REVIEWS

The Vasopressin System in Metabolic Syndrome and Insulin Resistance - a Mini-Review

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Abstract

Arginine vasopressin (AVP) or antidiuretic hormone is a neurohypophyseal hormone which plays a major role in water homeostass in humans. Through its specific receptors, AVP is also involved in peripheral vascular resistance inducing vasoconstriction and rise in blood pressure. Since measurement of plasma levels of AVP remains challenging in the clinical laboratory practice, immunodetection of copeptin - the C-terminal fragment of AVP precursor secreted in equimolar quantities - is currently used as a marker of AVP in various clinical settings, including as predictor of myocardial infarction. Research in the last several years indicated that AVP is also involved in glucose and lipid metabolism as shown by measurements of copeptin levels in insulin resistant conditions such as diabetes, metabolic syndrome or polycystic ovary syndrome. This paper is aimed to summarize the implication of AVP and its receptors in metabolic syndrome and insulin resistance and launched hypothesis how changes in water intake and hydration status can influence development of these metabolic conditions.

Keywords: copeptin, arginine vasopressin, AVP receptor, metabolic syndrome

Rezumat

Arginin-vasopresina (AVP) sau hormonul antidiuretic este un hormon neurohipofizar cu rol major în homeostazia apei la om. Prin receptori specifici, AVP este de asemenea implicată în rezistența vasculară, determinând vasoconstricție și creșterea presiunii arteriale. Deoarece măsurarea AVP în plasmă este dificilă, imunodetecția copeptinei plasmatice - fragmentul C-terminal al precursorului AVP, secretat în cantități echimolare - este utilizată ca marker al AVP în diverse situații clinice, inclusiv ca predictor în infarctul de miocard. Cercetările din ultimii ani au indicat că AVP este de asemenea implicată în metabolismul glucidic și lipidic, după cum reiese din determinările copeptinei în afecțiuni caracterizate de insulino-rezistență, ca diabetul zaharat, sindromul metabolic sau sindromul de ovar polichistic. Această lucrare are ca scop expunerea rolului AVP și a receptorilor săi în sindromul metabolic și rezistența la insulină, și a ipotezei privind rolul aportului lichidian și a hidratării în aceste afecțiuni metabolice.

1. INTRODUCTION

Metabolic syndrome (MetS), type 2 diabetes, and consequent cardiovascular complications are serious healthcare problems worldwide[1,2]. The prevalence of MetS or its components around the world is variable in different ethnic populations[3,4], and this can be explained by interactions between susceptibility genes specifically expressed in certain ethnic groups and environmental factors[5]. Nonetheless, the number of people affected by these conditions is continuously increasing at a global

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level[4,6] and along with it the mortality and morbidity of populations[7,8]. Cardiovascular disease (CVD) is the main cause of mortality in people suffering from MetS and/or diabetes[9].The research in this field is ongoing, in the attempt to elucidate the pathophysiological mechanisms and pathways involved in MetS, and to find reliable biomarkers for diagnosis and disease prognosis, as well as therapeutic targets.

For the last years, copeptin, the C-terminal fragment of arginine vasopressin (AVP) precursor was in the focus of research. Copeptin serves as a substitute for AVP concentration. Copeptin was tested in a multitude of clinical settings, from a marker in acute and chronic illness to disease predictor. Of note, copeptin was found useful to differentiate between conditions of polyuria–polydipsia syndrome and electrolyte disturbances[10-12]; it was described as a marker in critical illness[13], sepsis[14-17], renal dysfunction[18,19], arterial hypertension[20-22], myocardial infarction and heart failure[23-27]. Moreover, it was described in regard to metabolic disturbances, such as metabolic syndrome, obesity, type 2 diabetes and insulin resistance[28-31]. Since copeptin is a surrogate marker of AVP secretion, AVP together with its receptors are attractive points of research in the pathophysiology of different diseases and may serve as well as therapeutic targets.

The aim of this paper is to summarize the role of AVP system, including copeptin in regard to metabolic disturbances.

2. THE VASOPRESSIN SYSTEM

Arginine vasopressin (AVP) is a neurohormone synthesized primarily in the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, stored and released from the posterior pituitary. It is closely related to oxytocin, and both of them are nonapeptides highly conserved which have presumably evolved from a common ancestral nonapeptide, vasotocin[32].

AVP is primarily involved in fluid homeostasis by inducing water reabsorption at the kidney level. It is released from the neurohypophysis in response to increased plasma osmolality, low plasma volume and/or hypotension. Hypoxia, nausea, hypoglycemia or nonspecific stress may also induce AVP release[33,34]. Besides its well known effects on osmoregulation (antidiuresis) and vascular tone (vasoconstriction) AVP is involved in glucose metabolism with effects on neoglucogenesis, glycogenolysis and modulation of insulin and glucagon secretion from the pancreas; it also regulates ACTH secretion from the anterior pituitary and endocrine stress response[35-38].

In humans, AVP biological action is produced through three types of receptors (V1aR, V2R and V1bR) with specific tissue distribution. Receptors V1aRs are encoded by AVPR1A gene (Chr 12) and largely distributed in the body while V1bRs are encoded by AVPR1B gene (Chr1) and particularly expressed in the pituitary and pancreas. AVP receptors type 2 (V2R) are encoded by AVPR2 gene (Chr X) and are mainly expressed in the collecting duct of the kidney[39,40]. The distribution of these receptors can explain the involvement of AVP in various pathological states.

The hormone is encoded in humans by the AVP gene (Chr 20), which derives from a larger precursor - pre-provasopressin- which is proteolytically processed to generate neurophysin II and copeptin along with AVP. Thus, AVP and copeptin are co-released in the circulation in response to specific stimuli[41]. Biological function of copeptin remains unknown possibly contributing to AVP processing during the axonal transport[42-44]. In the last years, the C-terminal fragment of AVP precursor – copeptin - was revealed to be a good marker of AVP secretion[17]. The necessity to find a marker for AVP secretion comes from the fact that AVP molecule is unstable rendering its measurement difficult in the laboratory. In the blood, AVP is largely bound to platelets and it has a short half-life. Moreover, as a small molecule, AVP detection is challenging in immunoassays and tests are of low sensitivity[45-47]. Copeptin by contrast, being a glycopeptide is more stable in plasma or ex-vivo conditions, even at room temperature[47]. In practice, copeptin was revealed to be a sensible surrogate marker for the AVP release since is secreted in equimolar amounts with AVP. Several previous studies validated the efficacy of copeptin measurements to estimate the AVP concentration in plasma[48-50]. For all these reasons copeptin became in the last decade a subject of intensive research efforts in metabolic and cardio-vascular diseases.

3. VASOPRESSIN SYSTEM AND METABOLIC DISORDERS

Evidence for involvement of AVP system in cardiometabolic disorders comes from studies in both humans and mice at biological and genetic levels.

3.1. AVP and AVP receptors in glucose homeostasis

Vasopressin infusion increases blood glucose in non-diabetic humans and rats[51,52]. In addition, AVP levels are increased in rats with streptozotocin-induced diabetes[53,54] and in people with diabetes, both type 1 and

type 2[55]. Studies on mice showed that AVP is involved in glucose homeostasis regulation via V1a and V1b receptors. Knock-out mice invalidated for V1a or V1b receptor genes show particular phenotypes with metabolic derangements, including insulin hypersensitivity, enhanced glucose tolerance ($V1bR^{(-/-)}$ mice), to insulin resistance, obesity, and impaired glucose tolerance ($V1aR^{(-/-)}$ mice)[56-59].

Interestingly, $V1aR^{(-/-)}$ deficient mice showed a phenotype resembling MetS, including hyperglycemia, decreased insulin sensitivity and predisposition to obesity. However, low level of triglycerides[57,58] suggest an increased fat metabolism compared to glucose due to altered expression of V1a receptors. These mice have decreased insulin signal in the adipocytes and increased glycogenolysis[58]. In contrast, $V1bR^{(-/-)}$ deficient mice had lower plasma insulin and glucagon with increased sensitivity to insulin. Glucose metabolism in the adipose tissue of these mice was altered, as well as lipid metabolism consisting in decreased lipolysis and increased lipogenesis probably promoted by the increased insulin sensitivity[37,56]. Mice deficient for both types of receptors, V1a and V1b, displayed impaired glucose tolerance when fed a high-fat diet, similar to $V1aR^{(-/-)}$ mice. These observations suggest that involvement of V1aR in glucose metabolism is larger than that of V1bR[59].

Recently, in an interesting study in rats, Taveau et al[60] demonstrated that constant high AVP levels alter glucose metabolism. In this research, lean and obese rats were subject to different levels of circulating AVP. Chronic increased levels of AVP determined higher glucose level in lean healthy rats while obese Zucker rats (i.e. obese insulin-resistant) developed impaired glucose tolerance and hyperinsulinemia. These effects were mediated in part through V1aR, as shown by selective blockade of V1a receptor, which led to an improvement of glucose intolerance in these animals. Moreover, a higher hydration status and lower AVP levels induced by increased water intake improved hepatic steatosis associated with obesity.

It should be indicated that a phenotype similar to $V1aR^{(-/-)}$ knock-out mice was found in humans. Thus, in Scandinavian population, subjects carrying the T allele of single nucleotide polymorphism (SNP) rs1042615 in the vasopressin receptor 1A gene had higher plasma glucose and lower triglycerides levels. In addition, in men, rs1042615 T allele was associated with increased prevalence of diabetes in overweight subjects or undergoing a high-fat diet[61].These data sustain the idea that disturbances in AVP signaling pathway can intervene in the development of insulin resistance and MetS.

3.2. Copeptin in MetS, insulin resistance and type 2 diabetes

Evaluation of plasma AVP concentration in relation to various conditions was accomplished in the recent years through the measurement of copeptin levels. The link between AVP, copeptin and MetS and insulin resistance as well as cardiovascular disease has gained more and more interest. Several recent studies have concluded on the association between copeptin level and several metabolic conditions. Thus, in a series of Swedish studies on a large population (4742 individuals) copeptin levels were associated with MetS, obesity and high blood pressure[28]. Elevated copeptin was also associated with diabetes at baseline being able to predict the increased risk for type 2 diabetes independently of other major risk factors such as glucose and insulin levels[62]. In another study, the association of copeptin with the risk for developing diabetes was higher in women[63]. Similar results on association between copeptin and MetS were found in African-Americans (1293 individuals) and non-Hispanic whites (1197 individuals) in USA. It is noteworthy however that these subjects came from a predominantly hypertensive cohort[27].

In longitudinal studies, copeptin was also associated with microalbuminuria independently of diabetes or hypertension[29]. Association with microalbuminuria was demonstrated in another large cohort (n=7593) in Netherlands, which investigated the predictive value of urinary albumin excretion for renal and cardiovascular disease progression[64]. These are intriguing observations, knowing that microalbuminuria is an independent risk factor for cardiovascular disease in diabetic and non-diabetic populations[64,65].

High levels of copeptin were also found in other conditions of insulin resistance, such as polycystic ovary syndrome (PCOS) in women population[66,67]. PCOS is carrying 2-4 fold risk of MetS68 compared to the general population. Copeptin levels were higher in obese PCOS women, compared with non-obese PCOS or controls. Copeptin also negatively correlated with brachial artery flow-mediated vasodilation (FMD), a potential marker for future cardiovascular risk[69]. In PCOS women, copeptin correlated with carotid intima-media thickness and besides insulin, with HOMAIR index of insulin resistance and free testosterone[67]. Thus, copeptin appears to provide information on cardio-metabolic risk in hyperandrogenic women.

Roussel et al investigated the associations of plasma copeptin and allelic variants of AVP gene with insulin secretion and the risk for dysglycemia in a large French cohort (n=5110) followed-up for a period of 9 years[70]. The results plead again for the role of AVP in meta-

bolic disorders. Copeptin was associated with reduced insulin sensitivity and increased risk for impaired fasting glucose and type 2 diabetes. Genetic investigation showed in the same manner positive results, with certain allelic variants of AVP gene being associated with increased risk of hyperglycemia; additionally, in men these genetic variants correlated well with increased copeptin level, thus supporting a causative role of AVP in these metabolic disorders.

3.3. Copeptin as a marker of cardiovascular disease

Copeptin was evaluated as a diagnostic and prognostic tool in various clinical situations, alone or together with classical or other novel biomarkers. Plasma copeptin level proved to be a good marker for myocardial infarction during the first hours of evolution[23,24,71]. Its early detection, when conventional biomarkers like troponin are not yet increased[23,72], can add a diagnostic value in the acute situation of suspicion for myocardial infarction. However, copeptin alone for a rapid diagnosis of exclusion of acute myocardial infarction has a small value and it cannot substitute serial measurements of troponin. Therefore, to rule-out acute myocardial infarction, copeptin has low specificity[73,74]. On the other hand, determination of copeptin and troponin together significantly increases diagnosis sensitivity[23]. Increased copeptin early in the setting of myocardial infarction can be the result of baroreceptor stimulation after the drop in cardiac output and of high endogenous stress, thus stimulating AVP system[75].

In heart failure, high AVP levels are associated with poor prognosis. Utilization of copeptin as a surrogate for AVP concentration was useful and accurate for the disease prognosis. In patients with heart failure, high copeptin levels showed a worse prognosis[26,76]. Its measurement along other heart failure markers, as NT-proBNP adds important prognosis information and is useful for risk stratification of patients early after acute myocardial infarction, which may lead to better treatment of these patients[77]. In addition, research has showed that copeptin is an independent risk factor for CVD and premature mortality, especially in patients with type 2 diabetes[78].

4. Regulation of AVP through fluid intake

Although the associations found in studies involving copeptin do not demonstrate causality, much of the data in this field of research supports the link between increased AVP and metabolic disturbances and CVD risk. Strategies aiming the vasopressin system are therefore suitable in conditions associated with high activity of AVP system.

AVP secretion increases in conditions of high plasma osmolality, and consequently plasma copeptin level increases as well[48]. Restriction of water intake increases AVP secretion. It was shown that low water intake was associated with new development of hyperglycemia[79]. Reducing AVP level by increasing hydration status, i.e. by increasing fluid intake, has been proposed as an easily applicable measure that might have an impact on reducing the metabolic risk associated with high AVP levels[80]. Experiments in animals carried by Taveau et al support this hypothesis: rats with higher water intake had lower AVP, lower insulin resistance and lower liver steatosis[60].

A specific copeptin cut-off level associated with a certain disease risk has not been established yet. However, it is known that almost 50% of the European population has lower daily water intake than what is recommended by the *European Food Safety Authority*[80]. In view of this data, a higher or at least recommended water intake seems an accessible measure in the purpose of reduction AVP / copeptin levels, aiming by these means to reduce the metabolic risk.

The nature of fluid intake also influences AVP/copeptin level. Thus, in a study by Roussel et al. sweet drinks intake was positively related to copeptin, in opposition to water intake[50]. It is well known that alcohol has an inhibitory effect on AVP secretion by blocking voltage-gated calcium channels in nerve terminals in the neurohypophysis[81]. Which are the elements that modulate AVP secretion in different populations with specific dietary habits, for example in people who do not consume alcohol, remains an intriguing point of research in relation with metabolic profile of these populations. Other consequences of increased AVP in people with a suboptimal hydration status can by speculated in regards to its role as neuromodulator / neurotransmitter in the brain, with possible effects on eating behavior in relation to stress response in the brain, controlled by AVP[82].

In conclusion, there is an increasing body of evidence for the involvement of AVP system in metabolic disturbances. Whether it implies increased AVP or altered receptor signaling, definitively vasopressin actions are not confined to the water balance alone. Copeptin, reflecting AVP secretion is a useful biomarker for diagnosis and prognosis in cardiometabolic diseases. Therapeutic intervention in this pathway, even through simple measures, such as increasing water consumption, may have beneficial effects on reducing the risk of

MetS, type 2 diabetes and their possible complications. Future studies will allow a better understanding of the relationship between fluid intake, AVP system and cardiometabolic diseases.

Conflict of interest: none declared.

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