COPEPTIN: STRUCTURE, FUNCTION AND CLINICAL SIGNIFICANCE IN FEBRILE CONVULSION

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Article History: **Received:** 16.05.2023 **Revised:** 04.06.2023 **Accepted:** 28.06.2023

Abstract:
Copeptin, a C-terminal part of the precursor pre-provasopressin is a novel biomarker of arginine-vasopressin (AVP) system. Measurements of AVP concentration are not used in clinical practice because of technical difficulties. Copeptin is synthesized in stoichiometric ratio with AVP, hence it reflects vasopressin concentration in human plasma and serum. This review outlines current research concerning the role of copeptin as a prognostic marker in different diseases and its potential clinical value.

Keywords: Copeptin, AVP, febrile convulsion.

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DOI: 10.53555/ecb/2023.12.1085

Introduction:

Copeptin (COP) the C-terminal fragment of provassopressin was reported to have prognostic value in various diseases including acute coronary syndromes cerebral hemorrhage congestive heart failure , pulmonary diseases or sepsis Moreover, COP was suggested to improve early diagnosis and prognosis assessment of patients with suspected acute coronary syndrome.**(1)**

Copeptin is a glycosylated, 39-amino-acid long polypeptide with a weight of 5kDa molecular which had leucine-rich core segment **(2)**

Copeptin structure And release:

Arginine vasopressin is produced as a larger precursor pre- pro arginine vasopressin by magnocellular and parvocellular neurons within the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. Pre-proAVP is produced by magnocellular neurons of the PVN and SON, is packaged into neurosecretory granules, and is transported axonally to the posterior pituitary, also called the neurohypophysis, enroute, pre-proAVP is enzymatically processed into four peptides: the N-terminal signal peptide, the active hormone AVP, neurophysin 2, and the C-terminal copeptin, upon activation with various stimuli, the stored peptides AVP, neurophysin 2, and copeptin are secreted into the circulatory system in equimolar amounts, the pre- proAVP produced in parvocellular neurons in the PVN is transported by axons projecting to the median eminence where it is processed and secreted into the hypothalamic-hypophysial portal vessels and ultimately reaches its destination, the anterior pituitary,a third portion is produced by parvocellular neurons of the PVN, the medial amygdala, the bed nucleus of the stria terminalis, and the suprachiasmatic nucleus, with projections toward distinct brain regions **(3)**

Together, there are at least three distinct pathways by which AVP exerts its functions, first, AVP regulates water absorption via the posterior pituitary, second, AVP is critically involved in the hypothalamic-pituitary- adrenal (HPA) stress axis via the posterior pituitary third, AVP remaining in the CNS contributes to behavior and cognitive function **(4)**

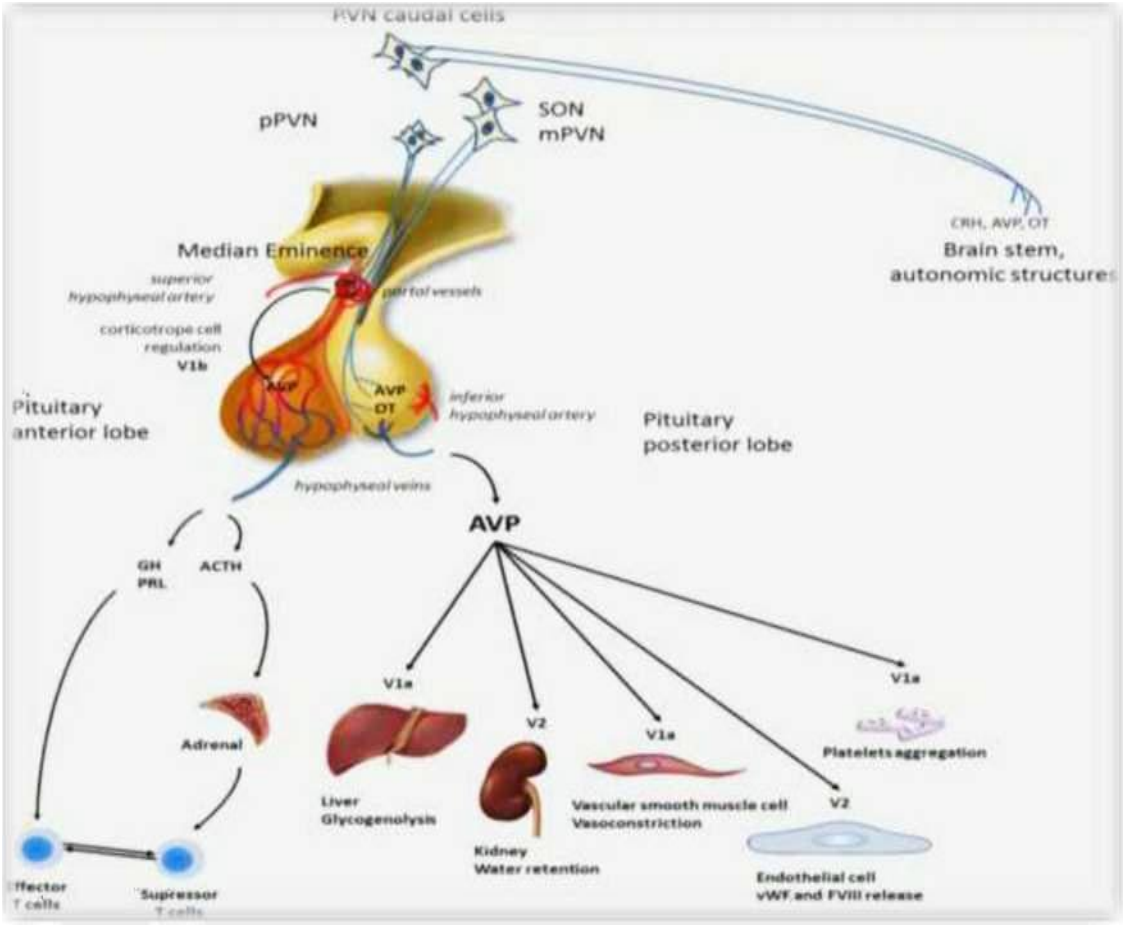

Fig (1): Schematic representation of the role of arginine vasopressin(AVP) ***(4)***

Function of vasopressin and copeptin:

The main physiological functions of AVP are the homeostasis of fluid balance and the regulation of vascular tone and the endocrine stress response,

the receptors for AVP have been divided into three major types, V1a, V1b (or V3), and V2, according to their pharmacological and G-protein-coupled properties. AVP released into the circulatory system functions as a peripheral hormone by binding to its receptors located at the plasma membrane of various target cells, the V1a receptor is predominantly found in vascular smooth muscle and is involved in the control of vasoconstrictor effects and blood pressure regulation, V1b receptors are primarily located on specialized cells, called corticotrophs, in the anterior pituitary gland, where they stimulate the release of adrenocorticotropic hormone (ACTH) synergistically with corticotropinreleasing hormone (CRH), the V2 receptor expressed on kidney cells is responsible for water reabsorption in the collecting ducts by activating aquaporin-2 channels, whereas its expression on endothelial cells of the vasculature and platelets makes AVP an important hormone in hemostasis, V1a and V1b receptors are found in the brain. Finally, AVP binds to the oxytocin receptor, which further increases its complexity

Much less is known about the physiological functions of copeptin than about those of AVP, the role for copeptin as a prolactin-releasing factor has been proposed but not confirmed,Copeptin could be a chaperone- like molecule that is involved in the folding of the AVP precursor, copeptin is reported to interact with the calnexin-calreticulin system, which prevents the export of misfolded, glucose-tagged proteins from the endoplasmic reticulum, folding of the monomeric AVP precursor is inefficient in the absence of copeptin, which could contribute to the pathogenesis of some forms of central diabetes insipidus

It has been demonstrated that copeptin levels correlate well with vasopressin levels during physiological changes in plasma osmolality, from water excess to dehydration, and also in pathologic states **(5)**

Copeptin gene and expression:

The gene that controls copeptin secretion is located on the 20th chromosome p13 loculus,after its transcription, the copeptin will be derived from the third exon of the three exons encoding mRNA together with the last 17 amino acids of the C-terminus of neurophysin-II (NP-II), the other two exons will be translated into the signal peptide, AVP and the rest of NP-II, following the translation of preprovasopressin mRNA 168 amino acid long preprovasopressin, which is a major pre-peptide, will be produced, this 168 amino acids peptide will be segmented into 23 amino acid signal peptide, 9 amino acid AVP, 93 amino acid disulfide rich or cysteine rich NP-II and 39 amino acid copeptin, the process of preprovasopressin segmentation is a result of a cascade of four hydrolytic enzymatic reactions mediated by endopeptidase exopeptidase, monooxygenase and lyase respectively during its axonal transport , AVP is derived from preprovasopressin along with NP-II and copeptin **(6)**

Copeptin as asurrogate marker for AVP:

The measurement of AVP is complex due to several pre-analytical obstacles; thus, the detection of AVP is unsuited for clinical diagnostics and is limited to a few specialized laboratories ,For example, 90% of AVP in the circulatory system is bound to platelets,which falsifies the actual amounts of circulating AVP, AVP is a bioactive peptide hormone that is tightly regulated and rapidly cleared from the circulation, with an in vivo half-life of less than 30 min and to make matters worse, AVP is unstable in isolated plasma, even when stored at -20°C, In contrast, copeptin does not have such limitations, Several copeptin assays are currently available, but the only assays with sufficient technical descriptions and clinical data to justify their routine clinical use are the original sandwich immu-noluminometric assay, and its automated immunofluorescent successor (on the KRYPTOR platform), In conclusion, the great advantages of copeptin measurement are the remarkably high sensitivity of this robust AVP surrogate marker, its extreme stability once collected in blood sampling tubes, and the fact that only 50 gl of serum or plasma are needed for the assay**.(7)**

Copeptin and correlation with medical diseases:

Copeptin and kidney diseases:

In Autosomal dominant polycystic kidney disease (ADPKD), rise in vasopressin (and copeptin) stimulates the formation of cAMP (3‘,5‘- cyclic AMP), which promotes cell proliferation and cyst growth leading to kidney enlargement and a subsequent decline in kidney function.**(8)**

Increased levels of copeptin independently predict decline in eGFR, and suggest that copeptin can be used to identify individuals at higher risk for development of chronic kidney disease. Why increased copeptin was associated with GFR and with CKD? The exact mechanisms regarding the relationship between copeptin, albuminuria and GFR are not known but two mechanisms were suggested, first , as copeptin is cleared by kidney excretion, copeptin levels would tend to increase

as kidney function decreases, second, in patients with lower kidney function, more copeptin is released, because the AVP system is activated due impaired urine concentrating capacity to maintain water homeostasis, however, these ideas were challenged as it was shown that copeptin was not associated with GFR in healthy living kidney donors and copeptin levels did not change after donation despite a significant drop in kidney function after nephrectomy, these data suggest that GFR alone is not a principal determinant of copeptin. Indeed, longitudinal studies in humans have shown that plasma copeptin levels increase before eGFR decreases.In most studies copeptin was positively associated with urinary albumin/protein excretion, population-based studies have shown copeptin to be strongly associated with microalbuminuria**(9)**

Copeptin and sepsis:

Copeptin level was found to be elevated in sepsis in many previous studies , other studies found that plasma copeptin was significantly higher in patients who died from sepsis than that in patients who survived.**(10)**

copeptin was a sensitive predictor of mortality in patients with sepsis and its level increased with disease severity,In addition, it could be a promising predictor of MOF (multible organ failure) development**(11)**

Copeptin and cardiac diseases: Heart failure:

Heart failure affects the atrial tension and increases the level of arginine vasopressin (AVP). Heart failure can also activate the renin angiotensin aldosterone system (RAAS), the sympathetic nervous system, and the AVP system As a result, the serum level of AVP play an important role in congestive heart failure assessment, However, the properties of AVP limit its further application in the clinic, the half-life of AVP is short in serum and it is difficult to detect the AVP concentrations in vitro is a homologous peptide to AVP and It is more stable and easier to detect in serum **(12)**

During CHF, the level of copeptin also increases and is positively correlated with the AVP level**,** therefore the serum copeptin level is becoming more and more popular for CHF prediction, other study also found that there was a significant positive correlation between increased an copeptin level and the risk of mortality from HF **(13)**

Other study indicate that the level of plasma copeptin increases with the exacerbation of HFrEF (heart failure with reduce ejection fraction) in patients, copeptin is involved in the whole process of progression in HFrEF Patients, as a result, the copeptin value might be applicable to predict and assess HFrEF in the clinic **(14)**

Copeptin and diabetes inspidius:

Recent studies in adults have shown greater sensitivity and specificity of copeptin versus AVP to discriminate etiologies of polyuriapolydipsia syndrome, reported that determination of copeptin was helpful and efficient for differential diagnosis of diabetes insipidus Other studies showed that, without prior thirsting, a single baseline copeptin level greater than 21.4 pmol/L differentiated nephrogenic DI from other etiologies with 100% sensitivity and specificity, making WDT (water debrivation test) unnecessary in those cases **(15)**

To our knowledge, none of the previous pediatric studies worked on copeptin as a diagnostic tool in polyuria-polydipsia syndrome, nevertheless, this new surrogate biomarker of vasopres- sin secretion offers four major advantages for a quick etiological diagnosis of polyuria-polydipsia syndrome, unlike AVP, copeptin is much more stable in vitro (1 week at room temperature) ***)*** In our clinical chemistry laboratory, the copeptin-automated assay is also well suited for infants or children's samples because only 50 mL of plasma is required, moreover, results can be returned rapidly (< 1 h), finally, compared to the WDT, simple copeptin assessment does not threaten the hemodynamic status of children, moreover, its cost is reduced compared to the full-day hospitalization required for WDT, Thus, in pediatrics, copeptin is a promising biomarker to discriminate nephrogenic diabetes insipidus from central diabetes insipidus and primary polydipsia, further application needs future investigation in order to establish the pediatric normal range considering age, gender, body mass index, and Tanner stages **(16)**

Copeptin and diabetes mellitus:

It has been known since 1979 that individuals with diabetes have elevated vasopressin levels ,however, the exact causes of this elevation are not yet known, recently it was discovered that diabetic rats, in contrast to control rats, have increased hypothalamic vasopressin synthesis due to upregulated chloride transporters and an excitatory response evoked by the neurotransmitter GABA, these findings thus reveal a potential mechanistic explanation for elevated vasopressin concentration in diabetes **(17)**

Others previously showed that elevated fasting plasma concentration of vasopressin, measured as copeptin, strongly and independently predicts new

onset type 2 diabetes and is associated with all components of the metabolic syndrome (i.e., abdominal obesity, insulin resistance, hypertension, chronic inflammation and microalbuminuria) Furthermore, a human Mendelian randomization study suggested causality between elevated vasopressin concentration and elevatedplasma glucose concentration **(17)**

Copeptin and traumatic brain injury:

A strong correlation between copeptin plasma concentration and unfavorable outcome was found in traumatic parenchymal cerebral hemorrhage Moreover, in patients with severe head injury plasma copeptin concentration has been shown to be significantly correlated with the severity of trauma, the initial GCS and the mortality, these results confirmed that copeptin is a predictor of unfavorable outcome in patients with severe head trauma and could be used as a prognostic biomarker Similar results have been obtained in a study involving a pediatric population **(18)**

Copeptin and ischemic strok:

There is a correlation between serum copeptin and stroke severity, was postulated that early measurement of plasma copeptin could provide better prognostic information for patients with acute stroke and help in decision making for therapeutic interventions Additionally, was stated that copeptin represents a novel, reliable, and promising blood marker to predict stroke after transient ischemic attack (TIA), adding prognostic information **(19)**

Other study showed that serum copeptin had a significantly statistical correlation with the size of cerebral infarction, This with cerebral infarction in whom MRI was available, copeptin levels paralleled lesion size, median copeptin levels in patients with a small lesion were about half the levels in patients with medium lesions ,whereas levels were greatest in patients witha large lesion**(20)**

Correlation between copeptin and febrile convulsion:

who reported that circulating copeptin was significantly higher in children with FS compared to febrile controls and in a multivariable regression model, seizures were the major determinant of serum copeptin independently of clinical and baseline laboratory indices with no differences between febrile and epileptic seizures Other study reported that decrease discriminative ability of copeptin for prediction of complex FS could be attributed to the rapid decline of plasma levels of vasopressin due to depletion of its stores**(21)**

Febrile convulsion are associated with significantly altered immune and neuroendocrinal responses to infection, extent of induced alterations correlates with severity of infection, elevated serum levels of copeptin could discriminate febrile children susceptible to develop seizure, but can not.

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