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Absence of a diurnal rhythm of oxytocin and arginine-vasopressin in human cerebrospinal fluid, blood and saliva

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ABSTRACT

Purpose: The aims of our study were to determine first circadian influences on central concentrations of the neuropeptides oxytocin and arginine-vasopressin and second to investigate if these central concentrations are associated with those in the peripheral compartments blood and saliva in neurocritical care patients.

We therefore included patients with external ventricular drain who attended a neurosurgical intensive care unit and were not exposed to painful or stressful stimuli during the sampling period. For this purpose, blood, cerebrospinal fluid and saliva were collected in a 24-hour-interval at the timepoints 06:00, 12:00, 18:00 and 24:00.

Results: In none of the three body fluids examined, significant time-dependent fluctuations of oxytocin and arginine-vasopressin concentrations could be detected during the 24-hour sampling period. The only exception was the subgroup of postmenopausal women whose oxytocin concentrations in cerebrospinal fluid at 12:00 were significantly higher than at 18:00. Correlations of blood and cerebrospinal fluid and blood and saliva neuropeptide levels were very weak to weak at each timepoint. Cerebrospinal fluid and saliva oxytocin levels showed a moderate correlation at 06:00 but did correlate very weak at the other timepoints.

Conclusions: Central as well as peripheral oxytocin and arginine-vasopressin concentrations in neurocritical care patients did not show significant diurnal fluctuations. No strong correlations between central and peripheral neuropeptide concentrations could be detected under basal conditions. If investigators even though decide to use saliva concentrations as surrogate parameter for central neuropeptide activity, they have to consider that correlations of cerebrospinal fluid and saliva oxytocin seem to be highest in the early morning.

1. Introduction

The nonapeptides oxytocin (OXT) and arginine-vasopressin (AVP) are synthesized in the hypothalamic nuclei supraopticus and paraventricularis and stored in the posterior pituitary lobe. Once released into the blood, they exert their traditional known functions regulating birth and lactation (OXT) as well as blood pressure, water and electrolyte homeostasis (AVP) (Norsk, 1996; Anand and Skinner, 2012; Gutkowska et al., 2014). When secreted within the central nervous system, OXT and AVP act as neuropeptides which play a critical role in bonding, socio-emotional behavior, cognition and psychopathology (Kormos and Gaszner, 2013; Baribeau and Anagnostou, 2015; Jurek and Neumann, 2018). Studies on surgical and intensive care patients are scarce, although the hypothalamic neuropeptide system is involved in the development of posttraumatic stress disorder which is frequent in patients after major surgery and may significantly influence psychological as well as functional outcome in the critically ill (El-Gabalawy et al., 2019).

Peripheral neuropeptide concentrations are usually assessed by blood levels. Central neuropeptide activity, which is of interest in the development of psychopathologies, however, is best represented by cerebrospinal fluid (CSF) concentrations (Landgraf and Neumann, 2004; Neumann and Landgraf, 2012). As CSF access is always invasive, many human studies use peripheral compartments like blood or saliva as surrogate parameter for central neuropeptide activity (Grewen et al., 2010; Feldman et al., 2011; Bhandari et al., 2014; Fancourt et al.,

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2016). However, it remains unclear to which extent and under which conditions peripheral neuropeptide levels reflect central concentrations.

Further, researchers in the field often assume a circadian rhythmicity of especially central OXT, although central concentrations of hypothalamic neuropeptides were investigated in only a few human studies with very limited and heterogenous in-patient collectives (Amico et al., 1983; Amico et al., 1985; Barreca et al., 1988; Kuboyama et al., 1988). Animal studies revealed conflicting results (Kalsbeek et al., 1995). Regarding peripheral neuropeptides, diurnal variations have been shown for AVP in healthy humans, but not in hospitalized patients (George et al., 1975; Barreca et al., 1988; Graugaard-Jensen et al., 2017). For plasma OXT, a peak in the early morning in pregnant women is assumed, as births mostly occur in the morning hours. However, this could not be confirmed in non-pregnant women (Forsling, 2000; Graugaard-Jensen et al., 2014).

The aim of our study was to examine circadian rhythmicity of central OXT and AVP levels in critical care patients with free access to ventricular CSF under basal conditions. Further, we simultaneously measured peripheral neuropeptide concentrations in blood and saliva to investigate the relationship between central and peripheral compartments. As hypothalamic neuropeptides are getting increasing attention in the field of intensive care, we intend to provide data that facilitate the design of future studies in a modern surgical critical care setting.

2. Patients and methods

The study was approved by the Institutional Review Board of the Medical Faculty of the Technical University of Munich (reference number 5459/12). We prospectively studied 20 patients (8 male, 6 premenopausal female, 6 postmenopausal female, median age 54.5 years, range 34–75 years) with extraventricular drain treated at the operative Intensive Care Unit because of intracranial hemorrhage or tumor who had overcome the acute phase of their illness, 5–28 days after the ictus (median 8.5 days). Only patients who were awake and able to give written informed consent themselves were included in the study. Patients did not obtain any sedative medication during the examination period. They attended the ICU only for monitoring, did not receive any kind of intervention and did not show elevated intracranial pressure throughout the examination period. Diabetes insipidus, excessive salt wasting or acute infections were exclusion criteria. Patients were allowed to eat and drink ad libitum and additionally received a standard intravenous fluid intake of 100 ml/h. They were not strictly confined to bed as mobilization and physiotherapy during daytime was performed according to institutional standard protocols. Lights went on at 06:00 and out at 22:00, and the light sources were only partially artificial as windows were in every room and shades were open at daytime.

15 of the 20 included patients suffered from aneurysmal subarachnoid hemorrhage, and their neurological status at the time of the incident had been assessed by the emergency physician applying the Hunt and Hess scale (Rosen and Macdonald, 2005). Three months after the ictus, the patients´ neurological status was assessed in the neurosurgical outpatient clinic and documented by means of the Glasgow outcome score (GOS). Outcome was generally classified as good with a median GOS of 4.5 (range 3–5) (McMillan et al., 2016). Two patients were transferred to an external rehab hospital and missed the three months follow-up-examination. For patient characteristics see Table 1.

Samples of plasma, CSF and saliva were collected from each patient over one 24-hour period at 06:00, 12:00, 18:00 and 24:00, starting at 06:00. Plasma was drawn from the pre-existing arterial or central-venous line, CSF was collected simultaneously from the ventricular drain. Pre-chilled plastic EDTA tubes were used for the collection of plasma and CSF. Saliva samples were collected in a pre-chilled saliva collection system (Salivette®, Sarstedt, Germany) with a solid base for saliva absorption and a conical tube for centrifugation and recovery of the collected saliva. Samples were centrifuged for 10 min at 1300*g* at 4 °C and stored at −80 °C until analysis. Plasma, CSF and saliva samples were treated identically, i.e., extracted and analyzed in the same batch at the same time as described before (Kagerbauer et al., 2013; Martin et al., 2014, 2018). In short, LiChroprep® Si60 (Merck) was used, heat-activated at 700 °C for 3 h. 20 mg of LiChroprep® Si60 in 1 ml distilled water were added to the sample, mixed for 30 min, washed twice with distilled water and 0.01 N HCl and eluded with 60% acetone. The lyophilized extracts and the evaporated saliva samples were analyzed for oxytocin and arginine-vasopressin in a highly sensitive and specific radioimmunoassay (RIAgnosis, Regensburg, Germany) Assay sensitivity was in the 0.5 pg range, cross-reactivities with related peptides were < 0.7% and intra- and inter-assay variabilities < 10%.

Table 1
Patient characteristics.

Age	Sex	Diagnosis	Day after ictus	HH	GOS
61	m	SAH	14	III	4
57	f post	SAH	7	II	5
47	f pre	SAH	24	II	4
52	f post	SAH	5	III	5
68	m	Meningioma with postoperative ICH	5		3
61	m	SAH	10	II	5
51	f pre	SAH	6	II	5
63	m	SAH	5	III	5
59	m	SAH	5	II	5
58	f post	SAH	5	III	4
40	f pre	SAH	18	III	n.a.
52	f post	Nonaneurysmal SAH	16		n.a.
34	f pre	Meningioma with postoperative ICH	5		4
48	m	SAH	19	III	4
75	m	Traumatic brain injury	8		3
49	m	Hydrocephalus	28		3
50	f pre	SAH	10	II	5
45	f pre	SAH	9	II	4
57	f post	SAH	13	III	5
73	f post	SAH	7	IV	5

SAH = subarachnoid hemorrhage, m = male, f pre = premenopausal female, f post = postmenopausal female, HH = Hunt/Hess scale† (determined by the emergency physician at the time of the incident), GOS = Glasgow Outcome Scale ‡ (determined after three months, two patients were lost to follow-up).
†Hunt and Hess scale (modified): I. minimal headache; II. moderate to severe headache, meningism; III. drowsiness, confusion; IV. stupor; V. coma.
‡Glasgow outcome scale: 1. death; 2. persistent vegetative state; 3. severe disability; 4. moderate disability, independence in daily life; 5. good recovery.

Statistical analysis was performed using R (Version 3.5.2, The R Foundation for Statistical Computing, Vienna, Austria). Neuropeptide concentrations in the three compartments were compared by means of Friedman-test with post-hoc Wilcoxon test and Bonferroni correction according to the multiple testing problem.

The time course of OXT and AVP concentrations in the three compartments blood, CSF and saliva was analyzed by factorial ANOVA for the whole patient collective and for the three subgroups male, premenopausal female and postmenopausal female. Post-hoc analysis for the subgroups was performed by pairwise comparisons using Wilcoxon rank-sum test. The patients´ individual time courses are shown as line graphs separately for the three subgroups. A mixed linear-effect model was applied to elicit the influence of sex and age. Correlations of blood and CSF, blood and saliva and CSF and saliva concentrations of OXT and AVP were assessed using Spearman's rank correlation coefficient at each of the four timepoints.

Hypothesis testing was performed on exploratory two-sided 5% significance levels.

3. Results

Regarding OXT, the three different compartments showed significant differences in concentration levels ($p < .001$). AVP blood and

Table 2a
Median and interquartile range [Q25; Q75] of OXT concentrations in pg/ml at the four timepoints in CSF, blood and saliva for the whole patient collective.

Timepoint	CSF	Blood	Saliva
06:00	**4.44** [3.98; 4.87]	**2.19** [1.50; 2.92]	**1.47** [1.22; 2.04]
12:00	**4.69** [4.00; 5.00]	**2.40** [2.05; 2.79]	**1.66** [1.04; 1.91]
18:00	**4.29** [3.90; 4.97]	**2.31** [2.11; 2.66]	**1.39** [1.10; 1.82]
24:00	**4.48** [4.09; 5.01]	**2.20** [1.95; 2.69]	**1.48** [0.95; 1.97]

We chose bold to emphasize the medians (the "results") over the interquartile ranges (the +- range)

Table 2b
Median and interquartile range [Q25; Q75] of AVP concentrations in pg/ml at the four timepoints in CSF, blood and saliva for the whole patient collective.

Timepoint	CSF	Blood	Saliva
06:00	**2.99** [2.82; 3.87]	**2.92** [2.33; 3.27]	**3.19** [2.53; 4.31]
12:00	**3.20** [2.91; 3.33]	**2.74** [2.45; 3.19]	**3.87** [3.14; 4.26]
18:00	**3.16** [2.98; 3.72]	**3.12** [2.18; 3.44]	**3.26** [2.90; 5.30]
24:00	**3.31** [2.92; 3.57]	**2.85** [2.41; 3.22]	**3.91** [2.93; 4.99]

We chose bold to emphasize the medians (the "results") over the interquartile ranges (the +- range)

saliva as well as CSF and saliva concentrations also were significantly different ($p < .001$). Only AVP CSF and saliva values did not differ significantly. OXT CSF levels were higher than blood levels throughout, which is consistent with the existing literature (Jokinen et al., 2012; Striepens et al., 2013; Lefevre et al., 2017).

Medians and interquartile ranges of OXT and AVP concentrations in plasma, CSF and saliva at the four different timepoints are presented in Tables 2a and 2b. Line graphs of individual patient time courses in the three subgroups male, premenopausal female and postmenopausal female are shown in Fig. 1. Comparing the four timepoints, significant fluctuations could not be detected in any of the three body fluids. Differentiation between male and female patients did not reveal any significant changes either. The only significant observation could be made when analyzing the subgroups of pre- and postmenopausal women separately. Only in the subgroup of postmenopausal women, post-hoc analysis showed that OXT concentrations in CSF at 12:00 were significantly higher than at 18:00 ($p = .031$).

Regarding AVP, no time-dependent peak in plasma, CSF or saliva could be shown, irrespective of gender or menopausal status.

Applying a mixed linear-effect model, no influence of sex or age on the time course of neuropeptide concentrations in each of the compartments could be detected.

Correlations of OXT blood and saliva and blood and CSF levels were nearly all very weak to weak at the different timepoints. Only CSF and saliva levels of OXT showed a moderate correlation at 06:00, but very weak to weak correlations at the other timepoints (Table 3a). Correlations of AVP levels between the three compartments were all very weak to weak (Table 3b).

4. Discussion

4.1. Plasma OXT and AVP

Plasma AVP peaks during the night in healthy humans, which is supposed to be responsible for reduced nocturnal urine production (George et al., 1975; Graugaard-Jensen et al., 2014), whereas plasma concentrations of OXT did not show diurnal variations in non-pregnant women (Graugaard-Jensen et al., 2014, 2017). Our findings which show no circadian rhythmicity of blood OXT levels are in accord with the results of these studies.

Although in healthy humans, plasma AVP shows a maximum during the night, many clinical studies including our work could not show diurnal variations of AVP blood levels (Amico et al., 1985; Barreca et al., 1988; Kuboyama et al., 1988). As peripheral AVP concentrations are influenced by fluid intake, this finding in a clinical setting can at least partially be explained by the continuous application of intravenous fluids (Guelinckx et al., 2016).

4.2. CSF concentrations of OXT and AVP

CSF levels which represent central neuropeptide activity (Landgraf and Neumann, 2004) have been obtained in only four human studies that date back to the 1980´s with an overall very low number of patients. Amico and coworkers examined blood and CSF OXT levels in six patients of whom two had to be excluded. Four patients remained, one of them being male and three being obviously premenopausal female due to their age. In the samples obtained from lumbar CSF at 06:00, 12:00, 18:00 and 24:00 a significant CSF peak of OXT could be found at 12:00, but no corresponding peak in blood (Amico et al., 1983). The OXT peak in CSF at noon was confirmed by Kuboyama and coworkers in four patients (one male, three female, one of them probably premenopausal) 5–9 days after clipping of ruptured cerebral aneurysms. CSF was obtained intracranially from a drain in the basal cistern (Kuboyama et al., 1988). According to the results of these two studies, the described OXT CSF peak at noon seemed to be unaffected by intrinsic factors like patient age and sex and by extrinsic factors such as artificial light, disturbed sleep-wake-pattern and medication, for example corticosteroids, anticonvulsive agents or sedatives like benzodiazepines. A more recent study by Lefevre and coworkers examined intraoperative CSF samples from neurosurgical patients. Although their primary endpoint was not diurnal fluctuations of neuropeptide levels in the CSF, they found no influence of sampling time on CSF OXT concentrations (Lefevre et al., 2017) which supports our findings.

AVP levels examined in human CSF showed no circadian variations (Amico et al., 1985; Barreca et al., 1988).

Our patient collective is larger that of the historical studies including patients of different age and sex. As subarachnoid hemorrhage in the subacute phase is the most common diagnosis, our patient collective is comparable with that of Kuboyama and coworkers (Kuboyama et al., 1988). Furthermore, we tried to include almost equal numbers of males and pre- and postmenopausal females.

In our study we tried to achieve conditions which were as homogenous as possible in an intensive care unit setting and close to basal conditions. Patients were not exposed to acute stressful or painful stimuli as they did not receive any kind of intervention during the examination period. Hyperosmotic or hypovolemic stimuli were also avoided. We only included patients who were awake and seemed to recover well from their cerebral injury which we confirmed by a three-months follow-up where the median GOS was 4.5. Patients did not receive any sedative medication. Despite this careful patient selection, we could not reproduce the findings of Amico and Kuboyama showing an OXT CSF peak at noon. Only the group of postmenopausal women showed a hint to circadian variations in OXT CSF levels with OXT concentrations at 12:00 being significantly higher than at 18:00. This is somehow astonishing because postmenopausal women are considered to lose circadian robustness in general as they show for example more sleep abnormalities than premenopausal women (Gomez-Santos et al., 2016). On the other hand, alterations of OXT levels by the estrous cycle can be ruled out in the postmenopausal state. Given the multitude of subgroup analyses this might also be a false positive finding emerging from the multiple testing problem.

The question why historical studies showed such a marked peak in CSF oxytocin whereas our study did not, warrants further considerations: First, strict immobilization was avoided wherever possible, while critical care patients in the past were often strictly refined to bed. In detail, our patients received physiotherapy and, where possible, mobilization as maintenance of activities during daytime plays an increasing role in modern critical care medicine (Engwall et al., 2015;

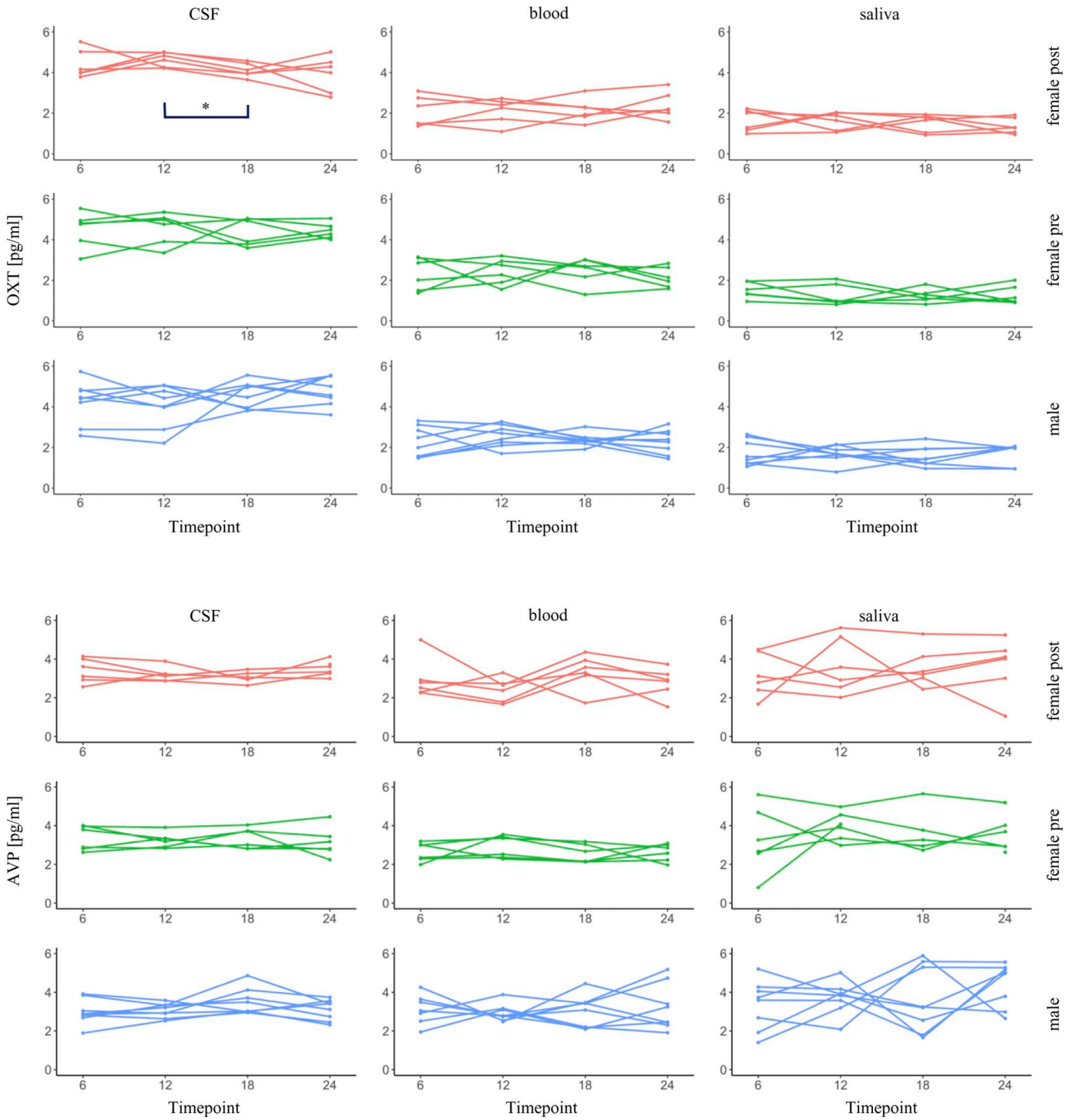

Fig. 1. Line graphs of patients representing the individual time courses of oxytocin (OXT) and arginine-vasopressin (AVP) concentrations in the three compartments CSF, blood and saliva in post- and premenopausal female as well as in male patients. Especially for OXT, it is visible that concentration levels in the three compartments differ from each other. CSF levels are higher than blood levels of OXT which is consistent with the existing literature. The only significant observation was that OXT CSF levels in postmenopausal women were higher at 12:00 than at 18:00 (*, $p = .031$).

McKenna et al., 2018). In this context, animal studies showed, that chronic restraint stress influences the OXT system by increasing the number of OXT immunoreactive cells in the hypothalamus (Li et al., 2016). Second, we maintained a day-night rhythm and emphasized on natural light sources. Third, patients did not receive any pain- or stressful interventions during the observation period. This is important, as studies in animals showed alterations of OXT levels due to handling and injections (Devarajan and Rusak, 2004; Walker et al., 2017).

Taken together, we could not confirm the findings of small historical studies in a modern critical care environment, focusing on mobilization, day-night rhythm and avoidance of interventions.

4.3. Saliva concentrations of OXT and AVP

To the present, no data on circadian variations of OXT and AVP saliva levels exist, even though it might be an alternative measurement

Table 3a
Spearman's rank correlation coefficients (rho) of OXT concentrations at the four timepoints.

Timepoint	Blood-CSF	Blood-saliva	CSF-saliva
06:00	0.330	−0.058	0.402
12:00	−0.263	−0.058	0.065
18:00	0.081	−0.070	0.068
24:00	0.198	−0.017	−0.092

Values did not show statistical significance.

Table 3b
Spearman's rank correlation coefficients (rho) of AVP concentrations at the four timepoints.

Timepoint	Blood-CSF	Blood-saliva	CSF-saliva
06:00	−0.162	−0.353	−0.168
12:00	−0.208	−0.100	−0.131
18:00	0.135	−0.091	0.120
24:00	0.204	−0.035	0.081

Values did not show statistical significance.

to analyze central neuropeptides (Carter et al., 2007). The lack of diurnal variations in saliva is concordant to our findings in blood and CSF.

4.4. Correlations of blood, CSF and saliva neuropeptide concentrations

As CSF is difficult to obtain and requires invasive procedures, many investigators use blood or other body fluids as surrogate parameters. However, correlations between blood and CSF levels of neuropeptides are assumed to be weak under basal conditions (Kagerbauer et al., 2013; Rutigliano et al., 2016). CSF levels of OXT however, seem to correlate better with saliva than with blood and therefore, saliva concentrations might be a good surrogate parameter for central OXT activity at least under certain circumstances (Martin et al., 2018). In our study, correlations of OXT and AVP levels in the three compartments blood, CSF and saliva were very weak or weak at almost every timepoint, suggesting that, under basal conditions, one cannot necessarily draw conclusions on central neuropeptide activity from peripheral concentrations. Furthermore, our study revealed one more interesting aspect: Whereas all other correlations were very weak to weak, a moderate correlation of OXT CSF and saliva concentrations could be shown at 06:00. Saliva flow is known to show circadian variations with a minimum at 06:00 and a maximum flow rate at 18:00 and therefore might be more concentrated in the morning (Dawes, 1972; Proctor, 2016). This fact suggests that the time of collection has to be considered when using saliva concentrations as surrogate parameter for central neuropeptide activity.

4.5. Strengths and limitations

Body fluids: We present to our knowledge the first study that simultaneously measured neuropeptide concentrations in three different body compartments under conditions that are close to basal in the course of a 24-hour period. Especially central and peripheral OXT release is not elucidated in this context so far. (Jurek and Neumann, 2018). Centrally released neuropeptides reach the ventricles via diffusion through the extracellular space (Landgraf and Neumann, 2004), and it might take some more time for concentration changes to be detected in the lumbar CSF, therefore, central neuropeptide levels have been shown to depend on the location of sampling (Amico et al., 1989). A great advantage of our study was the chance to collect CSF directly from the ventricles thus avoiding a time shift in concentration changes due to CSF circulation.

Method of measurement: One concern that is often raised in studies investigating neuropeptide concentrations in human body fluids is that methods of measurement are not yet standardized (McCullough et al., 2013). In the last years, a multitude of commercially available assays has been developed and, due to their easy handling, ELISA methods without extraction, that are assumed to measure unbound neuropeptide concentrations are frequently used (MacLean et al., 2019). Additionally, liquid chromatography and mass spectrometry have been shown to be appropriate at least for OXT measurement (Jurek and Neumann, 2018).

However, it still remains unclear which method is the most suitable for which purpose (MacLean et al., 2019). Different assays show divergent results that do not necessarily correlate, especially when central and peripheral neuropeptide levels are compared with each other (Lefevre et al., 2017). Therefore, it cannot be excluded that the chosen method of neuropeptide measurement influences the results of a study. However, repeated CSF sampling in humans like we did in the present study, does not allow to take amounts that are big enough to apply and compare different RIA or ELISA methods. Being restricted to one method of measurement we chose a highly sensitive RIA with extraction, as RIA was the method that was used in previous studies that we refer to (Amico et al., 1983, 1985; Barreca et al., 1988; Kuboyama et al., 1988; Amico et al., 1989). This facilitated comparability and interpretation of our results.

Patient cohort: The investigation of circadian rhythmicity requires repetitive sampling of CSF. Therefore, we had to choose patients with indwelling ventricular catheters who are hospitalized in an intensive care environment. Repetitive CSF sampling (every six hours) in healthy volunteers is not feasible in our opinion. In fact, the missing circadian rhythmicity of neuropeptides in our patient population cannot be generalized to healthy and non-hospitalized people.

We included 20 patients and provided therefore the largest sample on OXT and AVP concentrations in three different body compartments with repetitive measurements so far. In order to minimize disturbing factors that are common on an intensive care unit, we did not include patients on sedative medication or patients suffering from elevated intracranial pressure, seizures, hypothalamic damage or injury in eloquent brain regions, as these factors seem to influence cerebral neuropeptide levels (Seckl and Lightman, 1988; Sun et al., 1996; Zhou et al., 2015). These exclusion criteria decreased the number of patients observed in this study. However, the described elimination of disruptive patient-immanent factors made our neurosurgical population and consequently the results more homogenous and therefore may be transferred to other critical care patients. This is of particular interest as the central neuropeptide system might play an important role in psychological a well as functional outcome and quality of life in patients after major surgery and critical care and further studies on these patient collectives are required.

5. Conclusions

The present study did not show any circadian rhythmicity for central neuropeptides in a cohort of awake and unsedated neurocritical care patients.

Correlations between central and peripheral OXT and AVP concentrations were weak and at best moderate, a fact that confirms the finding of former studies that peripheral neuropeptide concentrations are not suitable to predict central neuropeptide levels under basal conditions.

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Author contributions

SMK: study design, data acquisition and interpretation, manuscript drafting.

JMD: data acquisition and interpretation.

JM: study design, critical feedback on the manuscript.

JG: study design, critical feedback on the manuscript.

BJ: data interpretation, critical feedback on the manuscript.

AH: data analysis, data interpretation.

AHP: study design, data acquisition and interpretation, critical feedback on the manuscript.

The final version of the manuscript has been approved by all authors.

Declaration of Competing Interest

None.

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