Copeptin (Not Only) in Water and Sodium Disorders

Jan Drugda[1], Filip Gabalec[1], Jiří Horáček[1,*]

ABSTRACT
Arginine vasopressin (AVP) is a key regulator of fluid balance and vascular tone. Its diagnostic utility in various disorders is limited by its short half-life, pulsatile secretion, and preanalytical instability. Copeptin, the C-terminal fragment of preprovasopressin, is secreted in equimolar amounts with AVP and offers a stable, easily measurable surrogate marker. This review highlights the clinical relevance of copeptin in the differential diagnosis of polyuria-polydipsia syndrome, hyponatraemia, critical illness, cardiovascular disease and diabetes mellitus. Copeptin improves diagnostic accuracy, particularly in differentiating types of diabetes insipidus and in the early exclusion of acute myocardial infarction. It also shows prognostic value in heart failure, stroke, and diabetic complications. Given its broad diagnostic potential and analytical advantages, copeptin represents a valuable biomarker for AVP-related pathologies.

KEYWORDS
Copeptin; polyuria; polydipsia; diabetes insipidus; hyponatraemia; SIADH

AUTHOR AFFILIATIONS
[1] 4th Department of Internal Medicine, University Hospital Hradec Králové, Faculty of Medicine in Hradec Králové, Charles University, Hradec Králové, Czech Republic
* Corresponding author: 4th Department of Internal Medicine, University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic; jiri.horacek@fnhk.cz

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VASOPRESSIN

Arginine vasopressin (AVP), or antidiuretic hormone (ADH), regulates fluid homeostasis and vascular tone. It is a peptide hormone produced mainly by magnocellular neurosecretory neurons of the hypothalamic supraoptic nucleus and subsequently stored in the posterior pituitary, from where it is then secreted into the circulation. It regulates osmolarity via the arginine vasopressin 2 receptor (V2) in the kidneys, promoting water reabsorption from tubular fluid (1). Part of the AVP is also directly secreted from parvocellular neurons of the paraventricular nucleus into the hypothalamic-hypophyseal portal system, stimulating the production of adrenocorticotropic hormone (ACTH) and prolactin via the arginine vasopressin 1b receptor (V1b) (2). AVP also affects vascular tone, platelet aggregation, and factor VIII release via the endothelial arginine vasopressin 1a receptor (V1a) (3) (Figure 1). Additionally, AVP participates in the regulation of inflammation and exhibits several neuro-behavioural properties that remain to be studied.

As a result of the aforementioned, AVP plays a major role in the pathophysiology of several water and sodium disorders. Therefore, measuring AVP levels in such disorders could significantly help in differential diagnosis. However, direct measurement of AVP levels is significantly limited by its short half-life of approximately 24 minutes (4), secretory pulsatility, and rapid in vitro degradation, which requires complicated preanalytical steps and makes interpretation rather difficult. Hence, there has been a search for a surrogate marker, and copeptin seems to be the most promising one.

COPEPTIN

Copeptin (or CT-proAVP) is a 39 amino acid long glycosylated fragment of preprovasopressin (5). This prohormone is synthesised in the hypothalamic nuclei, packed into neurosecretory granules, and then proteolytically cleaved to copeptin alongside AVP and neurophysin II during transport to the posterior pituitary (Figure 2). Copeptin was first described in 1972 (6), but despite 50 years of intense research, its physiological role remains unknown, although it may possibly contribute to the three-dimensional folding of AVP (7). Copeptin secretion is equimolar to AVP in response to the same stimuli (high plasma osmolarity, low blood volume, stress, angiotensin II, etc.). Furthermore, it has a longer half-life with stable plasma concentrations and slower in vitro degradation (8), making it an ideal marker for AVP release.

There are several methods for measuring copeptin, but unfortunately, not all of them yield the same results. Currently, most studies use automated immunofluorescent assay (KRYPTOR), a successor to the original sandwich immunoluminometric assay (LIA) (9). There are also various enzyme-linked immunosorbent assays (ELISAs) that, however, have shown poor diagnostic accuracy, which is why they are generally not recommended. The commonly used cut-off values for copeptin were established using LIA or KRYPTOR (from 1.0 to 13.8 pmol/l with higher median levels in men than in women) (9).

POLYURIA-POLYDIPSIA SYNDROME

The polyuria-polydipsia syndrome is a condition characterized by excessive urination (polyuria) greater than 3 litres per day, in combination with excessive water intake due to increased thirst (polydipsia). Though polyuria can be caused by several different conditions, the polyuria-polydipsia syndrome in the narrower sense includes only primary polydipsia and central and nephrogenic diabetes insipidus (10). Primary polydipsia is caused by habitual or compulsive excessive fluid intake because of

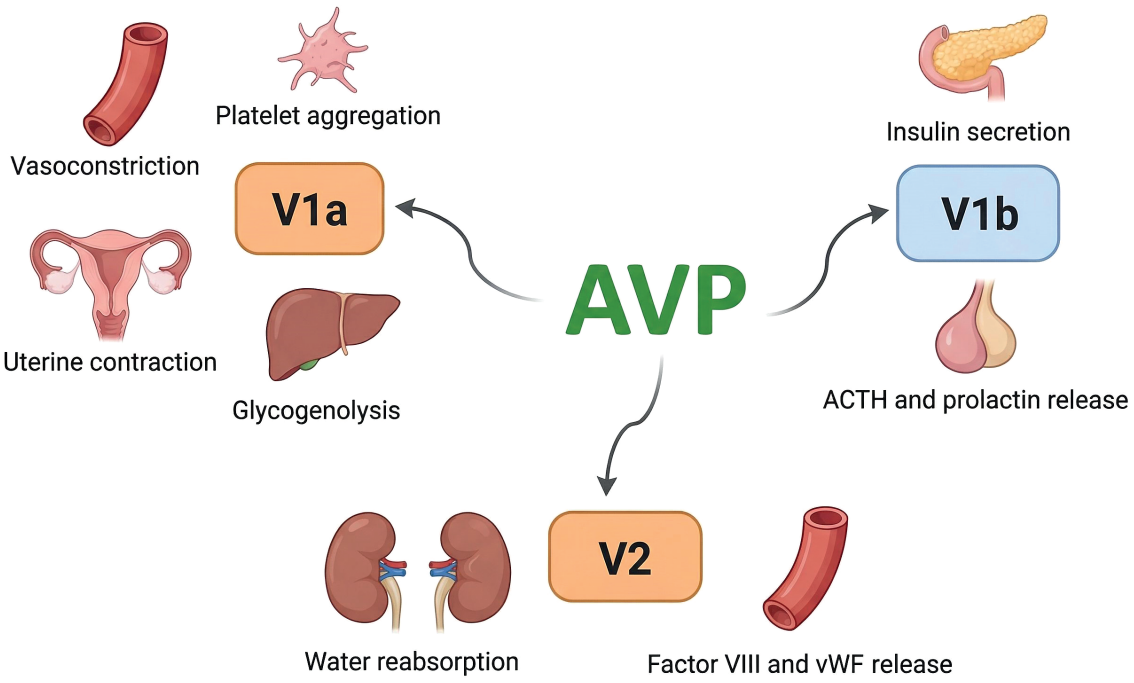

Fig. 1 Overview of AVP receptors.

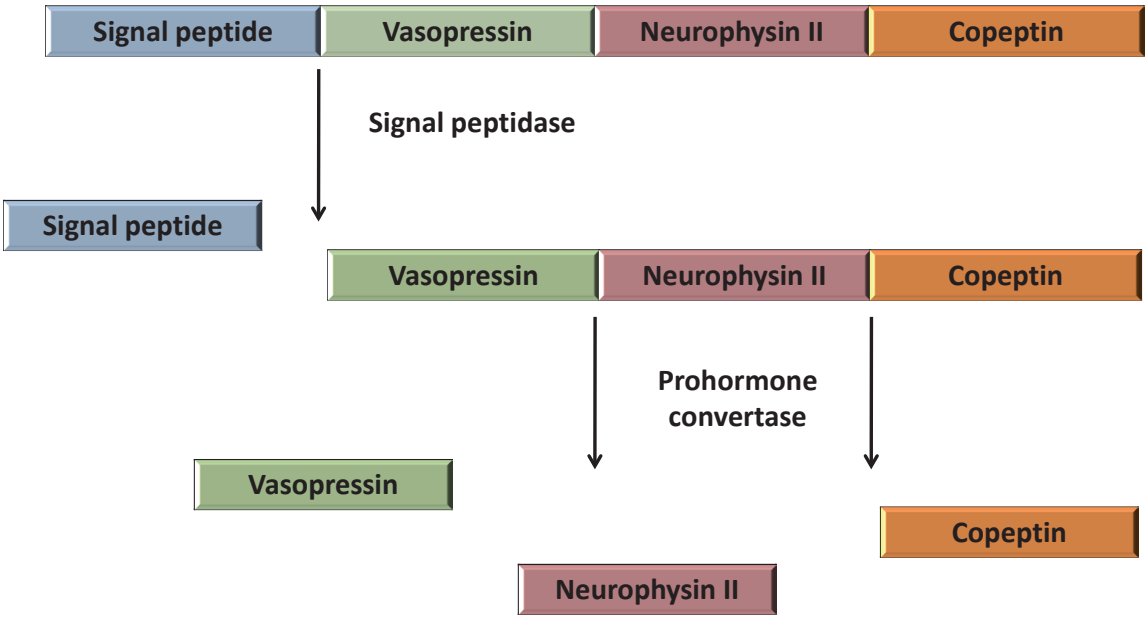

Fig. 2 Synthesis of copeptin from preprovasopressin.

a psychological disorder (psychogenic polydipsia) or due to a hypothalamic disorder affecting the centre of thirst (dipsogenic polydipsia). Central diabetes insipidus (AVP deficiency) is caused by insufficient AVP secretion in the hypothalamus or by damaged pituitary stalk, typically due to tumorous, inflammatory, or haemorrhagic conditions. Nephrogenic diabetes insipidus (resistance to AVP) is characterized by the kidneys' insensitivity to AVP, caused by metabolic issues, certain drugs, or multiple kidney disorders (11).

Correctly distinguishing between these entities is crucial because inadequate treatment could lead to further complications. However, the differential diagnosis can be quite difficult. Medical history and physical examination are helpful but usually not enough; that is why functional tests were developed. The most widely used is the water deprivation test, followed by the desmopressin test. The water deprivation test helps to distinguish between primary polydipsia and diabetes insipidus, and the desmopressin test can discriminate between central and nephrogenic

Preparation
Withhold drugs effecting urine output for at least 24 hours (diuretics, glucocorticoids, SGLT-2 inhibitors).
Patient lies in supine position. Two intravenous cannulas: one for blood sampling and the other for infusion.
Baseline serum sodium, glucose, urea, plasma osmolality and copeptin are obtained prior to infusion.
Hypertonic saline infusion phase
Bolus dose of 250 ml 3% saline is given over 15 minutes, followed by 0.15 ml/Kg/min.
Serum sodium and osmolality are measured every 30 minutes.
The infusion is stopped if the serum sodium increases to >150 mmol/L.
Stimulated plasma copeptin is measured after the infusion is stopped.
Heart rate and blood pressure are continuously monitored throughout the phase.
Hypotonic fluid administration phase
Patient is asked to drink water at 30 ml/Kg within 30 minutes.
This is followed by intravenous infusion of 5% glucose at 500 ml/hour for 1 hour.
Serum sodium is measured after the completion of 5% glucose infusion to ensure its return to normal values.
Heart rate and blood pressure are continuously monitored throughout the phase.

Fig. 3 Example of hypertonic saline test protocol (14).

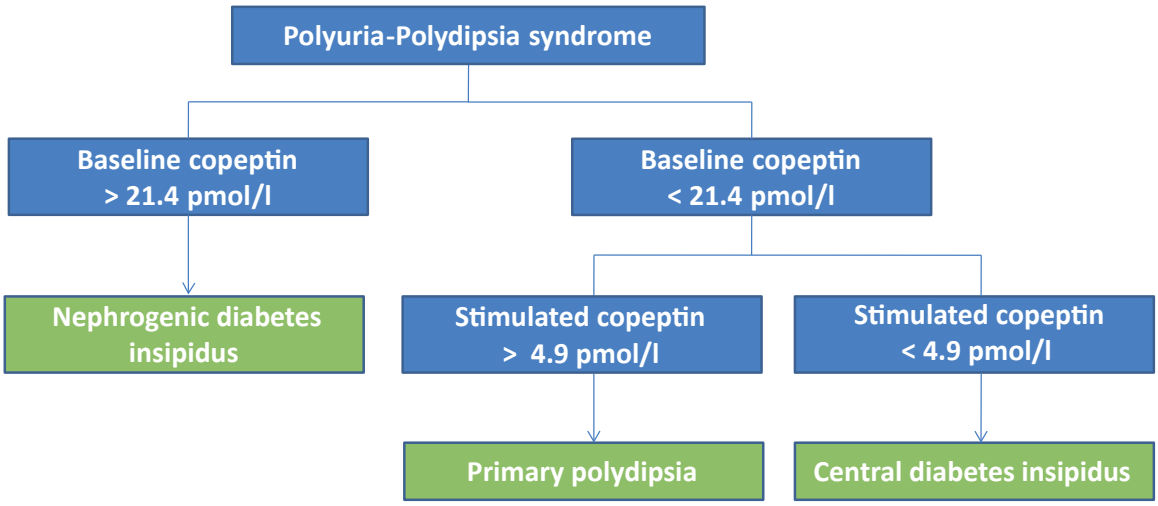

Fig. 4 Diagnostic algorithm of polyuria-polydipsia using copeptin.

diabetes insipidus. The water deprivation test has a decent sensitivity for severe central diabetes insipidus, but its sensitivity decreases in partial forms (12). On top of that, it could be stressful, uncomfortable, and potentially dangerous for the patient as it requires strict fluid restriction for up to 18 hours according to some protocols. Therefore, a search has been conducted for a surrogate test to replace water deprivation, and that is where copeptin comes into play.

Without prior testing, a baseline copeptin level greater than 21.4 pmol/L differentiates nephrogenic diabetes insipidus from other aetiologies with 100% specificity and sensitivity (13), making the desmopressin test unnecessary. Discrimination of central diabetes insipidus from primary polydipsia still requires functional testing, but the water deprivation test can be avoided using the 3% saline test. There are several protocols for the 3% saline infusion test that differ in infusion rates, frequency of monitoring, and the cut-off for infusion termination. However, the principle is still the same. After baseline blood sampling, you must create a state of hyperosmolarity and mild hypernatremia by administering a 3% saline infusion to stimulate AVP secretion (evaluated by copeptin). Frequent blood sampling is necessary to stop infusion in a timely manner to maintain safety (Figure 3). After taking the final sample, water intake is resumed, and 5% glucose is usually administered to restore normal fluid balance. Stimulated copeptin levels greater than 4.9 pmol/l can differentiate patients with central (complete or partial) diabetes insipidus from patients with primary polydipsia with 94% specificity and 94.4% sensitivity (13), exceeding the accuracy of the water deprivation test (Figure 4).

HYPONATRAEMIA

The differential diagnosis of hyponatraemia (serum sodium less than 135 mmol/l) is quite broad; however, most of the conditions causing hyponatraemia are associated with an excess of AVP. That includes mainly the syndrome of inappropriate AVP secretion (SIADH) and conditions with decreased effective circulating volume, such as severe dehydration, congestive heart failure, or liver cirrhosis (these can stimulate AVP secretion even without hyperosmolarity) (15). Thus, measuring copeptin in hyponatraemic patients seemed obvious and promising.

Copeptin shows the strongest diagnostic value in patients with hyponatraemia due to primary polydipsia, because of suppressed AVP secretion (16). Among patients with AVP-dependent hyponatraemia, those with sodium depletion show significantly higher median copeptin values than those with SIADH. However, there is a significant overlap between these two groups, making it challenging to establish reliable cut-off values. The copeptin-to-urinary sodium (copeptin / U-Na) ratio appears more promising. According to Fenske et al., a ratio of copeptin to urinary sodium (copeptin/U-Na) ratio of less than 30 pmol/mmol is superior to previously used markers (urinary sodium, serum urate level and fractional uric acid and sodium excretion) in distinguishing primary from secondary copeptin release (16, 17). Another diagnostic challenge is to distinguish SIADH from diuretic-induced hyponatraemia. In this case fractional uric acid excretion is still the most reliable option, because copeptin levels do not differ significantly between the two groups (16).

CRITICAL ILLNESS AND CARDIOVASCULAR DISEASE

Considering stress as one of the stimuli for AVP secretion, copeptin levels may serve as a decent biochemical marker of stress. There is an increasing amount of data to support the concept. According to Ristagno et al. (18), copeptin levels on admission to the ICU were significantly higher than those in the control group. Higher admission copeptin was associated with ICU death and predicted subsequent organ dysfunction (similar to free cortisol levels).

The role of copeptin in the diagnosis of acute myocardial infarction is increasing as well. Copeptin performs even better than troponin I (TnI) in ruling out myocardial infarction in patients within the first two hours after

the onset of chest pain. Additionally, the combination of copeptin and TnI improved diagnostic performance even more (19, 20).

In heart failure, higher copeptin correlates with a worse prognosis and risk of hospitalisation, so in the future it could possibly be used as a predictor of adverse outcomes and help to assess the severity of heart failure (21). According to Schill et al., copeptin can even predict the development of heart failure in older adults (22).

Copeptin is also helpful in distinguishing stroke patients from stroke-free patients in the emergency department environment. However, the levels of copeptin do not correlate with the severity of the stroke and outcome of the patient (23).

DIABETES MELLITUS

Vasopressin actively participates in glucose metabolism by promoting glycogenolysis and gluconeogenesis in the liver (via the V1a receptor) and increasing both glucagon and insulin (depending on glycemia) secretion in the pancreas (via the V1b receptor) (24). That is probably why elevated copeptin is an independent predictor of type 2 diabetes mellitus development. It may also be helpful in assessing complications of diabetes mellitus, as higher copeptin levels positively correlate with glycosylated haemoglobin, serum creatinine and the urinary albumin to creatinine ratio, and negatively with glomerular filtration rate (25). Thus, it could be used as a predictor of renal function deterioration in diabetic patients.

CONCLUSION

Copeptin has emerged as a reliable and clinically valuable surrogate marker for arginine vasopressin, overcoming the limitations of direct AVP measurement. Its diagnostic and prognostic utility spans a wide range of conditions, including water balance disorders, hyponatraemia, cardiovascular disease, and diabetes mellitus. With its stability, ease of measurement, and strong correlation with AVP secretion, copeptin offers a powerful tool for improving diagnostic accuracy and guiding patient management in both acute and chronic settings. Considering the current knowledge and ongoing research, the use of copeptin in clinical practice is expected to continue expanding.

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