Kardiologia Polska 2015; 73, 6: 383–386; DOI: 10.5603/KP.a2015.0053 ISSN 0022–9032



# The role of vasopressinergic system in metabolic syndrome

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## INTRODUCTION

With the growing problem of obesity in developed countries, metabolic syndrome (MS) has become an important clinical issue and public health challenge. Thus, intensive research has been undertaken to elucidate the basis of this condition, and potentially to develop methods to prevent it. Recently, more attention has been paid to the role of the vasopressinergic system in the pathogenesis of MS. The aim of the current literature review is to present state-of-the-art knowledge on the role of the vasopressinergic system in MS.

## HISTORY

Studies on MS were initiated already in the 1920s when a relation between hypertension and hyperglycaemia was reported. In late 1980s, insulin resistance was linked to compensatory hyperinsulinaemia and both were established as important risk factors for cardiovascular disease. This constellation was initially called syndrome X, encompassing hyperinsulinaemia, hyperglycaemia, diabetes type 2, obesity, hypertension, elevated serum very-low-density lipoprotein (VLDL) level, and low high-density lipoprotein (HDL) level. Later, abdominal obesity was added to this concept and a new term of MS was introduced [1].

## DEFINITION

Taking into account the complex pathogenesis of MS, in 2009 the International Diabetes Federation (IDF), American Heart Association (AHA), and the National Heart, Lung and Blood Institute (NHLBI) proposed a common definition of MS which is diagnosed based on the presence of 3 of 5 criteria shown in Table 1 [2].

## EPIDEMIOLOGY

With the current epidemics of overweight and obesity in developed countries, MS has become an important clinical problem. According to IDF, MS is present in one fourth of the adult population worldwide. The rates of MS in various countries are estimated to range from 10% to 80% depending on the current economic status, age, gender, and race [3]. The presence of MS is positively associated with body mass index (BMI) as this condition has been diagnosed in as many as 60% of obese subjects (BMI ≥ 30 kg/m$^2$) [4]. According to the current definition, MS is present in 40.1% of adults in the United States [2]. The incidence of MS was shown to increase with age. In Europe, the rates of MS are 43–78% in women and 24–65% in men depending on the region [5]. Based on the IDF criteria, MS was diagnosed in 20% of women and 23% of men in Poland [6].

## PATHOGENESIS

Modifiable risk factors, such as abdominal obesity and low physical activity, were shown to play an important role in the

Table 1. Diagnostic criteria of the metabolic syndrome

| Risk factors | Values |
|---|---|
| Abdominal obesity — waist circumference* | Men > 94 cm<br>Women > 80 cm |
| Elevated plasma triglyceride level | 150 mg/dL |
| Low plasma high-density lipoprotein cholesterol level | Men < 40 mg/dL<br>Women < 50 mg/dL |
| Elevated blood pressure | Systolic ≥ 130 mm Hg<br>or diastolic ≥ 85 mm Hg |
| Elevated fasting plasma glucose level or diabetes type 2 | ≥ 100 mg/dL |

*Criteria for Caucasians according to International Diabetes Federation

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**Received:** 13.01.2015 **Accepted:** 29.01.2015 **Available as AoP:** 06.03.2015

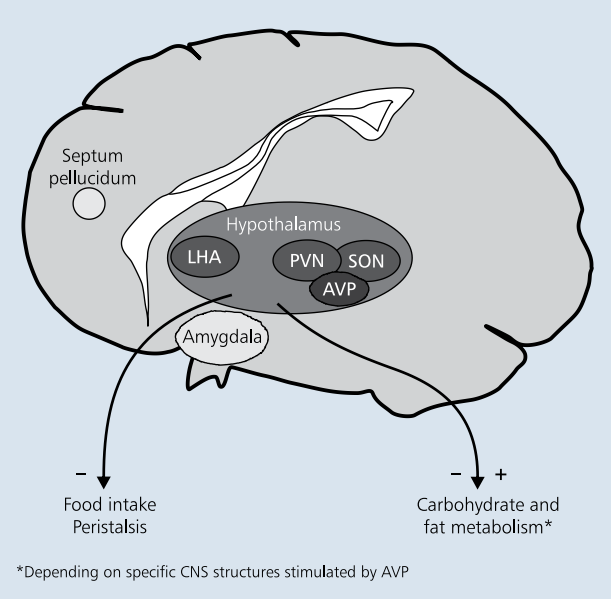


Figure 1. Effect of the vasopressinergic system on energy balance; AVP — arginine vasopressin; CNS — central nervous system; LHA — lateral hypothalamic area; PVN — paraventricular nucleus; SON — supraoptic nucleus

pathogenesis of MS. Other important factors include the effect of genetic factors, age, and ethnic background [2].

An increased lipolytic activity is seen in obesity, leading to an excessive increase in the serum level of free fatty acids which limit peripheral glucose uptake and reduce insulin sensitivity, resulting in insulin resistance. Free fatty acids also increase tissue triglyceride stores and stimulate VLDL release to blood, also increasing insulin resistance. The latter leads to increased serum triglyceride and low-density lipoprotein levels and reduces HDL level. Body compensatory response to insulin resistance is an increase in blood glucose level, leading to diabetes type 2. Hyperglycaemia contributes to vascular damage, including of renal vessels, which might lead to sodium retention and development of hypertension [7]. A twofold increase in mortality and a threefold increase in the rates of myocardial infarction and stroke was found in subjects with MS compared to those without MS [8].

Recently, more attention has been paid to the role of stress-inducing factors in the pathogenesis of MS. Abnormal regulation of the hypothalamus-pituitary-adrenal (HPA) axis was shown in subjects with abdominal obesity. In addition, hyperinsulinaemia increased arginine vasopressin (AVP)-induced adrenocorticotropic hormone (ACTH) release from the pituitary [9]. Enhörning et al. [10] reported a significant increase in vasopressinergic system activity in patients with abdominal obesity and diabetes type 2. AVP is also known to affect regulation of food intake (Fig. 1) [11]. Thus, the vasopressinergic system seems to play a major role in the pathogenesis of MS.

## VASOPRESSINERGIC SYSTEM — GENERAL CHARACTERISTICS

The precursor hormone for vasopressinergic system peptides, preproarginine vasopressin (preproAVP) is synthesized in the paraventricular nucleus (PVN) and the supraoptic nucleus of the hypothalamus. AVP, neurophysin II, and copeptin (C-terminal proAVP) are formed from preproAVP during its axonal transport from the hypothalamus to the pituitary gland. AVP release to blood is stimulated by, among others, an increase in plasma osmolarity and hypovolemia [12]. In turn, AVP is involved in the regulation of multiple physiologic processes such as blood pressure homeostasis, diuresis, platelet aggregation, ACTH release, and carbohydrate and fat metabolism [13].

AVP affects tissue and organ activity via its receptors: V1a (V1aR), V1b (V1bR), and V2 (V2R). V1aR participate in hepatic gluconeogenesis and glycogenolysis, platelet aggregation, and vasoconstriction. V1bR is more specific compared to V1aR, as it is mostly located in the pituitary, pancreas, and white adipose tissue. V1bR are sensitive to blood glucose level, stimulate insulin and glucagon release, and participate in stress response by affecting ACTH release from the pituitary [14–16]. Diuresis is mostly regulated by V2R, located mainly in renal collecting ducts [14].

Vasopressin is unstable in plasma, with the mean half-life of just 24 min, resulting in a low sensitivity of its laboratory measurements. Thus, the activity of the vasopressinergic system is evaluated by plasma copeptin level measurements. Equimolar amounts of AVP and copeptin were found to be produced from preproAVP in the hypothalamus. Similarly to AVP, plasma copeptin level depends on plasma osmolarity but in contrast to AVP, copeptin is characterised by a longer plasma half-life and stability at room temperature for as much as 14 days [17].

## FOOD INTAKE AND THE VASOPRESSINERGIC SYSTEM

Vasopressinergic neurons are located in the hypothalamus which is also responsible for the regulation of food intake (Fig. 1). Available data suggest that brain areas particularly involved in this process include PVN and the lateral hypothalamic area (LHA) [18]. Efferent vasopressinergic fibres run from the hypothalamus to the nucleus tractus solitarii (NTS) which participates in the transmission of taste sensory inputs and receives information on plasma glucose level [19]. The presence of V1aR was shown in multiple central nervous system structures that participate in the regulation of food intake, including the amygdala, LHA, nucleus accumbens, area postrema, and neurons of cranial nerves V, VII, IX, and X [20].

Experimental studies seem to confirm participation of AVP in food intake. Administration of AVP directly into PVN led to hyperglycaemia in Wistar rats [21]. Similarly, AVP microinjections directly into NTS also contributed to a significant increase in plasma glucose level in Wistar rats. In mice,

activation of vasopressinergic neurons in PVN by exogenous ligands stimulating AVP receptors resulted in an acute reduction of food intake [11]. A similar phenomenon was observed in transgenic mice lacking the V1aR gene (V1aR-KO). It was suggested that AVP plays a role in central regulation of food intake by interacting with other neurotransmitters including neuropeptide Y, vasoactive intestinal polypeptide, melanocortin, and opioids [22].

## METABOLIC SYNDROME AND THE VASOPRESSINERGIC SYSTEM

The involvement of the vasopressinergic system in central regulation of food intake suggests its important role in maintaining body energy homeostasis, and also in metabolic disturbances.

*In vitro* studies showed that administering AVP to cultured rat hepatocytes stimulated triglyceride and glucose synthesis [23]. Fat metabolism was altered in mice lacking the V1aR, with low triglyceride levels and high plasma glucose levels. Those animals were also found to have an increased risk of obesity and diabetes type 2 compared to the control group [21]. In contrast, mice lacking the V1bR developed a phenotype characterised by better glucose tolerance and insulin sensitivity [14].

Similarly, reduced plasma glucose and copeptin levels and increased triglyceride levels were reported in carriers of rs1042615 T allele — one of four tag single nucleotide polymorphism of the human V1aR gene — compared to CC carriers. In addition, an association was found between this polymorphism and an increased risk of diabetes type 2 in overweight subjects and those on a high-fat diet. The same group showed an association between V1bR gene polymorphism and high BMI and diabetes type 2. In several clinical studies, an increase in plasma copeptin level was reported in subjects with MS or its components including hypertension, abdominal obesity, hyperinsulinaemia, and diabetes type 2. An effect of low physical activity and high-fat diet on a significant increase in plasma copeptin level was also observed. In subsequent studies, the same authors confirmed that copeptin may serve as an early marker of diabetes type 2 [24].

The vasopressinergic system has been long known to participate in the stress response. Stress-inducing factors result in AVP-mediated hyperactivation of the HPA axis, leading to excessive glucocorticosteroid release, resulting in alteration of processes that play a major role in the regulation of carbohydrate and fat metabolism, and thus contributing to the development of obesity and diabetes type 2. Both *in vivo* and *in vitro* experimental studies showed a lack of negative feedback between glucocorticosteroids and AVP, which is characteristic for the role of corticotropin-releasing hormone (CRH) in the regulation of HPA axis hormone levels. *In vivo* studies in rats indicate that upon stimulation, AVP reaches higher levels compared to CRH [25]. Thus, stress conditions may result in AVP-mediated hyperstimulation of the HPA axis, resulting in excessive release of glucocorticosteroids with secondary alterations of carbohydrate and fat metabolism, leading to the development of obesity, diabetes type 2, and MS [24].

## SUMMARY

Available literature data suggest that the vasopressinergic system plays a major role in the pathogenesis of MS, affecting its components including abdominal obesity and diabetes type 2.

***Conflict of interest:*** *none declared*

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