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Review

The vasopressin system — From antidiuresis to psychopathology

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Abstract

Vasopressin is a neuropeptide with multiple functions. In addition to its predominantly antidiuretic action after peripheral secretion from the posterior pituitary, it seems to fulfill – together with its receptor subtypes – all requirements for a neuropeptide system critically involved in higher brain functions, including cognitive abilities and emotionality. Following somatodendritic and axonal release in distinct brain areas, vasopressin acts as a neuromodulator and neurotransmitter in multiple and varying modes of interneuronal communication. Accordingly, changes in vasopressin expression and release patterns may have wide-spread consequences. As shown in mice, rats, voles, and humans, central vasopressin release along a continuum may be beneficial to the individual, serving to adjust physiology and behavior in stressful scenarios, possibly at the potential expense of increasing susceptibility to disease. Indeed, if over-expressed and over-released, it may contribute to hyper-anxiety and depression-like behaviors. A vasopressin deficit, in turn, may cause signs of both diabetes insipidus and total hypo-anxiety. The identification of genetic polymorphisms underlying these phenomena does not only explain individual variation in social memory and emotionality, but also help to characterize potential targets for therapeutic interventions. The capability of both responding to stressful stimuli and mediating genetic polymorphisms makes the vasopressin system a key mediator for converging (i.e., environmentally and genetically driven) behavioral regulation.

Keywords: Vasopressin; Diabetes insipidus; Social memory; Anxiety; HAB; Polymorphism

Contents

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1. The vasopressin system

The nonapeptide vasopressin, also known as antidiuretic hormone, is mainly synthesized in subregions of the hypothalamus and has primarily antidiuretic effects. Though already chemically described by Du Vigneaud et al. in 1953, it was not until the last three decades that it was additionally identified as a neuropeptide produced in the brain and acting on brain functions, capable of influencing a wide variety of behavioral traits (De Wied et al., 1993; Landgraf and Neumann, 2004). Whereas some of the central effects occur in parallel with its peripheral action as a hormone (e.g. thirst and maintenance of water balance), vasopressin is also accountable for the regulation of higher brain functions such as learning/memory and emotionality, which are primarily independent of its hormonal effects (Fig. 1).

Evolutionarily, vasopressin derives, like oxytocin, from vasotocin, prevailing in non-mammals (Acher and Chauvet, 1988). In humans, the vasopressin gene is located on the distal part of the short arm of chromosome 20 (20p13), in rats it is found on chromosome 3 (3q41), and in mice on chromosome 2 (2q73) (http://www.ncbi.nlm.nih.gov/). The vasopressin precursor is encoded in three exons, with vasopressin and the N-terminal region of neurophysin II being found on the first exon, the central region of neurophysin II on the second exon, and the C-terminal region of neurophysin II and the glycoprotein copeptin on the third exon (Land et al., 1982).

Cleavage of vasopressin from its prepropeptide is commenced by co-translational translocation into the cisternae of the rough endoplasmic reticulum, facilitated by the signal peptide. There, the signal peptide becomes separated, glycosylation of the glycoprotein is commenced, and intramolecular disulfide bonds are formed. The conversion of the propeptide into biologically active vasopressin is further accomplished in the Golgi apparatus, with the components being sorted into large dense-core vesicles. Finally, the peptides are cleaved and processed by multiple posttranslational modifications in the vesicles during their transport to the sites of release (Christensen and Rittig, 2006). Yet, no physiological roles for neurophysin or the glycoprotein have been identified.

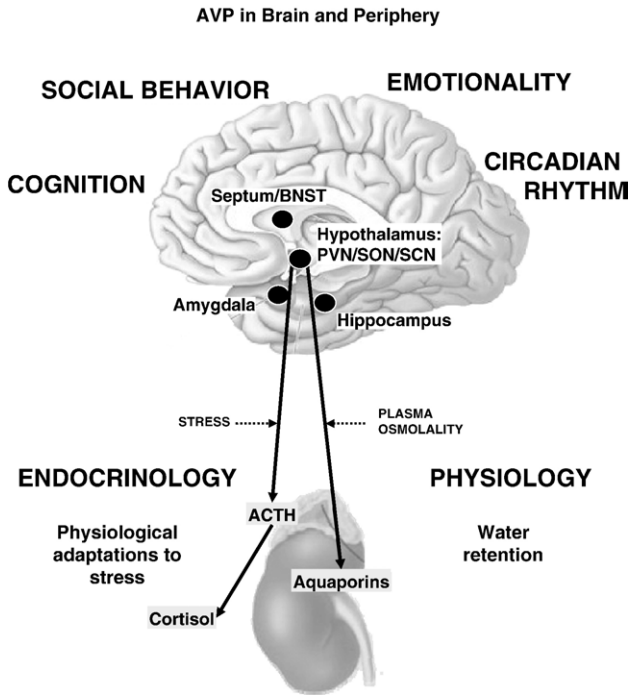

Fig. 1. Vasopressin in brain and periphery. Key behaviors mediated by vasopressin after central release within the brain and main body functions of vasopressin after secretion into the systemic circulation are indicated. BNST bed nucleus of the stria terminalis, PVN paraventricular nucleus, SON supraoptic nucleus, SCN suprachiasmatic nucleus, ACTH corticotropin.

In the hypothalamus, vasopressin is mainly synthesized in the magno- and parvocellular neurons of the paraventricular and supraoptic nuclei. Upon osmotic stress, vasopressin originating from magnocellular projections terminating in the posterior pituitary is secreted into the blood circulation as a neurohormone, forming together with oxytocin the hypothalamic–neurohypophysial axis. Vasopressin from the parvocellular part of the paraventricular nucleus is released along the hypothalamic–pituitary-adrenal (HPA) axis to trigger under stress, synergistically with the corticotropin-releasing hormone (CRH), the secretion of corticotropin (ACTH) from the anterior pituitary and finally corticosterone/cortisol from the adrenal glands (Engelmann et al., 2004). In addition, vasopressinergic fibers project from the hypothalamus to subregions of the hippocampus, septum, amygdala, and brainstem areas, where vasopressin is likely to serve as a neurotransmitter (Buijs et al., 1991). Moreover, particularly magnocellular hypothalamic neurons release vasopressin from their dendrites and somata. This mode of release and interneuronal communication includes subsequent diffusion through the brain's extracellular fluid, allowing vasopressin molecules to act as neuromodulators on receptors at some distance from their site of release. In this context, exposure to calcium mobilizers has been shown to prime the releasable pool of vasopressin in the dendrites, so that release can subsequently be evoked by depolarization-dependent activation. Interestingly, vasopressin itself appeared to be effective in inducing its dendritic release, but ineffective in producing long-lasting priming (Ludwig et al., 2005). Co-existence with classical neurotransmitters does not seem to exist in vasopressinergic paraventricular nucleus neurons, while co-expression with other neuropeptides, including oxytocin, CRH, and galanin was shown (Hokfelt et al., 2000). The latter was described to be co-expressed with vasopressin, but differentially routed to dendritic and axonal targets (Landry et al., 2003).

The bed nucleus of the stria terminalis and of the medial amygdala were reported to be the two major extrahypothalamic sources of vasopressin, showing dense vasopressinergic immunoreactivity (Hallbeck et al., 1999). The bed nucleus of the stria terminalis projects, inter alia, to the lateral septum, amygdaloid areas, the lateral habenula, and the locus coeruleus, while the medial amygdala primarily projects to the lateral septum and the ventral hypothalamus. Both regions and their projections have been described as sexually dimorphic, with males having denser vasopressin immunoreactivity and projections than females (De Vries and Panzica, 2006). The same holds true for the medial preoptic area, where gender differences were found, but with