipation period, post-test period and twice post-recovery.

Results: In healthy volunteers, the median (25th–75th percentile) copeptin concentration peaked immediately during the post-test period at 5.1 (3.2–7.0) pmol/l, vs 3.7 (2.6–5.4) pmol/l at baseline. Over the measurement course, copeptin concentration significantly elevated (coefficient; 95% CI) (0.14; 0.06–0.23, $P=0.002$). The important predictors of increase in copeptin concentration were feelings of tension (0.06; 0.04–0.08, $P<0.001$) and avoidance (0.07; 0.04–0.10; $P<0.001$).

Copeptin and cortisol levels were associated (0.43; 0.13–0.72, $P<0.005$). Patients with DI had lower baseline concentrations (1.55 (1.2–3.1) pmol/l) when compared with healthy volunteers, $P=0.006$. Patients with DI showed no increase upon psychological stress (peak 2.15 pmol/l (1.5–2.28), $P=0.79$). By contrast, cortisol values were similar in patients and volunteers.

Conclusions: In healthy volunteers, copeptin levels significantly increased after psychological stress testing; this response was blunted in patients with DI.

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Introduction

Arginine vasopressin (AVP) is the main hormone regulating water homeostasis (1, 2, 3). AVP is also a stress hormone, acting as a potent synergistic factor with corticotrophin-releasing hormone to stimulate the secretion of adrenocorticotrophic hormone and cortisol (4). Owing to preanalytical difficulties, circulating AVP is cumbersome to measure (1, 3, 5). However, AVP is cleaved off a precursor molecule and co-secreted stoichiometrically, with three

other peptides, among them copeptin, which is easier to measure, stable *ex vivo* and rapidly quantifiable by sandwich immunoassay (1, 4). Mirroring AVP's role in water homeostasis, copeptin has been shown to aid in differentially diagnosing polyuria–polydipsia syndrome (6, 7) and hyponatraemia (8); mirroring AVP's role as a stress hormone, copeptin is a useful prognostic biomarker in several acute diseases, e.g. stroke or myocardial infarction (9, 10).

Copeptin concentrations are unassociated with age, lack consistent circadian rhythm (11), increase after exercise and show slightly but significantly higher median values in men vs women (1). However, little else has been published about physiological copeptin fluctuations, despite the ever-increasing literature regarding this biomarker's levels in different diseases. Thus, it is not understood as to what extent psychological stress alters copeptin secretion, knowledge that could affect this analyte's interpretation as a diagnostic or prognostic marker in clinical practice.

We hypothesised that copeptin levels would increase upon psychological stress in healthy volunteers, but not in patients with central diabetes insipidus (DI), a fluid balance disorder characterised by deficient AVP/copeptin secretion upon osmotic stimulation (12). We sought to test these hypotheses by conducting the present prospective observational study assessing copeptin kinetics in healthy volunteers and patients with DI following the Trier Social Stress Test (TSST), the most frequently used validated, standardised psychological test for stress hormone reactivity studies (13, 14).

Subjects and methods

Subjects and ethics

A total of 20 healthy volunteers and eight patients with central DI (four complete central DI and four partial central DI) confirmed by an adapted water deprivation test (15, 16) were included; their characteristics are summarised in Table 1. As per the exclusion criteria, the volunteers were in good physical health, without evidence of acute disease, history of chronic illness, BMI > 30 kg/m² or serum glucose > 7 mmol/l or serum sodium < 135 or > 145 mmol/l at baseline. No volunteer had any psychiatric disorder. All patients with DI were on desmopressin treatment. Of the eight patients with DI, four patients had a replacement therapy with L-thyroxine, three were substituted with hydrocortisone because of hypocortisolism, two patients were on i.m. testosterone every 12 weeks for secondary hypogonadism and one patient on GH substitution. Apart from hormone replacement therapy, one patient was treated for hypertension and anticoagulated for deep venous thrombosis and one patient took daily tardyferon ($n=1$ each). No other reported physical or psychiatric comorbidities.

The study was performed under the Helsinki Declaration principles, approved by the responsible Ethics Committee (*Ethikkommission beider Basel, EKBB*) and registered at clinicaltrials.gov (identifier NCT01866137).

Table 1 Baseline subject characteristics. Categorical variables are summarised with percentages (counts) and continuous variables with (IQR).

	Healthy volunteers ($n=20$)	Patients with DI ($n=8$)
Age (years)	22.5 (20.8–25.8)	46.1 (38.8–47.4)
Male gender	50.0% (10)	50.0% (4)
Caucasian ethnicity	100% (21)	100% (8)
Alcohol consumption (glasses/week)	3.00 (1.25–5.00)	0.50 (0.00–2.00)
Current smoker	20.0% (4)	33.3% (1)
Chronic diseases	0.0% (0)	25.0% (2)
Psychiatric disorder	0.0% (0)	0.0% (0)
Insomnia	5% (1)	0% (0)
Body temperature (°C)	37.0 (36.6–37.4)	37.0 (36.9–37.2)
Systolic blood pressure (mmHg)	114 (106–125)	125 (110–128)
Diastolic blood pressure (mmHg)	74.0 (68.0–80.5)	83.0 (74.0–86.0)
Heart rate (bpm)	65.0 (56.5–74.5)	67.5 (60.5–73.0)
Weight (kg)	70.0 (64.2–78.2)	73.0 (71.0–73.5)
Height (m)	1.71 (1.68–1.78)	1.75 (1.69–1.8)
BMI (kg/m ²)	22.8 (21.6–25.1)	21.8 (21.4–22.0)
Copeptin (pmol/l)	3.70 (2.55–5.40)	1.55 (1.2–3.1)
Cortisol (nmol/l)	431 (336–517)	307 (224–343)
VAS scores for stress components		
Discomfort	0.0 (0.0–1.0)	0.0 (0.0–0.5)
Anxiety	0.0 (0.0–0.0)	0.0 (0.0–0.5)
Tension	1.0 (0.0–2.0)	0.0 (0.0–1.5)
Avoidance	0.0 (0.0–1.0)	0.0 (0.0–1.5)

DI, diabetes insipidus; IQR, interquartile range: 25th–75th percentile; VAS, visual analogue scale (0, none at all, to 10, very pronounced).

After full explanation of the nature and purpose of all study procedures and elements, participants gave written informed consent.

Trier Social Stress Test

The TSST protocol included a waiting period (30 min), an anticipation period (10 min), a test period (10 min) and a recovery period (40 min) (14, 17). Right before the anticipation period, subjects were instructed regarding the tasks to be performed during the test period: delivering an extempore speech (first 5 min of test period) and verbally responding to a challenging arithmetic problem (second 5 min of test period), in both cases facing an audience. Subjects were then informed that the speech would be audio-recorded and video-recorded, with the recordings to, respectively, undergo voice frequency and nonverbal behaviour analyses. The test's audience comprised two trained actors, who were not to respond emotionally, but to maintain neutral facial expressions. These circumstances, as well as anticipation during speech preparation, have been shown to consistently evoke subjective stress and activate the hypothalamic–pituitary–adrenal axis and sympatho-adrenomedullary system (18, 19).

Study protocol

On the testing day, volunteers and patients arrived at 0800 h after 24-h abstinence from alcohol, a 10-h overnight fast and with last fluid intake allowed at 0600 h. Patients were asked to take their last desmopressin dose before 0600 h.

Before the 30 min waiting period, patients underwent physical examination and completed standardised anamnestic and clinical questionnaires. An i.v. catheter for blood sampling (EDTA KE/7.5, Serum Gel Z/7.5) was inserted just before the waiting period. Blood samples were collected immediately before the start of the anticipation period (baseline), after that period (+10 min), immediately after test performance (+20 min) and following recovery (+40 min, +60 min). Serum copeptin and serum cortisol concentrations were measured in all samples and to exclude osmotic stimulus, sodium, urea and glucose levels were determined at baseline and +60 min. Blood pressure and heart rate were measured and subjects completed a standardised stress perception questionnaire at every timepoint. In the questionnaire, feelings of discomfort, anxiety, tension and avoidance (desire to leave the situation) were each separately rated on a visual analogue scale (VAS) ranging from 0 (none) to 10 (very pronounced).

Biochemistry

Copeptin and cortisol concentrations were measured in single batches thawed from frozen (-20°C) supernatants of centrifuged serum gel tubes. Copeptin was quantitated by an immunofluorescent assay (BRAHMS CT-proAVP KRYPTOR, Thermo Scientific Biomarkers, Hennigsdorf, Germany) with a 0.9 pmol/l lower detection limit, an <2.0 pmol functional assay sensitivity and <3 to $<15\%$ (<5 to $<17\%$) intra-assay (inter-assay) coefficient of variation values, depending on analyte concentrations. According to the manufacturer, the healthy adult reference range (2.5th–97.5th percentiles) was 1.2–16.4 pmol/l; the median (interquartile range (IQR, 25th–75th percentiles)) value was 1.18 (1.0–1.3) pmol/l in nine patients with complete central DI (6).

Cortisol was measured by a chemiluminescence immunoassay (Siemens, Erlangen, Germany) with a reference range for morning cortisol levels of 171–536 nmol/l.

Sodium, urea and glucose were quantified immediately after blood withdrawal; determinations were carried out by automated chemical analyses in the University Hospital Basel Central Laboratory.

Statistical analysis

For continuous variables, the median (IQR) is given. For categorical variables, frequencies (counts), or *vice versa*,

Table 2 Median and interquartile range (IQR) for copeptin, cortisol, the four stress compounds, heart rate and blood pressure in healthy volunteers (A) and eight patients with DI (B).

Variable	Baseline ^a	+ 10 min ^b	+ 20 min ^c	+ 40 min ^d	+ 60 min ^d
(A) Healthy volunteers					
Copeptin	3.70 (2.55–5.40)	4.00 (2.80–5.70)	5.10 (3.20–7.00)	3.70 (2.45–5.30)	3.80 (2.42–5.00)
Cortisol	431.0 (336.0–517.0)	472.0 (414.0–555.0)	521.0 (484.5–696.5)	481.0 (428.5–627.0)	421.5 (353.8–533.2)
Discomfort	0.0 (0.0–1.5)	2.0 (0.5–3.5)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Anxiety	0.0 (0.0–0.0)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Tension	0.0 (0.0–1.0)	3.0 (2.0–4.0)	2.0 (1.0–3.5)	0.0 (0.0–0.5)	0.0 (0.0–0.0)
Avoidance	0.0 (0.0–0.0)	2.0 (1.0–3.5)	2.0 (0.0–2.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Heart rate	57 (53–64)	66 (61–77)	66 (62–75)	59 (56–67)	60 (54–68)
Systolic blood pressure (mmHg)	109 (104–127)	120 (113–136)	131 (118–144)	114 (104–123)	113 (105–125)
Diastolic blood pressure (mmHg)	72 (68–78)	75 (69–83)	83 (76–87)	76.50 (70–79)	74.5 (66–78)
(B) Patients with DI					
Copeptin	1.55 (1.2–3.1)	1.90 (1.38–2.55)	1.90 (1.60–2.65)	2.10 (1.35–2.5)	2.15 (1.5–2.28)
Cortisol	307.0 (224.0–343.0)	426.0 (359.0–459.0)	454.0 (452.0–519.0)	420.0 (396.0–567.0)	311.5 (299.0–325.5)
Discomfort	0.0 (0.0–0.5)	1.5 (0.0–3.0)	1.0 (0.0–3.0)	0.0 (0.0–1.5)	0.0 (0.0–0.0)
Anxiety	0.0 (0.0–0.5)	1.0 (0.0–3.5)	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.0 (0.0–0.0)
Tension	0.0 (0.0–1.5)	2.0 (1.0–5.5)	2.0 (2.0–3.5)	0.0 (0.0–0.5)	0.0 (0.0–0.0)
Avoidance	0.0 (0.0–1.5)	1.5 (1.0–4.0)	1.0 (0.0–3.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Heart rate	62 (54–70)	65 (62–80)	70 (58–81)	60 (54–72)	65 (57–74)
Systolic blood pressure (mmHg)	116 (111–121)	122 (114–140)	124 (123–132)	118 (109–123)	116 (107–124)
Diastolic blood pressure (mmHg)	75 (65–78)	80 (77–83)	84 (80–85)	79 (74–80)	74 (68–76)

^aPre-anticipation period.

^bPost-anticipation period.

^cPost-test period.

^dPost-recovery.

Figure 1

Subjective stress perception: VAS scores for (a) discomfort, (b) anxiety, (c) tension and (d) avoidance at different timepoints before, during and after the TSST. TSST, Trier Social Stress Test; VAS, visual analogue scale (0, none, to 10, very pronounced.).

are reported. To compare serial copeptin or serial cortisol concentrations, or both, mixed models were used to account for non-independence of measurements within subjects; hormone levels were log-transformed before inclusion. The categorical variable treatment (TSST) was used as a fixed effect. For every subject, separate intercepts and separate slopes were fitted for each measurement time. The models used a within-group (serial) autocorrelation structure, leading to considerably better model fits than did ignoring within-group correlations. For each model and fixed effect, the coefficient, the approximate 95% CI, the denominator degrees of freedom, the *t*-statistic and the associated *P* value were calculated. Testing was two tailed; $P \leq 0.05$ was deemed significant.

Results

As reflected by median VAS scores for feelings of discomfort, anxiety, tension and avoidance, subjective stress perception peaked at the end of the anticipation period (+10 min measurement point) (Table 2 and Fig. 1a, b, c and d). Median copeptin and cortisol concentrations peaked at the end of the test period (+20 min timepoint) (Table 2 and Fig. 2a and b), respectively, rising by 1.4 pmol/l (38%) and 90 nmol/l (21%) from baseline.

Over the measurement course, the TSST significantly increased copeptin levels (coefficient; 95% CI) (0.14; 0.06–0.23, $P=0.002$) (Table 3). The most important predictors of increase in copeptin concentration were feelings of tension (0.06; 0.04–0.08, $P<0.001$) and avoidance (0.07; 0.04–0.10, $P<0.001$). The TSST also significantly raised cortisol values (0.16; 0.09–0.23, $P<0.001$), which

result was mainly influenced by feelings of tension (0.03; 0.01–0.05, $P=0.006$). Levels of the two hormones were significantly associated (0.43; 0.13–0.72, $P<0.005$). Glucose, urea and sodium levels remained unchanged during the measurement course (data not shown).

Patients with DI in comparison with healthy volunteers had lower baseline copeptin levels (1.55; 1.2–3.1 vs 3.7; 2.9–5.4, $P=0.006$) (Table 1) and showed no significant increase (peak 2.15 (1.5–2.28) pmol/l) upon psychological stress, $P=0.79$ (Table 2 and Fig. 2a). By contrast, cortisol baseline levels and kinetics upon psychological stress were comparable to those in healthy volunteers (Table 2 and Fig. 2b). Owing to hydrocortisone treatment in three patients with DI, only five patients were considered for analysis of cortisol levels. Subjective stress perception was also similar compared with that of healthy volunteers (data not shown).

Discussion

This study's main novel finding was that copeptin levels, in parallel to cortisol levels, increased upon psychological stress in healthy volunteers, especially as embodied by feelings of tension and avoidance (desire for flight). This stands in contrast to patients with DI, where only an increase in cortisol concentration but no change in copeptin concentration was observed upon psychological stress.

This finding would appear to have two clinical implications. First, copeptin values may need to be interpreted cautiously in psychologically stressed patients. This caveat may be especially important in the emergency setting, where copeptin levels are, for example, applied for rapid rule-out of acute myocardial infarction (10).

Figure 2

Temporal progression of (a) copeptin concentrations and (b) cortisol concentration in 20 healthy adult volunteers and eight adults with central DI. Measurement time 0 (baseline) was before the TSST anticipation period, time +10 min was at the end of that period, time +20 min was at the end of the test period and times +40 and +60 min were after the recovery period. DI, diabetes insipidus.

Table 3 Effect of stress test on copeptin and cortisol levels in healthy volunteers.

Exposure variables	Effect of stress test on log-transformed marker level (coefficient, 95%CI)	P
Copeptin		
Overall stress	0.14; -0.06 to 0.23	0.002
Discomfort	0.04; -0.00 to 0.07	0.03
Anxiety	0.05; -0.00 to 0.11	0.07
Tension	0.06; 0.04 to 0.08	<0.001
Avoidance	0.07; 0.04 to 0.10	<0.001
Cortisol		
Overall stress test	0.16; 0.09 to 0.23	<0.001
Discomfort	0.02; -0.01 to 0.04	0.19
Anxiety	0.03; -0.01 to 0.08	0.15
Tension	0.03; 0.01 to 0.05	0.006
Avoidance	0.03; -0.00 to 0.06	0.04

Copeptin cut-off values have also been suggested for diagnosis and treatment guidance in the polyuria–polydipsia syndrome (6). Altered copeptin levels upon psychological stress call into question fixed cut-offs in clinical routine, where blood is often taken while patients experience anxiety and tension.

Secondly, copeptin might represent a sensitive alternative to adrenocorticotrophic hormone or cortisol to measure individual perception of psychological stress. In contrast to cortisol, no cross-reactivity with other steroid hormones is known for copeptin. While cortisol levels follow a circadian rhythm, no consistent circadian rhythm was found for copeptin levels thus far, although tested only in a small sample of patients (1, 11). Moreover, copeptin was shown to mirror individual stress levels more subtle than cortisol (20).

Recently, the role of vasopressin in social behaviour and stress has been investigated and shows that social information is partly processed by vasopressin (21, 22). It has been shown that the genetic mechanisms of inter-individual variation in the vasopressin–oxytocin pathway influence human social interaction (21). AVP therefore emerged together with oxytocin as a target for novel treatment approaches for mental disorders characterised by social dysfunction. In two studies, the intranasal administration of AVP resulted in a significant increase in salivary cortisol and heart rate compared with placebo in the TSST (23). This finding suggests that AVP is a key player in the sensation and regulation of stress and social threat; therefore, AVP antagonists have been considered for the treatment of major depression and may also be helpful in the treatment of stress-related disorders and disorders that are characterised by interpersonal violence, such as antisocial personality disorders (21).

Patients with central DI have endogenous AVP/copeptin deficiency upon osmotic stimulation. Even in an absence of change in osmolality, physical stress normally results in a rise in AVP secretion secondary to increased hypothalamic–pituitary–adrenal axis activity (24). In this study, we showed that patients with central DI could not secrete copeptin in situations of psychological stress. Interestingly, however, their subjective stress perception and cortisol secretion seemed to be normal. This finding of normal cortisol response to acute stress in adults with central DI agrees with a recent work in children with this condition (25).

Our study had limitations. First, it had a small, single-centre sample. However, as baseline fasting copeptin levels in our volunteer cohort were comparable to those observed in other healthy volunteers (1, 3), we consider it probable that our results in healthy volunteers were robust. The sample size of our patients with DI ($n=8$) is rather small and needs validation in further studies; however, our results are of interest showing for the first time that patients with central DI and AVP/copeptin deficiency are not able to react to psychological stress with an increase in AVP/copeptin concentration but show a normal cortisol response. However, as a further limitation, we cannot fully exclude an influence of exogenous desmopressin administration on copeptin levels in patients with DI. Secondly, the volunteer sample predominantly comprised young adults, whereas in clinical practice, copeptin is measured in all age groups. However, copeptin concentrations have been shown not to be associated with age (1, 26); we therefore consider different results in an older population to be unlikely.

Thirdly, we relied on within-subject comparison. We decided against a control group not undergoing psychological stress testing, as previous data indicated no circadian rhythm of copeptin (1).

In conclusion, in healthy volunteers, median copeptin levels slightly but significantly rose upon psychological stress, stimulated mainly by feelings of tension and avoidance. This finding suggests that it may be important to consider patients' psychological stress when interpreting copeptin values. In contrast to healthy volunteers, patients with central DI appear to be unable to secrete copeptin upon psychological stress, but retain normal cortisol response.

Declaration of interest

M Christ-Crain and P Schuetz have received honoraria from Thermo Scientific Biomarkers (formerly BRAHMS AG), the copeptin assay developer/manufacturer, to fulfil speaking engagements and travel support to attend medical meetings. Thermo has also provided research grants to the Division of Endocrinology, Diabetes and Clinical Nutrition, University

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