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The role of copeptin in stress response: from mechanism to clinical application

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ABSTRACT

Biomarkers are a valuable tool for detecting and monitoring the body's physiological stress response and often make it possible to detect changes long before clinical symptoms appear. As objectively measurable indicators, biomarkers reflect normal function, disease states, or the body's response to treatment. Stress tests help to measure the intensity and duration of the stress response and provide a deeper insight into the health effects. While traditional physiological stress markers, such as body temperature, heart rate, and respiratory rate, are still used, molecular markers are gaining importance because they are more sensitive and specific. Among these, copeptin stands out as one of the most promising new biomarkers for clinical research and diagnosis. Copeptin is a peptide that is consistently secreted in equal amounts with arginine vasopressin (AVP) from a shared precursor, making it a stable surrogate marker for AVP release. Unlike AVP, which is unstable and difficult to measure, copeptin remains stable in the bloodstream, and can be accurately quantified in laboratories. Its clinical usefulness has been shown in diagnosing and predicting various disorders, especially those involving stress-related physiological responses. However, the exact biological role and disease-related actions of copeptin in the bloodstream are still unknown. Nonetheless, there is evidence that it can be used as a non-invasive, stable and early biomarker of stress in human and veterinary medicine.

Key words: stress response; neuroendocrine regulation; biomarkers; AVP; copeptin

Introduction

Stress is a physiological response experienced by all mammals and is essential for the maintenance of homeostasis. However, it can significantly affect the health and productivity of animals in various ways (TAKAHASHI et al., 2018). Hormones are complex chemical substances secreted directly into the bloodstream by the endocrine system. They play a crucial role in regulating metabolism and numerous physiological functions. Essentially, hormones serve as chemical messengers that ensure that the body functions properly and remains in balance. Additionally, they oversee many vital processes related to growth, metabolism, development, immune response, reproduction, behavior, and environmental adaptation (ABDELMAGEED and GÜZELGÜL, 2023). Biomarkers are critically important because they enable us to detect stress-induced damage long before pathology or pharmacological effects manifest. Several such indicators have been investigated as potential markers for various biological processes, highlighting the significant role of biomarkers in understanding stress and related phenomena (EWERT and CHANG,

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2018). They are measurable characteristics that can be objectively assessed, and reflect normal biological functions, disease processes, or the body's response to treatment. Clinical assessment, monitoring, and prediction of health conditions in individuals or populations rely on biomarkers to help plan appropriate therapeutic strategies. However, the ideal biomarker, that is safe, simple to measure, cost-effective for monitoring, modifiable with treatment, and consistent across genders and ethnicities, has yet to be found. Biomarkers are useful not only for diagnosing diseases, but also to track their progression, regression, and treatment outcomes. They should be detectable in body fluids or from external sources. Physiological indicators, such as respiration rate, pulse, and body temperature, are important indicators that reflect environmental, social, and psychological stress (JAIN et al., 2011; SAHU et al., 2011). Recently, copeptin has emerged as a novel biomarker in the clinical setting. Current research findings underline the crucial role of copeptin as a clinical marker, particularly for the diagnosis and prognosis of various diseases (BEGLINGER et al., 2017; CHRIST-CRAIN, 2019). This breakthrough was made possible through the development of a precise analytical method to measure a signal released in a stoichiometric manner alongside biologically active vasopressin. However, the biological and pathophysiological roles of copeptin, once it enters the bloodstream, are still not fully understood.

Arginine-vasopressin (AVP) – its physiological role and interaction between the AVP System and the Hypothalamus-Pituitary-Adrenal (HPA) Axis. Arginine vasopressin (AVP) and copeptin are released in equal amounts into the bloodstream from the same posterior pituitary gland under the influence of osmotic and haemodynamic stimuli. AVP plays an important role in regulating body fluid balance and vascular tone. The challenge is that measuring AVP levels in the laboratory is complex and inaccurate. The level of AVP is critically important for diagnosing and predicting a wide range of diseases, given its essential role in various vital physiological processes. The AVP peptide is derived from a 164 amino acid precursor protein (pro-AVP), and can be generated through two unique pathways. When synthesized in parvocellular PVN neurons, AVP is processed in the parvocellular neurons of the hypothalamus, where corticotropin-releasing hormone (CRH) is also produced. AVP and CRH are transported via the portal system to the anterior pituitary, where they work synergistically to stimulate the release of the adrenocorticotropic hormone (ACTH) from the anterior pituitary (Fig. 1). This leads to cortisol secretion from the adrenal glands. The coopera- tion between AVP and CRH in controlling ACTH release highlights the importance of this mechanism in the body's stress response, further emphasizing the potential of AVP and copeptin as markers for stress measurement (VAN GASTEL et al., 2015). AVP performs three primary functions: regulating vascular tone, managing the endocrine stress response, and maintaining fluid homeostasis. Its clinical significance is underscored by its vital role in controlling kidney function, osmotic balance, sodium levels, and blood pressure. AVP exerts its effects through three distinct G-protein-coupled receptors: the V1aR (vascular receptor), the V1bR (anterior pituitary receptor), and the V2R (antidiuresis receptor) (EVERS and WELLMANN, 2018).

However, accurately measuring AVP in clinical practice remains a significant challenge. One major issue is that approximately 90% of serum AVP is bound to platelets in circulation, greatly compromising measurement reliability. The use of AVP as a biomarker is difficult due to its instability in isolated plasma, even when stored at −20°C, and its short half-life of less than 30 minutes. Furthermore, the hormone's short half-life and low molecular stability can lead to inaccuracies, making it challenging to determine its true concentration, and limiting its diagnostic and prognostic usefulness (GONZALEZ et al., 2020). The clinical use of AVP concentration levels is limited by technical measurement difficulties (ŁUKASZYK and MAŁYSZKO, 2015). Since copeptin is produced stoichiometrically with AVP, it provides a reliable indicator of vasopressin levels in human plasma and serum. As AVP and copeptin are released in equimolar amounts, copeptin serves as a stable surrogate marker of AVP. Unlike AVP, copeptin has greater molecular stability and higher plasma concentrations, making it easier

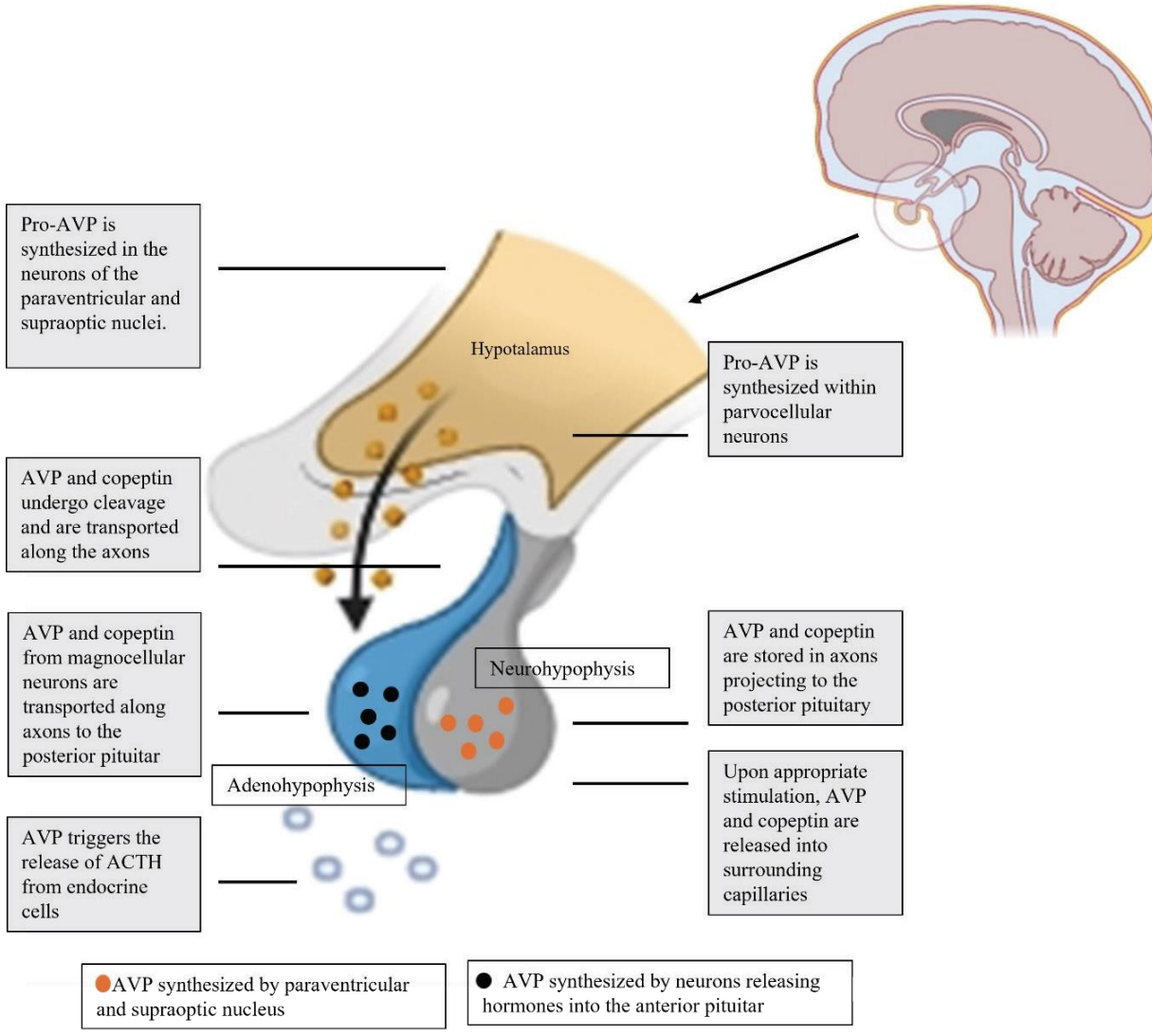

Fig. 1. AVP and copeptin are synthesized from a common precursor molecule produced in the magnocellular neurons of the hypothalamus. After processing, the resulting peptides are transported along axons and stored in the posterior pituitary. When appropriate neural stimulation depolarizes the AVP-producing neurons, AVP and copeptin are released simultaneously and in equal amounts into the capillaries of the posterior pituitary (modified from CHRIST-CRAIN and FENSKE, 2016).

to measure using various techniques such as the original sandwich immune luminometric assay (LIA), its automated immunofluorescent version (KRY- PTOR), and Enzyme-Linked I munosorbent Assay (ELISA).

Copeptin. In 1972, Holwerda first described copeptin, a glycosylated peptide extracted from the posterior lobe of the porcine pituitary gland (HOLWERDA, 1972). It consists of 39 amino acids and its molecular weight is approximately 5 kDa. Copeptin belongs to the leucine-rich core region at the C-terminal of the precursor of arginine-vasopressin (pro-AVP). This peptide is normally glycosylated (FENSKE et al., 2018). The development of a reliable radio-immunoassay made it possible to measure copeptin at physiological concentrations in plasma, in parallel with pro-AVP-derived peptides (KATAN and CHRIST - CRAIN, 2010). In general, plasma AVP and plasma copeptin concentrations are well balanced and parallel in the same individual under different health and disease conditions. At the same time, plasma osmolality stays almost within normal

ranges. Intracohort reference intervals are based on osmolality, corrected for the effects of pro-AVP-derived copeptin.

Copeptin in clinical practice. In patients with chronic heart failure (CHF), high amounts of AVP and copeptin are important signs, even when blood salt levels are low. This high amount is key to understanding how the body responds to cardiac injury and dysfunction. AVP and copeptin both have important roles in managing water balance and heart health. Copeptin, a stable fragment of the AVP prohormone, serves as a reliable biomarker for assessing vasopressin system activation following cardiac injury (OZMEN et al., 2021). The increase in AVP and copeptin in CHF is mostly the result of non-water balance signals, such as blood vessel and heart pressure, pain, angiotensin-2, and signals from the central nervous system, more than wate -related causes. These signals can be stronger than the water triggers, mainly when there is swelling, causing more AVP and copeptin to be released (BOLIGNANO et al., 2014). This response can contribute to water retention, vasoconstriction, and worsening heart failure symptoms. Therefore, AVP and copeptin levels are not only important markers for understanding the underlying mechanisms of heart failure, but also potential tools for monitoring the progression and severity of cardiac damage in CHF patients (JIA et al., 2017).

Beyond its role in cardiovascular diseases, copeptin also plays a significant role in respirato- ry disorders. Elevated plasma copeptin levels are associated with increased AVP levels, and have been linked to poor outcomes in respiratory conditions. In patients with community-acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD), high copeptin levels predict disease deterioration, mortality, and exacerbations (KOLDITZ et al., 2012; ZHAO et al., 2014; KARAKIOULAKI et al., 2021). Copeptin also serves as a useful biomarker for prognosis in heart failure and respiratory diseases. It has shown better predictive value for short-term mortality than NT-proBNP in acute lung injury, cardiopulmonary edema, and acute respiratory distress syndrome. Additionally, copeptin plays an importantrole in diagnosing and assessing risk in pulmonary hypertension and pulmonary embolism patients (HELLENKAMP et al., 2018).

Copeptin serves as a clinically informative biomarker in gynecological contexts, reflecting maternal and fetal stress responses, and has been associated with conditions such as preeclampsia and the hormonal stress surge during labor. In human studies, a clear association has been observed between copeptin levels and preeclampsia, with copeptin showing potential as a predictor of disease severity (WELLMAN et al., 2014; EVERS and WELLMANN, 2018). Copeptin is a significant stress biomarker during the spike in fetal stress hormones triggered by maternal labor during vaginal delivery. Neuronal hypoxia caused by transient cerebral hypoperfusion due to the mother's uterine contractions is the main cause of copeptin release at birth. Studies have shown that copeptin levels in arterial plasma are 1.8 times higher than in venous plasma immediately after birth in the umbilical cord blood of healthy newborns (WELLMANN et al., 2010; BLOHM et al., 2019).

Copeptin has emerged as a valuable biomar- ker in neurological disorders, reflecting the activa- tion of the stress axis, and providing prognostic insight into cerebrovascular risk. In line with this, KATAN et al. (2011) reported that copeptin may have predictive value in stratifying the risk of future ischemic events, as only higher levels of copeptin (not cortisol) were associated with recurrent cerebrovascular events, including both stroke and transient ischemic attack (MONTELLANO et al., 2021).

As an independent predictor of future risk for diabetes mellitus (DM), copeptin has shown significant promise in risk assessment and the development of novel therapeutic strategies for DM prevention and treatment (ENHÖRNING et al., 2010). Highlighting its broader role in metabolic and renal dysfunction, elevated copeptin concentrations have been associated with microalbuminuria, as well as the prediction of diabetes and obesity, though not with the full cluster of metabolic syndrome (ENHÖRNING et al., 2013). Copeptin has also yielded encouraging results in the differential diagnosis between cerebral salt-wasting syndrome and the syndrome of inappropriate antidiuretic hormone

hypersecretion (SIADH). While elevated AVP levels in SIADH lead to hyponatremia and increased urine osmolarity, the copeptin-to-urinary sodium ratio has proven to be a more accurate diagnostic tooldue to theconsiderable overlap in copeptin values between these two conditions (FENSKE et al., 2009).

While most clinical studies have focused on human medicine, promising data from veterinary and animal models further support the clinical relevance of copeptin. In a porcine model of acute myocardial infarction (AMI), serum copeptin levels rose significantly within 1 hour post-infarction, peaked at 3 hours, and returned to baseline within 2–3 days. Furthermore, copeptin levels negatively correlated with key cardiac function indicators, including left ventricular ejection fraction (LVEF), cardiac output (CO), and stroke volume (SV), while showing a positive correlation with left ventricular end-systolic volume (LVESV), suggesting its potential as a dynamic biomarker of cardiac dysfunction in large animal models (LI et al., 2023). Similar findings have been reported in rodent models. In 14-day -old Wistar rats exposed to ventilatory stress conditions, including respiratory alkalosis, hypoxia, high positive end-expiratory pressure (PEEP), hemorrhage, and psychological stress, copeptin levels increased five- to ten-fold (L'ABATE et al., 2013). These data demonstrate copeptin's sensitivity as a biomarker of acute somatic stress, and support its application in elucidating the mechanisms of stress physiology in animal models. In canine models, data remain limited. A study evaluating salivary copeptin in dogs with separation anxiety found no statistically significant difference in absolute values between anxious and control groups, although group trends varied (PIERANTONI et al., 2022). In dogs with heart disease, ranging from healthy to those with congestive heart failure, copeptin levels did not differ significantly between stages, though a weak inverse correlation with age was observed (LAVIGNE et al., 2025). Additionally, several preliminary studies and case reports have tested commercial ELISA kits for copeptin mea- surement in canine serum under various osmotic conditions or disease states, including diabetes and endocrine disorders, indicating growing interest in its veterinary application (SPRINGFIELD and SCHERMERHORN, 2023; SCHERMERHORN and CALO, 2024).

Additionally, while human data are robust, veterinary applications of copeptin are still emerging. Future research should focus on establishing species-specific reference ranges, validating assays, and conducting longitudinal studies to understand copeptin dynamics better in veterinary patients. Additionally, standardization of measurement techniques and multicenter studies are needed to ensure reproducibility and reliability. Investigating copeptin in various clinical conditions across different species could further elucidate its diagnostic and prognostic potential, guiding its integration into routine veterinary practice.

Conclusions

The same precursor releases copeptin and AVP in equimolar amounts. In contrast to AVP, which is difficult to quantify due to its instability and short half-life, copeptin remains stable in circulation, allowing for its reliable detection in plasma and serum. In clinical practice, copeptin has gradually become a dependable indicator of vasopressinergic activation in response to osmotic and hemodynamic stimuli due to its numerous advantages over AVP. Copeptin has emerged as a new prognostic marker in a variety of diseases, such as sepsis, chronic obstructive pulmonary disease, heart failure, and myocardial infarction. Copeptin is a diagnostic marker in diabetes insipidus and in patients with diabetes mellitus, and copeptin may also have predictive value in stratifying the risk of future ischemic events. Future research should focus on species-specific reference ranges, valida- tion of commercial assays, and longitudinal studies exploring copeptin dynamics in veterinary patients.

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SAŽETAK

Biološkipokazateljistresasuvrijedanalatzaotkrivanjeipraćenjefiziološkogodgovora organizma na stres te često omogućuju uočavanje promjena mnogo prije pojave kliničkih simptoma. Kao objektivno mjerljivi pokazatelji, biomarkeri odražavaju urednu funkciju, bolest ili odgovor tijela na liječenje. Testovi stresa pomažu u mjerenju intenziteta i trajanja odgovora na stres te pružaju dublji uvid u zdravstvene učinke. Iako se i dalje primjenjuju tradicionalni fiziološki pokazatelji stresa, poput tjelesne temperature odnosno srčane i respiratorne frekvencije, molekularni markeri sve više dobivaju na važnosti zbog svoje veće osjetljivosti i specifičnosti. Među njima se ističe kopeptin kao jedan od najperspektivnijih novih biomarkera za klinička istraživanja i dijagnostiku. Kopeptin je peptid koji se u jednakim količinama luči zajedno s arginin-vazopresinom (AVP) iz zajedničkog prekursora, što ga čini stabilnim zamjenskim markerom za lučenje AVP-a. Za razliku od AVP-a, koji je nestabilan i teško mjerljiv, kopeptin je stabilan u krvotoku i može se precizno kvantificirati u laboratorijima. Njegova je klinička korisnost dokazana u dijagnostici i predviđanju različitih poremećaja, osobito onih koji uključuju fiziološke reakcije na stres. Međutim, točna biološka uloga i djelovanje kopeptina u krvotoku povezano s bolestima još nisu u potpunosti razjašnjeni. Unatoč tome, postoje dokazi da se u humanoj i veterinarskoj medicini može primjenjivati kao neinvazivan, stabilan i rani biomarker stresa.

Ključne riječi: odgovor na stres; neuroendokrina regulacija; biomarkeri; AVP; kopeptin