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Another Side of the Antidiuretic Hormone, Vasopressin: Its Role in Stress Regulation

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ABSTRACT: Vasopressin (AVP) is an ancient molecule of the salt-water homeostasis. On the other hand, in the brain AVP can be found in many regions, where it has a prominent role in the regulation of stress and stress related diseases, too. During acute stress AVP regulates the adrenocorticotropin secretion in a time and stressor specific manner. Its role seems to be especially critical during the perinatal period. Despite earlier theories, during chronic stress the role of AVP has never been highlighted. AVP seems to be also responsible for our mood. Its high level is accompanied by higher level of anxiety and depression. Pharmacological intervention of the AVP secretion could influence not only the salt-water homeostasis, but might have strong impact on our stress state and behaviour.

Key words: Vasopressin, Stress, ACTH, Corticosterone, Anxiety, Depression

Introduction

Arginine vasopressin (AVP), also known as antidiuretic hormone, is a peptide hormone. Its main source in the blood is the neuronal lobe of the hypophysis (NL). The hormones of the NL are not synthesised in the gland itself, but in the magnocellular cells of the supraopticus (SON) and paraventricular (PVN) hypothalamic nuclei. The brain also contains several populations of AVP containing smaller, parvocellular neurons whose projections remain within the brain (1).

Role of vasopressin in physiological processes

The fundamental function of AVP is to conserve body water when body is threatened with dehydration. Through V2 receptors in the renal collecting duct, AVP induces translocation of aquaporin-2 water channels to the apical plasma membrane, allowing water resorption. Through V1a receptors AVP can cause contraction of almost any smooth muscle (2). Due to vasoconstriction AVP increases the blood pressure. This effect appears small in healthy individuals; however it becomes important during hypovolemic shock.

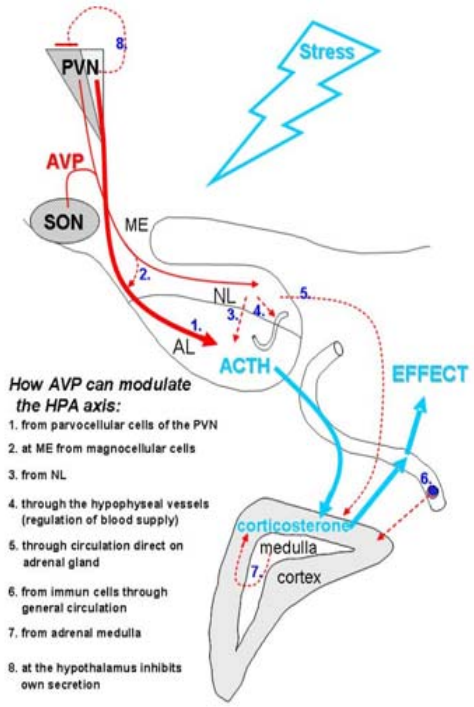
The behavior of an animal is influenced by a central circadian clock in the suprachiasmatic nucleus. AVP is the only substance to date that has been shown to be released in a circadian rhythm to the cerebrospinal fluid. AVP is important in the regulation of social interactions (3). In knockout (KO) mice a prominent role of V1b receptors were found in agression. In respect to social bonds, monogamous voles have less AVP in their lateral septum and more in their amygdala compared to non-monogamous voles. There is a clear correlation of AVP and parental behavior of voles as well. With strong connection to its role in social interactions the AVP has a role in social memory, too. AVP in the olfactory bulb plays a prominent role in the olfactory memory formation, thereby influencing social recognition. Several studies indicate a general beneficial effect of AVP administration on spatial memory, too.

Stress

Maintenance of the homeostasis in a constantly changing environment is a fundamental process of life. Stress is defined as anything that throws the body out of homeostatic balance. Already Hans Selye, the father of stress concept discovered that the basis of the adaptation is the hypothalamo-pituitary-adrenal (HPA) axis (4).

HPA axis and vasopressin

The neurons of the magnocellular PVN and SON project through the median eminence (ME) to the NL being involved in the water balance. This AVP pool might have an effect on the regulation of the adrenocorticotropin (ACTH) secretion as well, especially during osmotic stimuli (5) (Fig.1). The more medially situated parvocellular PVN contains AVP in colocalization with corticotropin-releasing hormone (CRH) and through a release into the portal vasculature at the ME regulate ACTH secretion (6). AVP may cause ACTH secretion through mobilization of NL CRH and/or AVP might have a local action on the control of anterior lobe (AL) microcirculation as well (7). ACTH, through the systemic circulation, induces the secretion of glucocorticoids (in rodents mainly corticosterone) from the adrenal cortex. Regulation of corticosterone secretion is critical for life and is necessary for the mammalian stress response. AVP reaches the adrenal gland through general circulation and also from the adrenal medulla, thereby having a direct impact on corticosterone secretion. AVP may also modulate responses to stress by expression and release from immune cells (8).



Acute stress

Several animal studies support the role of AVP in acute HPA axis regulation. Intraventricular administration of AVP antiserum blocked the release of ACTH induced by electrical stimulation of the PVN. Additionally the pretreatment of rats with AVP antiserum inhibited the ACTH response to restraint, formalin and ether stress without affecting the resting levels (9). The resting ACTH and corticosterone

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plasma levels of the natural AVP KO rat line, the Brattleboro rats appear to be normal, too. Their HPA response to acute stress was highly stressor specific with at least a tendency of reduced ACTH elevations in most case. Two Wistar rat lines, selectively bred for high- (HAB) and low-anxiety-related behavior (LAB) in the elevated plus maze (EPM) test were described with lower AVP immunoreactivity and AVP mRNA content in the PVN of LAB rats (3). The ACTH elevation was diminished in LAB rats after EPM.

AVP may influence the HPA axis through V1b receptors located mainly in the AL. The lack of V1b receptor did not influence the resting ACTH and corticosterone levels. Restraint or aggressive contact-induced secretion of ACTH and corticosterone was also similar in wild type and V1bR KO mice, but the hypoglycemia-, lipopolysaccharide-, forced swim- and ethanol-intoxication-induced elevations was significantly diminished. The selective, nonpeptide V1b receptor antagonist (SSR149415) was able to diminish the restraint-induced ACTH increase by 50% and inhibited the response to ether exposure but failed to inhibit the HPA axis during forced swimming (FS).

Taken together AVP participates in acute stress-induced HPA axis regulation, although the effect of AVP is limited and might depend upon the situation/test (stress-dependent role of AVP). AVP might be responsible for the recovery of the corticosterone secretion to the basal level after acute stimulation (time-dependent role of AVP) (10).

Chronic stress

Enhanced release of AVP during chronic stress and the relative resistance to feedback inhibition of ACTH release stimulated by AVP has been proposed to explain how chronic stressful stimulation results in steadily high adrenocortical hormone levels (6).

Previous data with AVP-deficient Brattleboro rats suggested that the lack of AVP did not affect the development of the chronic hyperactivity of the HPA-axis during 2 weeks repeated restraint, strepozotocin induced diabetes mellitus or chronic morphine treatment (11). The prolonged (5 weeks) chronic mild stress-induced HPA axis activation was not affected by the lack of AVP in Brattleboro rats, too.

Moreover, there were no differences in the HPA axis activation of V1b receptor KO and wild type mice after chronic restraint (9). Recent studies in repeatedly restrained rats show only minor effects of SSR149415 on ACTH responses to a novel stress. The non-selective V1 antagonist was unable to inhibit ACTH responses to hypertonic saline injection in repeatedly stressed rats, too.

Taken together in the absence of AVP ACTH secretion is sufficient to elicit full adrenal glucocorticoid responses. In addition, AVP does not mediate the hyperresponsiveness of ACTH responses to a novel stress.

Perinatal period

In rats the HPA-axis is already functional in late gestation. However, plasma levels decrease dramatically during the first two postnatal days and remain low until postnatal day 14 (12). During this period the response of the HPA-axis to stressful stimuli is markedly reduced (13). It was assumed that the diminished production and/or transport of hypothalamic secretagogues may also decrease corticosterone stress responses. Indeed, the glucocorticoid regulation of hypothalamic CRH gene expression is not mature in the stress hyporesponsive period. In contrast, the regulation of hypothalamic AVP gene expression matures very early (14). Passive immunization to AVP in 8-day-old rats prevented the hypoglycemia-induced ACTH-rise without affecting the basal levels, while the CRH immunization was ineffective. One can hypothesize that the involvement of AVP is stressor specific. However, this assumption is unlikely, as AVP-deficiency in Brattleboro rat pups abolished the ACTH response to widely different stressors (15). The data from genetic models were also repeated by SSR149415 with the same results. An unexpected finding of these experiments were the dissociation of the ACTH and corticosterone secretion, as AVP-deficiency abolished only the stressor-induced ACTH enhancement, but the serum corticosterone elevations remained intact.

We can conclude that AVP is the main regulator of the ACTH secretion during the perinatal period. However, ACTH rise does not precede the corticosterone elevations.

Stress related disorders and vasopressin

Anxiety and depression are behavioral states associated with stress. Overactivation of the HPA axis is the most consistently described biological abnormality in depression (16). Patient with major depression have significantly elevated plasma and hypothalamic AVP levels compared to healthy controls.

The widely used test of depression, the FS induces a significant increase in AVP release in both the SON and PVN and also in the septum and amygdala (3). The lack of AVP in Brattleboro rats resulted in a less anxious state on the EPM and a less depressive state in the FS (2, 3). LAB rats, selected upon their behavior on the EPM test, show similar behavior profile and AVP “deficiency” to Brattleboro rats further supporting the role of AVP in anxiety and depression. Administration of V1a receptor antagonist decreases the anxiety- and depressive-like behavior in HAB rats. Male V1a receptor KO mice display significantly less anxiety-related behavior than wildtype on a variety of tasks. Interestingly V1b receptor KO mice do not have an anxiolitic phenotype.

The presented results confirmed the strong correlation between AVP and anxiety and depressive-like behaviors in animal models. The fact that V1b antagonist is effective even after hypophysectomy suggest a separation between HPA axis regulation and behavior.

Conclusion

During the latest decades it turned out that AVP has a much broader effect than just to regulate the salt-water homeostasis. Based upon the results presented above AVP is a key regulator of the stress- axis (Fig.1) and has a strong impact on the stress-related behavior, as well. Nowadays AVP agonists and antagonists are widely used in clinical praxis from resuscitation till the treatment of hyponatremia, heamorrhagic shock etc (17). We should be aware that these pharmacological interventions could influence not only the salt-water homeostasis, but might have strong impact on our stress state and behaviour.

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