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## The role of vasopressin in the activity of the central nervous system and in the pathogenesis and therapy of schizophrenia

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### ABSTRACT

Vasopressin - pituitary neurohormone, in addition to the essential role of which is to regulate blood pressure and affecting the body's water balance, it is involved in other processes such as social behaviour, memory processes and learning. It also plays an important role in modulating anxiety. This hormone seems indispensable for the creation of proper social interactions, and its low plasma levels correlate with the dysfunction of interpersonal relationships. In this article, we review and summarize the studies on the role of vasopressin in the pathogenesis and therapy of schizophrenia. Despite some potential limitations in peer-reviewed studies, the literature suggests the potential role of vasopressin in the pathogenesis of schizophrenia and the possible therapeutic application in this psychiatric disorder.

**Keywords:** vasopressin, schizophrenia, central nervous system, pathogenesis

### 1. INTRODUCTION

Research on schizophrenia has a long history in the development of science. Many scientists have chosen this disease as the goal of their research and investigation. As a result,

over the years newer theories of the pathogenesis and treatment of this disease emerged. However, due to the serious nature, which is not rarely associated with the impossibility of functioning in society and a huge stigma, many researchers are still looking for new solutions that can contribute to improving the quality of life of people suffering from schizophrenia.

The aim of this study is to analyze and present the results of recent studies dedicated to the link between vasopressin (ADH, AVP) and schizophrenia in the field of pathogenesis and potential treatment.

## **2. THE ROLE OF VASOPRESSIN IN A HUMAN ORGANISM**

Vasopressin is a cyclic nonapeptide with a molecular weight of 1084 Da, produced in the form of prohormones in the vasopressinergic neurons of the supraoptic and paraventricular nucleus [1]. The N-terminal portion of prohormone forms the signal peptide, the middle part is vasopressin and the C-terminal end is neurophysin II, which binds vasopressin. It is transported from the hypothalamus in the form of neurosecretory granules and its final storage is the posterior lobe of the pituitary gland, from where it is subsequently released. Structurally vasopressin is similar to oxytocin.

Within the ring, it contains a disulfide bond between the cysteine residues at positions 1 and 6 of the molecule. This hormone is transported in the blood in the form of loose connections with plasma globulins. It occurs in blood serum at a concentration of  $10^{-12}$  -  $10^{-14}$  mol / L. Its half-life in humans is 18 minutes.

Enzymatic inactivation of vasopressin occurs in the liver and kidneys, and consists in disrupting the disulfide bond between cysteine residues [2].

The main factor stimulating the release of vasopressin from the nerve endings is the increase in plasma osmolality by 1-2% over the normal value [3]. This causes the neurones of the supraoptic nucleus to shrink, which leads to increased pulsation in the fibres of these neurones and increased release of the hormone from the nerve endings. Other factors that stimulate the release of vasopressin are reduction in blood volume and blood pressure by 5-10%, which stimulates aortic and sinus baroreceptors and volume receptors of the low-pressure part of the circulatory system, which in turn leads to an increase in the release of vasopressin by reflex.

Other factors affecting the release of vasopressin include: stimulation of vasopressin neurons by angiotensin II, injuries, emotional stimuli, prostaglandins and nicotine [4]. Inhibition of vasopressin release is caused by increased blood volume, increased blood pressure and alcohol.

Vasopressin interacts with  $V_{1A}$ ,  $V_{1B}$  and  $V_2$  receptors, which are associated with the protein G. Hormone activity is based on inhibition of water secretion involving membrane receptors and cAMP. This process is based on increasing passive water transport in kidney's distal endothelial cells by stimulation of  $V_2$  receptors. The stimulation of the  $V_2$  receptors consists of the incorporation of the water channel protein aquaporin 2 (AQP2) into the lateral channel wall and the collecting coil.

The stimulation of  $V_2$  receptors by vasopressin stimulates adenylate cyclase and increases the cAMP concentration, which stimulates AQP2 phosphorylation via protein kinase A. This process, by changing the properties of aquaporin 2, allows it to interact with other proteins, thanks to which it can be incorporated into the tubule membrane.

It contributes to the increase of water reabsorption, increase of extracellular fluid and simultaneous increase of urine osmolarity and decrease of its volume.

This hormone also regulates the osmotic gradient by increasing cotransport of  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  in the thick portion of the arm ascending loop of Henle, increase the activity of urea transporters UT-A2 located in the straight vessels and shoulder descending loops of Henle and UT-A1 in the coil, which in turn leads to easier diffusion of urea.

As a result of affecting the  $V_{1A}$  and  $V_{1B}$  receptors, which stimulates the hydrolysis of phosphatidylinositol, it affects the concentration of  $\text{Ca}^{2+}$  ions. The process is related to the vasoconstriction effect of  $V_{1A}$  receptors. By stimulating these receptors, it strongly stimulates contraction of the smooth muscles in the blood vessels. With the help of these receptors it also affects the brain and spinal cord, where it acts as a neurotransmitter, as well as the liver by stimulating glycogenolysis. Activation of  $V_{1B}$  receptors by vasopressin and simultaneous secretion of corticotropin lead to an increase in the amount of ACTH released by the anterior pituitary lobe, resulting in an increased synthesis of steroid hormones in the adrenal cortex.

The other actions of vasopressin include inhibition of renin release and angiotensin production, increased sensitivity of the thirst system to osmotic stimuli, and smooth muscle contraction (mainly in the uterus and gastrointestinal tract when using high doses of the hormone) [5].

### **3. THE ROLE OF VASOPRESSIN IN A CENTRAL NERVOUS SYSTEM**

Vasopressin effect on the central nervous system manifests itself through the regulation of complex social behaviours, due to the presence in some regions of the brain, such as the hypothalamus, amygdala, hippocampal neurons and nerve endings releasing AVP [6]. One of the studies showed that increased levels of vasopressin in the prefrontal cortex and amygdala during acute stress affects the improvement of empathic behaviours [7].

It can also influence the change of social thresholds [8] and the processing of emotions by regulating the connections in the frontal orbital cortex [9]. Increased expression of vasopressin in the bed nucleus of the stria terminalis, paraventricular nucleus and supraoptic nucleus [10], may also contribute to the stimulation of aggression in men and its inhibition in women [11,12]. In one of the studies conducted in rats, behavioural changes were observed that were caused by the release of vasopressin in the relevant regions of the brain. Its release in areas of the brain unrelated to hormonal regulation may contribute to the occurrence of anxiety or depression [13].

The increase in  $V_{1A}$ R expression in the lateral septal nucleus in wild-type mice contributed to the small increase in anxiety behavior and changes associated with positive social opinions [14]. Administration of vasopressin may also result in the attenuation of neuronal reactions responding to negative social opinions. Significant involvement in this process shows lower activation of brain regions that are suspected of participating in mind theory, pain processing, and emotional identification of important visual cues in social perception [15].

Arginine vasopressin effect on the central nervous system may also be expressed through involvement in the control of memory processes and learning [16]. Studies on rats have shown a correlation between improvement of consolidation of olfactory information and specific recognition, and increased expression of vasopressin in the central nervous system [17].

AVP affects the improvement of social memory and social recognition also in people. Increased coding of positive and negative social information in male volunteers after nasal administration of arginine vasopressin has been shown [18].

Exposure to negative social factors causes vasopressin-regulated decrease in activity of the left temporoparietal junction responsible for social recognition, leading to easier categorisation of stimuli [19].

Current work is also focused on the participation of this peptide in the pathogenesis of various psychiatric disorders and the potential for its use in diagnosis and treatment.

#### **4. VASOPRESSIN IN MENTAL DISORDERS**

In animal studies, symptoms similar to the symptoms of schizophrenia have been shown to coexist with vasopressin deficiency [20]. Animal models also suggest that the behavioural disorders are accompanied by changes in acetylation on histone 3 lysine 9 (K9) in the region of hippocampus and prefrontal cortex, which may contribute to the impaired secretion of not only ADH, but also many other substances. The results of these tests gave the basis for further research on the hormonal stimulus in people suffering from mental disorders.

Previous studies with people in the field of neuroendocrinology of schizophrenia provide us with extensive data. Despite the fact that some investigations are limited by several factors, including the confusing influence of antipsychotics and methodological limitations, we can conclude that patients with schizophrenia seem to have rather clear endocrine profiles [21]. Particular attention should be given to the study of the possible effects of the posterior pituitary gland hormones [22].

Literature presents ample evidence that schizophrenic patients suffer from impaired water homeostasis as a result of pathological secretion of vasopressin but also aldosterone and atrial natriuretic peptide (ANP) [23,24]. One of the first studies investigating the level of vasopressin in the blood plasma of people with schizophrenia was conducted in 1989 by American researchers. They compared the level of ADH in schizophrenic patients and in healthy people. The researchers found that the average level of ADH in plasma is lower among schizophrenic patients than in the control group at comparable plasma osmolality values [25]. Similar research was carried out by Rubin et al. in 2014, in which the same conclusion was drawn. On this basis, it was considered that the reduction in the level of vasopressin may be an indicator of biological sensitivity in schizophrenia [26].

In the literature, we can also find several examples describing cases of symptoms of disturbed vasopressin management in people suffering from schizophrenia. Edoute et al. Described acute episode of schizophrenia, which was accompanied by the maximum dilution of urine, polydipsia and hyponatremia (100 mmol /l). The urinary flow rate was 10 ml /min [27].

Dubovský et al. presented a similar case of a patient who during the acute psychotic reaction showed syndrome of inappropriate antidiuretic hormone secretion (ADH). The syndrome resolved after the acute psychotic condition improved but returned during the second episode, only to resigned again with a remission of acute psychosis. It is therefore concluded that the acute psychotic episode caused the Schwartz-Bartter syndrom [28]. Ushnir K et al. described a case of schizophrenia with spontaneous water poisoning and diluted urine [29].

There are plenty of evidence for the disturbed economy of vasopressin co-occurring with schizophrenia in post-mortem research. One such study assessed the synthetic activity of vasopressin neurones in the back of the supraoptic nucleus. The materials consisted of hypothalamus from five patients with schizophrenia, who were treated with neuroleptics, and five matched controls from the Dutch brains bank, were fixed in formalin and embedded in paraffin.

The DSM-III or DSM-IV criteria were used for clinical diagnosis, while the histochemical markers used in the study of vasopressin synthase activity were: cell size, Golgi's apparatus size and the expression of mRNA of vasopressin and tyrosine hydroxylase by in situ hybridization. The results of morphometric evaluation and statistical analysis carried out in patients with schizophrenia indicated statistically significant differences of the markers in relation to the control group. On this basis, a suggestion of a suspected change in the activity of vasopressin neurones in the dorsolateral side of the supraoptic nucleus in schizophrenic patients treated with neuroleptics was proposed [30].

The above observations suggest a possible participation of vasopressin in the pathogenesis of schizophrenia. Social hormone arginine-vasopressin (AVP) modulate the social interactions and therefore may be involved in the pathogenesis of the disease. ADH metabolism may be altered in schizophrenia, but there are other possible causes of reduction of the levels of ADH in patients with schizophrenia for ex. reduced synthesis of ADH, expression of mRNA and translation [31].

One of the studies described a research to show the association of vasopressin genes with the occurrence of schizophrenia and the search for variants of genes causing disease in a large Arab-Israeli pedigree. In a previous study, the authors found evidence linking schizophrenia to chromosome 20p13, which contains genes encoding attractin (ATRN), pantothenate kinase 2 (PANK2), oxytocin (OXT) and arginine-vasopressin.

These genes in the described study were screened for mutation of individuals by means of intensive sequencing. Next, the frequency of occurrence of given variants of these genes was examined in all family members as well as in Arab-Israeli nuclear families and in the Jewish control samples. The possible functional role of these variants was also studied by studying their association with the expression of genes in the brain.

Seven genetic variants were identified in the OXT-AVP cluster, three of which were significantly related to the disease. Also, the 7-SNP haplotype was significantly associated with schizophrenia. Significant link between some variants in two samples from the general population was also found. Through the analysis of expression data, the existence of a possible functional role of two variants in the regulation of gene expression associated with the occurrence of schizophrenia was demonstrated [32].

## **5. THE ROLE OF VASOPRESSIN IN TREATMENT IN SCHIZOPHRENIA**

Role of neuropeptides in the normal development and function of the higher cortical processes together with their confirmed abnormalities in patients with schizophrenia have attracted more and more attention as the possibility of potentiation treatment for antipsychotic drugs in schizophrenia (Table 1).

**Table 1.** Characteristics of the reviewed research showing effects of vasopressin treatment in schizophrenia.

Researchers	Year	Study group	Testing time	Scales	Results
Bakharev VD. et al.	1984	47	3 months	Laboratory tests, PANSS	Improving emotional disorders, memory improvement, beneficial effect on apathetic-abulic manifestations
Iager AC. et al.	1986	10	3 months	PANSS	A small improvement in negative symptoms
Brambilla F. et al.	1989	10	40 days	Andreasen Scale	A significant improvement in negative symptoms
Hosseini SM. et al.	2014	40	8 weeks	PANSS	A significant improvement in negative symptoms
Geng CH. et al.	2017	259	12 weeks	PANSS, Wechsler-4	A significant improvement in negative symptoms. improving long-term memory, short-term memory, immediate memory, improve IQ

The first studies using vasopressin in psychiatric disorders were conducted in the nineties. Forty seven men suffering from paranoid schizophrenia alternating with paroxysmal attacks were treated with synthetic vasopressin. The therapeutic effect of the hormone has been confirmed by a complex of clinical, laboratory and pathophysiological techniques. Both objective test methods and subjective evaluation of the patients showed high efficacy of the drug, which was expressed in a clear psychoenergetic action, a beneficial effect on emotional disorders, improved memory and a beneficial effect on apathetic-abulic manifestations [33].

Iager and others studied patients with chronic schizophrenia. The patients completed a 3 month, double-blind, placebo-controlled study using a vasopressin analogue. There has been a slight improvement [34]. Three years later, a similar study was carried by Brambilla et al.

The work relied on treatment with vasopressin analogs of people suffering from schizophrenia. Six men and four women aged 28-63 diagnosed with schizophrenia (for at least six years) underwent the therapy. Patients received neuroleptic treatment and additionally first placebo for 20 days, followed by DDAVP for 20 days. Using a scale to test negative symptoms-

Andreasen Scale, it was postulated that after treatment with vasopressin there was a significant improvement in the negative symptomatology of schizophrenia [35].

Pioneering results of their research using AVP gave the basis for further work using nasal vasopressin. In 2014, Hosseini et al. carried out an assessment of the efficacy and safety of a nasal spray containing desmopressin, in addition to antipsychotic treatment. The aim of the study was to improve the negative symptoms of schizophrenia. Forty patients with diagnosed disease were randomly assigned to the DDAVP nasal spray group (at 20 µg / day) or to the placebo control group. All patients were in good general condition and additionally received a fixed dose of risperidone (5-6 mg). The follow-up lasted 8 weeks, during which every two weeks the participants were assessed using the PANSS- scale to assess the severity of negative and positive schizophrenia symptoms. The final results of the study clearly showed that patients using DDAVP showed significantly greater improvement in negative symptoms compared to the placebo group. In addition, no serious adverse drug reaction was observed [36].

Researchers also considered the effect of AVP on improving memory deficits, which are a symptom of patients with schizophrenia. Arginine-vasopressin (AVP) in the brain can improve learning and memory. Geng et al. conducted a multicenter, randomised, double-blind, controlled clinical trial evaluating the effects of a 12-week treatment with nasal vasopressin in patients with schizophrenia. 128 patients were in the study group and 131 were in control group. Before testing, during and after the study, patients were assessed for cognitive functions using the PANSS scale and the memory was examined using the Wechsler-4 scale. The results of the study showed that the group using AVP had significantly higher PANSS scores compared to the placebo group. The study group also achieved better results on the Wechsler-4 scale in the area of long-term, short-term and direct memory as well as IQ levels. These results were also maintained in 4.8 and in 12 weeks after treatment [37].

The study on rats conducted by T. Matsuoka studied the effect of the AVP analogue NC-1900 on social behaviour and locomotor activity in rats treated with MK-801, an NMDA antagonist receptor. Male rats were administered MK-801 or saline solution for 14 days.

Then, social behaviours and locomotor activity were measured 45 minutes after AVP analogue or saline injection together with the last MK-801 or a carrier. By specifying social interactions and measuring stereotypical behaviour and ataxia, it was determined that acute administration of NC-1900 caused a partially reversed hyperlocomotion induced by MK-801 and deficits in social interactions, whereas NC-1900 alone did not affect these behavioural changes in rats treated with saline for a long time.

The study suggested that the central AVP system may interact with glutamatergic and dopaminergic transmissions and points to the possible therapeutic interaction of arginine-vasopressin analogues with positive and negative symptoms of schizophrenia [38].

## **6. CONCLUSIONS**

These considerations lead to the conclusion that vasopressin, a neuropeptide hormone, which in the classical sense is discussed in terms of impact on the water balance of the body and blood pressure, also intrigued psychologists due to its participation in social interactions. Increasingly, it is also the area of interest of psychiatry, both in the context of its participation in the pathogenesis of schizophrenia and its potential use in the treatment of this disorder.

The use of products, which are analogs of vasopressin appear to be justified in the case of psychiatric disorders manifesting themselves through the clinical symptoms of social withdrawal, lack of need for social interaction or lack of satisfaction with such contacts (e.g. schizophrenia). Works on the role of vasopressin as the treatment of schizophrenia may prove to be important as the change in a certain way of thinking about the illness. In addition to previous research, which has focused attention of researchers in the last few decades, they bring a new stream of research on the neurotransmission system in the context of mental disorders.

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