Neuroendocrinology Letters Volume 40 No. 4 2019
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

REVIEW ARTICLE

Copeptin – a new diagnostic and prognostic biomarker in neurological and cardiovascular diseases

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Submitted: 2019-10-22 Accepted: 2019-11-10 Published online: 2019-12-12

Key words: **Copeptin; neurological; cardiovascular diseases – clinical significance**

Neuroendocrinol Lett 2019; **40**(5):207–214 **PMID:** 32112544 NEL400519R03

Abstract

Copeptin, arginine vasopressin (AVP)-associated 39 aminoacid glycopeptide, is a C-terminal part of pro-AVP. AVP acts through V1a, V1b, and V2 receptors. The effect on V1a receptors is connected with arterial vasoconstriction, on V2 with antidiuretic action, and on V1b with the secretion of ACTH, insulin, glucagon. Copeptin is found in the circulation in equimolar amounts with AVP. It is a very stable peptide and easy to estimate. Copeptin is a good diagnostic marker in many disorders in which vasopressinergic dysfunction plays a role in pathogenesis such as a polyuria-polydipsia syndrome, neurological disease (ischemic stroke, nontraumatic, intracerebral hemorrhage, aneurysmal subarachnoid hemorrhage and neurodegenerative disease (multiple sclerosis). Copeptin is a diagnostic and prognostic marker in cardiovascular diseases like heart failure (HF) and acute myocardial infarct (AMI). Copeptin is a sensitive diagnostic marker in the early stage of AMI especially in patients with non-ST segment elevation and post AMI complications. Copeptin is also an important diagnostic and prognostic marker in metabolic diseases (diabetes mellitus, metabolic syndrome, insulin resistance), connected with some neurological and cardiovascular diseases. In the future, these findings may have also therapeutic applications in conditions where the AVP receptor antagonist therapy is appropriate.

INTRODUCTION
COPEPTIN – STRUCTURE, SECRETION, DETERMINATION

Copeptin, arginine vasopressin (AVP)-associated 39-aminoacid glycopeptide, was described for the first time in 1972 by Holwerda (Holwerda 1972).

It is derived from 164-aminoacid precursor (pro-AVP), which besides copeptin also contains a signal peptide, AVP and neurophysin II. Copeptin is the C-terminal part of pro-AVP (Land *et al.* 1982). Pro-AVP is produced in the neurons of the supraoptic and paraventricular hypothalamic nuclei (Morgenthaler 2010). AVP, neurophysin, and copeptin are processed from the precursor peptide during axonal transport to the posterior part of pituitary.

It is worth to notice that pro-AVP is also synthesized in the parvocellular neurons where Corticotrophin Releasing Hormone (CRH) is produced and that fact may suggest possible cooperation between these two factors. CRH is released into

the pituitary portal system at the eminentia mediana and it stimulates ACTH production and secretion from adrenotropes (Morgenthaler 2010).

AVP acts through three known receptors: V1a, V2, V1b (Dobsa *et al.* 2013). V1a receptors are expressed in the cardiovascular system. The effect of AVP on V1a receptors produces strong arteriolar vasoconstriction. V1a receptors were found also in cardiac myocytes.

V2 receptors are found in the renal collecting ducts. Stimulation of V2 receptors causes antidiuretic effects.

The V1b receptors are expressed in the pituitary gland, liver, and pancreas. The effect of activation of V1b receptors in the adenohypophyseal part of the pituitary and the pancreatic islet cells is connected with an increase in the secretion of ACTH, insulin and glucagon (Morgenthaler 2013).

Copeptin is found in the circulation in equimolar amounts with AVP (Balanescu *et al.* 2011). Furthermore, a positive correlation between the release of AVP and copeptin was observed.

Of note, measurement of AVP concentration remains complicated due to the fact that AVP is unstable peptide and additionally it is bound by platelets. Contrary, copeptin as a very stable peptide is easy to measure (Dobsa *et al.* 2013).

Under physiological conditions, copeptin release responds to the hemodynamic and osmotic stimulus (Morgenthaler *et al.* 2008). In turn, water deprivation and hypertonic saline infusion lead to increase of serum copeptin concentrations (Morgenthaler *et al.* 2008). Conversely, injection of hypotonic saline causes a decrease of copeptin levels (Szinnai *et al.* 2007).

According to data from the literature, the measurement of copeptin in sera might serve as a useful tool in assessing the risk of complications as well as outcome in several diseases, where vasopressinergic disturbances may play a role in the pathogenesis (Morgenthaler *et al.* 2008, Morgenthaler 2010). Herein, we present the current knowledge concerning the consequences of fluctuating concentrations of copeptin in serum or plasma in the course of selected diseases.

NEUROLOGICAL DISORDERS

It has been shown that in the acute stages of intracerebral hemorrhage and ischemic stroke an activation of the hypothalamo-pituitary axis was observed. As arginine vasopressin has a synergistic effect with Corticotrophin Releasing Hormone (CRH) on the anterior pituitary ACTH secretion, it could at least partially stimulate the adrenal cortex to release of cortisol (Zhang *et al.* 2012). Furthermore, acute injury of the central nervous system leads also to disturbances in balance between the nervous system-immunological system and hormonal regulation (Woiciechowsky *et al.* 1998, Meisel *et al.* 2005, Chamorro *et al.* 2007).

It has been reported that in patients with ischemic stroke, aneurysmal subarachnoid hemorrhage and head injury plasma copeptin levels are increased (Katan *et al.* 2009, Zhu *et al.* 2011, Zhang *et al.* 2012). High concentrations of copeptin are associated with mortality rate and poor neurological outcome and early neurological deterioration (Katan *et al.* 2009, Zhang *et al.* 2012).

Ischemic stroke

An increase of copeptin was observed in patients with ischemic stroke and it was correlated with the severity of stroke defined by the NIHSS Score (National Institutes of Health Stroke Scale) (Katan *et al.* 2009).

It has been known that the brain edema after stroke leads to death. Increased activity of vasopressin (AVP) has an important role in the formation of brain edema (Zweifel *et al.* 2010, Zhang *et al.* 2012). Indeed, the involvement of AVP in the brain edema formation after ischemic stroke was documented in *in vitro* and *in vivo* experiments (Del Bigio *et al.* 1990, Vajda *et al.* 2001). It has been suggested that elevated secretion of cortisol and AVP after stroke episode causes water permeability in capillaries and glial cells and lead to edema of the brain (Chang *et al.* 2006). Moreover, some data exist that therapy with blockers of AVP receptors reduces brain edema. (Chang *et al.* 2006, Dobsa *et al.* 2013, Yu *et al.* 2012, Zweifel *et al.* 2010, Zhang *et al.* 2012). Therefore, measurement of copeptin may have prognostic significance indicating the possibility of brain edema after the stroke (Ameli *et al.* 2014).

According to the results of observational studies, higher copeptin levels are useful markers, which may predict mortality 1 year after the stroke (Urwyler *et al.* 2010). Sun *et al.* demonstrated that elevated copeptin concentrations were positively associated with mortality in ischemic stroke and contrary associated with hemorrhagic stroke (Sun *et al.* 2018).

Infections, especially bacterial pneumonia are also connected with increased death rate after the stroke. It has been known that both AVP and copeptin activate the CRH-ACTH-cortisol axis and the disturbed immunological-hormonal (mainly hypothalamo-pituitary) balance may lead to infections after stroke (Meisel *et al.* 2012, Chamorro *et al.* 2007, Meisel *et al.* 2005). Chamorro (Chamorro *et al.* 2007) demonstrated that infections observed early after acute ischemic stroke are connected with activation of the sympathetic adrenomedullar axis and with increase of catecholamines release (Chamorro *et al.* 2007). Activation of the sympathetic nervous system and stimulation of hypothalamo-pituitary adrenal regulation may lead to immune depression (Meisel *et al.* 2005, Chamorro *et al.* 2007).

Estimation of serum copeptin with a combination of CRP, WBC, and procalcitonin (PCT) during the stroke episode may have a prognostic significance (Fluri *et al.* 2012).

Nontraumatic intracerebral hemorrhage

Stroke in 87% is primarily diagnosed as an ischemic origin and in 13% as a hemorrhagic stroke (ICH)

including intracerebral subarachnoid hemorrhage (SAH).

It has been observed that elevation of copeptin in plasma positively correlates with hematoma volume and the Glasgow Coma Scale (GCS) as well as predicted 1-year mortality and other neurological disturbances (Senn *et al.* 2014). Plasma copeptin is believed to be a new prognostic marker of ICH (Zhang *et al.* 2012).

Traumatic brain injury

An increase of plasma copeptin was found in hemorrhagical stroke and also predicted 1-year mortality in brain trauma patients.

Copeptin has prognostic value in patients with traumatic brain injury and nontraumatic intracerebral hemorrhage (Yu *et al.* 2012).

Aneurysmal subarachnoid hemorrhage (SAH)

Increased plasma copeptin levels as a marker of stress response were significantly associated with the severity of SAH in the WFNS Scale (World Federation of Neurological Surgeons).

Higher copeptin levels were correlated with unfavorable clinical outcome and mortality (Fung *et al.* 2013).

Copeptin may serve as a useful marker for severity and prognosis in patients with subarachnoid hemorrhage (Jabbarli *et al.* 2018). It has been also suggested that copeptin is a new, better prognostic marker than other biomarkers in prediction of long-term clinical outcomes in patients with intracerebral hemorrhage (Yu *et al.* 2014). Furthermore,

copeptin has predictive value for early death in elderly patients with acute massive cerebral infarction (Li *et al.* 2012). Interestingly, Mindt at al. for first time measured copeptin in cerebrospinal fluid (CSF) in patients with subarachnoid hemorrhage (Mindt *et al.* 2019).

AVP and inflammation have been suggested to play a role in the etiology of cerebral vasospasm after subarachnoid hemorrhage (Trandafir *et al.* 2004). Thus, copeptin might be a marker of cerebral vasospasm and delayed ischemic neurologic deficit after aneurysmal subarachnoid hemorrhage (Fernandez *et al.* 2004).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammation, demyelination and axonal injury (Kamm *et al.* 2014). It has been speculated that copeptin might be a prognostic factor and a marker of inflammation, as well as an outcome indicator in diseases of the central nervous system (Dobsa *et al.* 2013). Previous reports revealed that the activity of vasopressin and hypothalamo-pituitary-adrenal (HPA) axis is increased in MS (Kumpfel *et al.* 2014).

On the other hand, obesity may increase the risk of developing MS (Wesnes *et al.* 2015).

Copeptin is associated with inflammation and obesity. Previously, we reported an elevation of plasma copeptin and cortisol in newly diagnosed, naïve to treatment MS patients (Baranowska-Bik *et al.* 2015). Alterations of copeptin and cortisol in MS may be connected with obesity (Baranowska-Bik *et al.* 2015).

CARDIOVASCULAR DISEASES

Heart failure

It has commonly known that reduced cardiac output in heart failure activates the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system and the AVP system. In chronic heart failure secretion of AVP is increased and associated with left ventricular dysfunction (Alehagen *et al.* 2011, Xu *et al.* 2018). Hyponatremia occurring in a course of heart failure may additionally stimulate the release of AVP and angiotensin II. From a clinical perspective, it has been revealed that vasopressin levels are increased in patients with chronic heart failure. In patients with congestive heart failure and after myocardial infarction the AVP system is also strongly activated. In details, endogenous stress during myocardial infarction (AMI) activates the AVP system and copeptin independent of necrosis of cardiac cells (Dobsa *et al.* 2013, Meune *et al.* 2011). This phenomenon has unfavorable consequences. Activation of V1a receptors that mediate vasoconstrictive properties and V2 receptors that mediate antidiuretic effects may lead to water retention and hyponatremia (Xu *et al.* 2018). Furthermore, stimulation of V1a and V2 receptors causes ventricular hypertrophy and myocardial remodeling (Goldsmith 2002). Finally, AVP through V1a receptors induces an increase of protein synthesis in myocytes, causes myocardial hypertrophy and decreases heart contractility in the mechanism of myocardial fibrosis as the result of cardiac fibroblasts stimulation (Fan *et al.* 2007, Fukuzawa *et al.* 1999, Dobsa *et al.* 2013). Therefore, evaluation of copeptin concentration together with β natriuretic peptide (e.g. NT pro BNP) may be a good diagnostic and prognostic method in patients with heart failure (HF) (Stoiser *et al.* 2006) especially when taking into account that copeptin levels may predict long-term clinical outcomes in patients with HF (Yoshikawa *et al.* 2018).

The measurement of plasma copeptin has not only prognostic significance but is useful in the establishment of indications to AVP receptor antagonist therapy (Griebel *et al.* 2003).

Copeptin has and prognostic value in other cardiovascular diseases (hypertension, acute coronary syndrome, stable coronary artery disease, congestive heart failure (Stoiser *et al.* 2006, Parizadeh *et al.* 2018, Sinning *et al.* 2014). In the older patients with heart failure elevated plasma copeptin and N-terminal pro BNP are associated with risk of cardiovascular death (Alehagen *et al.* 2011).

Acute myocardial infarct (AMI)

During acute myocardial infarct (AMI) endogenous stress activates the AVP system independently of cardiac cells necrosis (Meune *et al.* 2011) and leads to an increase of vasopressin and copeptin secretion (Lippi *et al.* 2012).

In the early stage of AMI (3-4 hrs. after the onset of chest pain), copeptin levels are increased, while troponin concentration is still within the normal range (Lotze et al 2011). Therefore, copeptin is a more sensitive marker in early diagnosis of AMI than serum troponin T (cTnT) (Khan *et al.* 2007, Keller *et al.* 2010, Dobsa *et al.* 2013, Abd El Baky Mahmoud *et al.* 2018). Normal values of copeptin in patients with chest pain may rule out of AMI (Reichlin *et al.* 2009, Mueller *et al.* 2018, Morawiec *et al.* 2018). Detection of copeptin is also important in patients with suspected AMI with non-ST segment elevation (Narayan *et al.* 2011, Giannitsis *et al.* 2011, Charpentier *et al.* 2012, O'Malley *et al.* 2014, Shin *et al.* 2018, Kip *et al.* 2018). Thus, combined measurement of copeptin and high – sensitivity Troponin T (cTnT) could be a sensitive test for fast and accurate AMI diagnosis (Ray *et al.* 2012, Raskovalova et al 2014, Lipinski *et al.* 2014, Mueller *et al.* 2018, Morawiec *et al.* 2018, Timoteo 2019). However, it has been reported that the ratio of copeptin/troponin was not associated with the area at risk final infarct size (Arnadottir *et al.* 2018).

Additionally, the elevation of copeptin may be a sensitive prognostic marker for cardiovascular events in patients with chronic coronary disease (Sabatine *et al.* 2012).

Assessment of copeptin may also be useful in the procedures of invasive cardiology as it has been suggested that higher copeptin may predict clinical outcomes after successful percutaneous coronary intervention in patients with AMI (Choi *et al.* 2018).

Moreover, copeptin evaluation could possibly serve as a marker of post-AMI complications.

Activation of V1a receptors by the AVP system after AMI may affect peripheral vasoconstriction and myocardial fibrosis (Fukuzawa *et al.* 1999, Goldsmith 1987, Fan *et al.* 2007).

Elevation of copeptin release is strongly associated with left ventricular dysfunction and remodeling during clinical heart failure after AMI (Kelly *et al.* 2008). Indeed, copeptin inversely correlated with left ventricular (LV) ejection fraction (LVEF) and was associated with volumes of ventricular remodeling and clinical heart failure after AMI. (Xu *et al.* 2018). Determination of copeptin and NT pro-BNP might be very useful in the assessment of heart failure with reduced left ventricular ejection fraction (Xu *et al.* 2018). Moreover, combined measurement of copeptin and NT-pro BNP concentrations were markers assessing the risk of cardiovascular death in older patients with HF (Alehagen *et al.* 2011). In addition, copeptin and high sensitivity troponin measured together may play a role in predicting outcome in patients with stable chronic heart failure (Tentzeris *et al.* 2011). It has been revealed recently that copeptin is an important marker among some novel biomarkers for diagnosis and prognosis of heart failure (Huang *et al.* 2018).

These data may lead to therapeutic procedures in post-AMI LV dysfunction (Kelly *et al.* 2008, Lauridsen *et al.* 2018). The selective V2 receptor antagonists "vaptans" vere administered with good results (Kelly *et al.* 2008).

Furthermore, copeptin could also serve as a good prognostic indicator of mortality in patients with heart failure after AMI as it is believed to have a prognostic value to predict 1-year mortality after myocardial infarction (Lattuca *et al.* 2019).

OTHER CARDIOVASCULAR EVENTS

Elevation of copeptin was observed in patients with acute aortic syndrome (Morello *et al.* 2018) as well as in degenerative aortic stenosis (Mizia-Stec *et al.* 2013). Determination of copeptin could be important in the evaluation of hemodynamic improvement achieved by the percutaneous balloon mitral valvuloplasty (PBMV) (Gunebakmaz *et al.* 2011).

The results of copeptin measurement may suggest that cardioversion of atrial fibrillation with or without high-flow oxygen supplement was not associated with myocardial injury (Lauridsen *et al.* 2018).

Furthermore, it has been observed that concentration of copeptin and brain natriuretic peptide (BNP) increases with the decline of glomerular fraction rate (GFR). On the other hand, cardiovascular disease (CVD) may lead to the death of patients with end-stage renal disease. Copeptin and BNP may be sensitive markers in the diagnosis of cardiovascular disease in patients with chronic kidney disease (Li *et al.* 2013). Bosselman *et al.* (Bosselman *et al.* 2013) suggested that new cardiovascular biomarkers are associated with renal function in heart failure. It has been shown that metabolic disturbances (diabetes, obesity and metabolic syndrome) play an important role in the pathogenesis of many neurological and cardiovascular diseases.

DIABETES MELLITUS, OBESITY AND METABOLIC SYNDROME

Vasopressin (AVP) may affect glucose metabolism. It mediates gluconeogenesis and glycogenolysis through vasopressin 1a receptors in the liver and stimulates glucagon or insulin through 1b receptors in the pancreas (Enhorning *et al.* 2010, Dobsa *et al.* 2013).

In patients with diabetes, higher copeptin levels are associated with albuminuria, and a decline of renal function (Villela-Torres *et al.* 2018) that is indicated by a decrease of eGFR (Boertien *et al.* 2013, Enhorning *et al.* 2013).

Copeptin is also a new marker of obesity, metabolic syndrome and insulin resistance (Saleem *et al.* 2009, Lundegaard *et al.* 2018, Jensen *et al.* 2019, Velho *et al.* 2018).

Furthermore, copeptin may also serve as predictor factor of abdominal obesity, diabetes mellitus and microalbuminuria (Enhorning *et al.* 2010, Enhorning *et al.* 2013).

OTHER DISEASES PULMONARY ARTERIAL HYPERTENSION (PAH)

In pulmonary hypertension activation of the AVP system lead to a negative inotropic effect on the right ventricle, ventricular remodeling and increased pulmonary vasoconstrictive response (Dobsa *et al.* 2013, Nickiel *et al.* 2013)

In patients with PAH copeptin levels are increased and very high copeptin levels are independent predictors of poor outcome (Stolz *et al.* 2007, Nickel *et al.* 2013, Winther *et al.* 2017, Castello *et al.* 2018).

ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Stimulation of the AVP system in individuals with chronic obstructive pulmonary disease (COPD) is a result of cardiovascular adaptation to hypoxemia (Dobsa *et al.* 2013). AVP has a negative inotropic effect on the right ventricle and increases pulmonary vasoconstriction in response to endotoxemia (Stolz *et al.* 2007).

Higher copeptin may be a prognostic biomarker of unfavorable outcome in patients with exacerbation of chronic obstructive pulmonary disease (COPD) (Stolz *et al.* 2007, Winther *et al.* 2017, Castello *et al.* 2018) independently of age, hypoxemia and lung dysfunction (Stolz *et al.* 2007).

PULMONARY EMBOLISM

It has been also reported that copeptin has prognostic impact in patients with pulmonary embolism (Hellenkamp *et al.* 2018).

CRITICAL ILLNESS

It has been commonly accepted that endogenous stress, endotoxins, and proinflammatory cytokines strongly stimulate the activity of the AVP system, as well the hypothalamo-pituitary-adrenal, sympathetic and renin-angiotensin-aldosterone systems in critically ill individuals (Chikanza *et al.* 2000). A marked increase of copeptin was observed in patients with critical illness such as septic shock, and hemorrhagic shock (Morgenthaler 2010, Koch *et al.* 2018). In the course of septic shock, reduced venous filling and arterial hypotension additionally activate the AVP system.

IN SUMMARY

It has been commonly accepted that copeptin is useful diagnostic biomarker for clinical practice in the differential diagnosis of polyuria – polydipsia syndrome (Timper *et al.* 2015, Fenske *et al.* 2018).

Evaluation of copeptin has also diagnostic and prognostic significance in many neurological diseases such as in ischemic stroke traumatic and nontraumatic intracerebral hemorrhage, multiple sclerosis as well as in cardiovascular diseases (heart failure, acute myocardial infarct) in pulmonary embolism, pulmonary arterial hypertension obstructive pulmonary disease and in some critical illness.

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