

Review article

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VASOPRESSIN IN VASCULAR REGULATION AND WATER HOMEOSTASIS IN THE BRAIN

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It is well known that vasopressin participates in the regulation of the cardiovascular system, water electrolyte balance and many functions of the central nervous system. Receptors for vasopressin are widely distributed throughout the brain. They are present in neurons, in astrocytes and their perivascular processes, in endothelial and smooth muscle cells of blood vessels and in choroid plexus. Such a location suggests that vasopressin may participate in the regulation of vascular resistance in cerebral circulation and water homeostasis in the brain. Present review of the data published on this subject suggests that endogenous vasopressin is involved in brain pathology rather than in physiological regulations. Numerous studies have shown increased release of vasopressin and expression of vasopressin receptors in the brain following ischemia, trauma or subarachnoid hemorrhage in patients and in animal models of these diseases. Moreover, it has been demonstrated that antagonists of vasopressin V_{1a} receptors are able to alleviate brain edema and spastic changes in blood vessels after subarachnoid hemorrhage. Vasopressin is also implicated in brain edema and in impairment of cerebral vasculature in hypo-osmotic states. The discussed results suggest that vasopressin V_{1a} receptors antagonists may be a useful tool for the treatment of some states associated with cerebrovascular pathology.

Key words: vasopressin, brain edema, post-SAH vasospasm, hyponatremia, cerebral blood vessels

INTRODUCTION

Vasopressin (AVP) is a peptidergic hormone which functions in the brain both as neurotransmitter and neuromodulator (1). It is produced mainly in the

magnocellular neurons of the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei, is transported along their axons and released in the posterior pituitary to the systemic blood, as proposed by Bargmann and Scharrer (2). Since the time of their work numerous studies on the location of vasopressin producing and responding neurons were performed using immunohistochemistry and *in situ* hybridization. Most of these studies were made in rats. It has been demonstrated that in the rat brain many extrahypothalamic structures (the bed nucleus of the stria terminalis, the medial amygdala, nucleus of the locus coeruleus, hippocampus, choroid plexus), in addition to hypothalamus, are capable to synthesize vasopressin, and that vasopressin containing nerve endings are widely distributed throughout the brain and the spinal cord (3, 4).

Biological effects of vasopressin are mediated by three distinct membrane receptors (V_{1a} , V_{1b} and V_2) which are members of the family of G protein-coupled ones (5). In the brain the V_{1a} , known as a vascular receptor, is present in most of the cells. *In situ* hybridization studies localized this receptor in neurons, in astrocytes, in extra- and intraparenchymal blood vessels and in *choroid plexus* (6-8). The presence of V_{1b} receptor was reported in the *hypothalamus*, *amygdala*, *cerebellum*, and in the circumventricular organs (9). In contrast, V_2 receptor mRNA in the adult rat brain was found only in the cerebellum (10). Binding of vasopressin to either V_{1a} or V_{1b} receptor activates phospholipase C and metabolism of phosphatidylinositol diphosphate (11). This leads to the generation of inositol 1,4,5-triphosphate and diacylglycerol, the stimulation of protein kinase C, and the release of Ca^{2+} from endoplasmic reticulum.

It is generally recognized that AVP participates in the regulation of the cardiovascular system, and water-electrolyte balance of the organism as well as in many functions of the central nervous system. The presence of AVP receptors in blood vessels, including capillary endothelium, and in the choroidal tissue suggests that vasopressin may participate in the regulation of vascular resistance in cerebral circulation and in water homeostasis in the brain.

In the last 20 years numerous studies were published which, indeed, have demonstrated that AVP affects the tone of cerebral blood vessels, the permeability of cerebral capillaries to water and regulation of cell volume in the brain. Majority of them indicated the role of AVP in brain pathology. The present paper summarizes this work.

VASOPRESSIN AND VASCULAR REGULATION

Vasopressin is considered a potent vasoconstrictor in most regional arteries, arterioles and in the microcirculation with few exceptions (12). It has been demonstrated that exogenous vasopressin dilates cerebral, coronary and pulmonary vasculatures when administered in low, physiological doses (12). In the cerebral vasculature dilation was observed in isolated cerebral arterioles or

pial vasculature in different species (13-16). The effects were, however, not uniform. Generally, dilation in response to AVP was observed in large arteries and arterioles, whereas in small arterioles no response or constriction was reported. Suzuki *et al* (13) showed that AVP dilated canine basilar arteries while decreasing vertebral blood flow. Similar conclusion was drawn from the experiments of Faraci *et al.* (14) who used slightly different approach. In their experiments microvascular pressure was measured in the rat pial arteries and segmental vascular resistance was calculated. The results of this study showed that in response to AVP (40 mU/kg iv) the resistance of large arteries decreased, pial artery pressure increased and autoregulatory increase in small vessel resistance occurred. The dilation following vasopressin administration was V_{1a} receptor- and nitric oxide (NO)-dependent, since it was not observed when V_{1a} receptor antagonist or inhibitor of NO synthase was administered prior to vasopressin (15, 16). According to Katusic's study on isolated canine arteries, AVP caused endothelium-dependent relaxation in the brain stem arteries but not in the branches of the middle cerebral artery (16). We consistently observe NO-dependent relaxation of the intact isolated middle cerebral artery of the rat in response to low doses of AVP (unpublished observation). Thus, the dilation of cerebral blood vessels to AVP seem to be both species- and region-dependent. In support of this statement are the studies which show that pial arteries of the cat (17) and human cerebral arteries (18) do not dilate but constrict during exposure to AVP. Interesting observation was published by Fernandez *et al.* (19) who measured changes in the cerebral blood flow after administration of vasopressin in the goat. Although they reported an increase in cerebrovascular resistance after AVP they also found that this effect was significantly augmented after the inhibition of the synthesis of NO. The latter result speaks in favor of the attenuation of AVP-dependent vasoconstriction by NO.

We have found that administration of vasopressin (0.5 IU Pitressin) into the internal carotid artery in the rat increases cerebral blood flow concomitantly with the increase of oxygen utilization. This effect was mimicked by vasopressin analog (dVDVP) that binds to V_2 vasopressin receptors and was blunted by the administration of the antagonist of these receptors (20). This observation suggested that dilation of cerebral blood vessels after AVP administration was indirect and was due to the increase of brain metabolism. Since the dose of AVP in these experiments was rather high (comparable to the maximal concentration observed in plasma during experimental Cushing response) the observed effect was not a physiological one. The physiological significance of all the data discussed so far requires more consistent study.

The demonstration of the role of vasopressin in cerebrovascular pathology was more convincing (21, 22). These studies have shown that the vasoconstricting effect of AVP was significantly enhanced in the spastic basilar artery after subarachnoid hemorrhage in the rat and that this vasospasm was alleviated by the pretreatment with V_1 receptor antagonist.

Another study which points to the role of vasopressin in the cerebral vascular pathology concerns hyponatremia which often develops in neurosurgical patients after brain trauma, subarachnoid hemorrhage or after surgery (23). In our studies on the isolated middle cerebral artery (MCA) of the rat, addition of AVP to the hyponatremic environment of the vessel resulted in its constriction, although during hyponatremia without vasopressin MCA dilated in hyponatremic medium (24). The dilation was not present after removal of endothelium, or pretreatment with NO synthesis inhibitor. The constriction after administration of AVP was blocked by V_{1a} receptor antagonist or nonselective antagonist of endothelin-1 (ET-1) receptor. This results suggest that under conditions of hyponatremia vasopressin stimulates endothelium to the release of ET-1 and not NO. In support of such a possibility are the results of the studies published by Spatz *et al.* (25) and Imai *et al.* (26) that vasopressin is capable to stimulate the production and release of ET-1 from cerebrovascular endothelium.

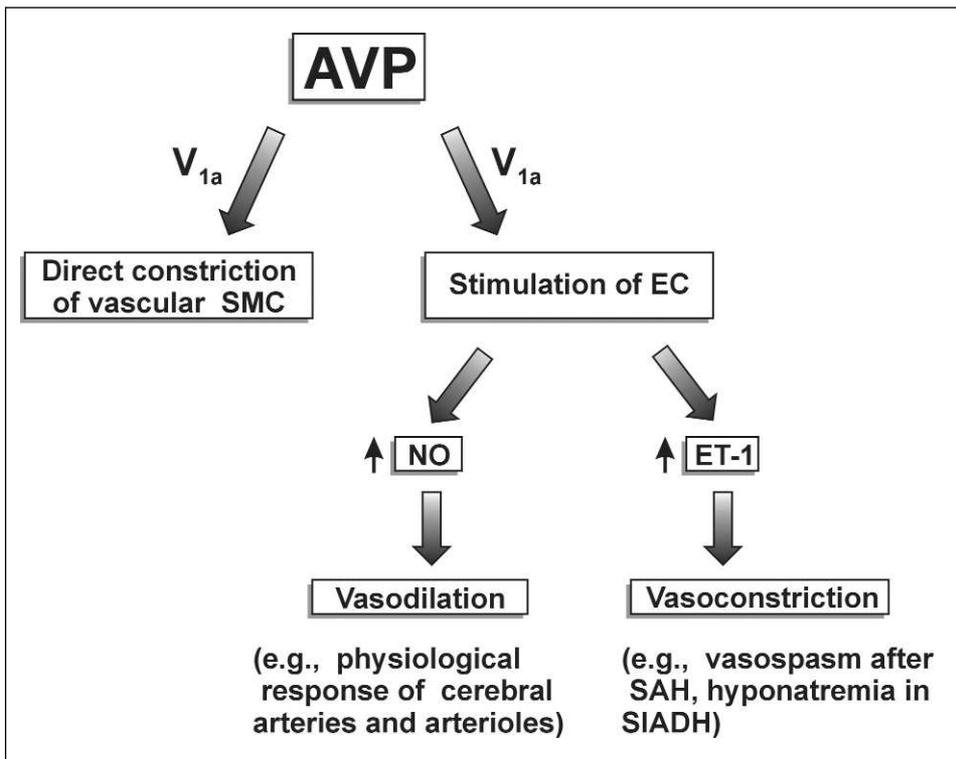


Fig. 1. The effects of vasopressin (AVP) on cerebral blood vessels (details in the text).

Abbreviations: SMC - smooth muscle cells, EC - endothelium, NO - nitric oxide, ET-1 - endothelin-1, SIADH – syndrome of inappropriate secretion of vasopressin..

The conclusion of the studies discussed in this section is that under physiological conditions vasopressin dilates larger cerebral arteries and larger arterioles in NO-dependent way but probably does not contribute significantly to the regulation of blood supply to the brain (*Fig. 1*). However, following subarachnoid hemorrhage or during hyponatremia associated with increased concentration of AVP in the plasma (as during the symptom of inappropriate secretion of vasopressin), vasopressin may result in vasoconstriction.

VASOPRESSIN AND ION/WATER HOMEOSTASIS

Few studies have demonstrated that vasopressin participates in the physiological regulation of ion/water homeostasis in the brain (27-29). Recent data published by Nierman *et al.*, (30) suggest that vasopressin and V_{1a} receptor agonists facilitate movement of water to the astrocytes during spacial buffering of K^+ . These study showed that evoked neuronal activity generated a radial water flux in the neocortex which was facilitated by vasopressin in V_{1a} receptor-dependent manner. The antagonist of V_{1a} receptor was also able to reduce this flux in the absence of vasopressin. The conclusion of this study was that vasopressin and V_{1a} receptors play a crucial role in the regulation of brain water and ion homeostasis, most probably by modulating aquaporin-mediated water flux through astrocyte plasma membranes. Although these results are very interesting, further studies are needed to disclose exact mechanism of this phenomenon.

Based on the data on the stimulatory effect of vasopressin on water transfer through the blood brain barrier (BBB) many experimental studies were performed

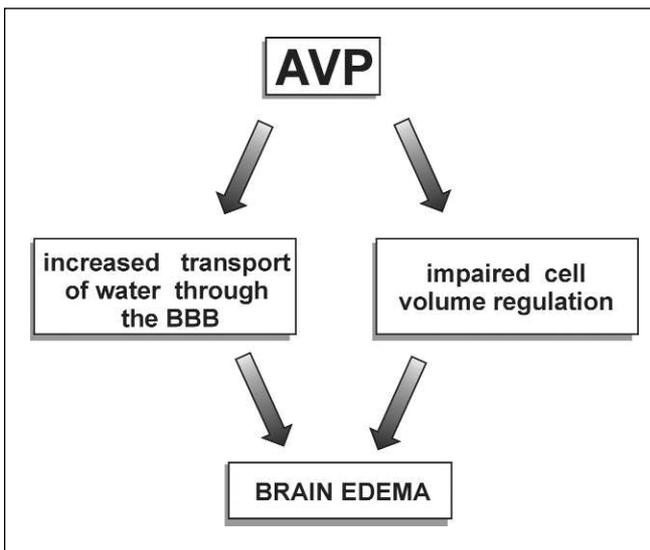


Fig. 2. The effect of vasopressin (AVP) on water homeostasis in the brain (details in the text). Abbreviation BBB demates blood - brain barrier.

to find out whether inhibition of vasopressin synthesis ameliorates brain edema following stroke, subarachnoid hemorrhage or brain trauma. (31-37). Possible participation of vasopressin in brain pathology following ischemia is supported by the observations of the increased expression of mRNA for vasopressin and increased plasma concentration of AVP following experimental ischemia (38, 39). The increased AVP plasma levels have been reported also in stroke patients (40).

It has been shown that administration of AVP exacerbates acute ischemic brain edema (32; 37) and this exacerbation can be reduced by the inhibitor of the release of AVP (37). Moreover, attenuation of brain swelling was observed following administration of V_{1a} , but not V_2 receptor, antagonists (31, 33, 34, 37).

Another disease in which vasopressin seems to participate deteriorating the recovery of neurosurgical patients is, above mentioned, hyponatremia (23). Results obtained by Arieff *et al.* (41) and Kozniewska *et al.* (42) indicate that brain cells adaptation to hyponatremia is impeded by vasopressin. The difficulty of cells to adapt in the presence of vasopressin is supported by the data published by others that vasopressin impairs ionic mechanisms responsible for the regulation of cell volume during hyponatremia (i.e., after osmotic cell swelling) (43, 44, 45).

Taken together, the studies discussed in this section suggest that vasopressin is one of the factors participating in vasogenic edema and cellular swelling after stroke and during hyponatremia (*Fig. 2*).

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