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Review

Overview of cellular electrophysiological actions of vasopressin

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Abstract

The nonapeptide vasopressin acts both as a hormone and as a neurotransmitter/neuromodulator. As a hormone, its target organs include kidney, blood vessels, liver, platelets and anterior pituitary. As a neurotransmitter/neuromodulator, vasopressin plays a role in autonomic functions, such as cardiovascular regulation and temperature regulation and is involved in complex behavioral and cognitive functions, such as sexual behavior, pair-bond formation and social recognition. At the neuronal level, vasopressin acts by enhancing membrane excitability and by modulating synaptic transmission. The present review will focus on the electrophysiological effects of vasopressin at the cellular level. A large proportion of the experiments summarized here have been performed in *in vitro* systems, especially in brain and spinal cord slices of the rat. Vasopressin exerts a powerful excitatory action on motoneurons of young rats and mice. It acts by generating a cationic inward current and/or by reducing a potassium conductance. In addition, vasopressin enhances the inhibitory synaptic input to motoneurons. By virtue of these actions, vasopressin may regulate the functioning of neuronal networks involved in motor control. In the amygdala, vasopressin can directly excite a subpopulation of neurons, whereas oxytocin, a related neuropeptide, can indirectly inhibit these same neurons. In the lateral septum, vasopressin exerts a similar dual action: it excites directly a neuronal subpopulation, but causes indirect inhibition of virtually all lateral septal neurons. The actions of vasopressin in the amygdala and lateral septum may represent at least part of the neuronal substrate by which vasopressin influences fear and anxiety-related behavior and social recognition, respectively. Central vasopressin can modulate cardiovascular parameters by causing excitation of spinal sympathetic preganglionic neurons, by increasing the inhibitory input to cardiac parasympathetic neurons in the nucleus ambiguus, by depressing the excitatory input to parabrachial neurons, or by inhibiting glutamate release at solitary tract axon terminals. By acting in or near the hypothalamic supraoptic nucleus, vasopressin can influence magnocellular neuron activity, suggesting that the peptide may exert some control on its own release at neurohypophyseal axon terminals. The central actions of vasopressin are mainly mediated by receptors of the V_{1A} type, although recent studies have also reported the presence of vasopressin V_{1B} receptors in the brain. Major unsolved problems are: (*i*) what is the transduction pathway activated following stimulation of central vasopressin V_{1A} receptors? (*ii*) What is the precise nature of the cation channels and/or potassium channels operated by vasopressin? (*iii*) Does vasopressin, by virtue of its second messenger(s), interfere with other neurotransmitter/neuromodulator systems? In recent years, information concerning the mechanism of action of vasopressin at the neuronal level and its possible role and function at the whole-animal level has been accumulating. Translation of peptide actions at the cellular level into autonomic, behavioral and cognitive effects requires an intermediate level of integration, i.e. the level of neuronal circuitry. Here, detailed information is lacking. Further progress will probably require the introduction of new techniques, such as targeted *in vivo* whole-cell recording, large-scale recordings from neuronal ensembles or *in vivo* imaging in small animals.

Keywords: Autonomic nervous system; Amygdala; Hypothalamus; Lateral septum; Motoneurons; Oxytocin; Second messenger; Whole-cell recording

Contents

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1. Introduction

The nonapeptide vasopressin acts both as a hormone and as a neuromodulator. As a hormone, its target organs include kidney, blood vessels, liver, platelets and anterior pituitary. In peripheral cells, vasopressin binds to three distinct receptors: (*i*) vasopressin V_{1A} receptors, which trigger phospholipase-Cβ (PLCβ) activation and calcium mobilization, and are present in smooth muscle, liver and platelets. (*ii*) vasopressin V_{1B} receptors, which are also coupled to PLCβ and are found in the anterior pituitary. (*iii*) vasopressin V_2 receptors, which are coupled to adenylyl cyclase, and are present in the kidney (Barberis et al., 1998; Birnbaumer, 2000; Schoneberg et al., 1998; Thibonnier et al., 1998). Although with somewhat less potency, vasopressin can also bind to oxytocin receptors. Peripheral oxytocin receptors, present in the uterus and in the mammary gland, are coupled to a PLCβ (Arnaudeau et al., 1994; Ku et al., 1995; Phaneuf et al., 1995, 1996).

In the brain, vasopressin exerts its effects mainly by binding to vasopressin V_{1A} receptors (Barberis and Tribollet, 1996; Raggenbass, 2001; Tribollet, 1992). Recently, the presence of vasopressin V_{1B} receptors in some central structures has also been reported (Hernando et al., 2001; Lolait et al., 1995; Stemmelin et al., 2005; Vaccari et al., 1998; Young et al., 2006). Central vasopressin plays a role in autonomic functions, such as cardiovascular regulation (Toba et al., 1998), temperature regulation (Roth et al., 2004) and neocortical water-flux modulation (Niermann et al., 2001) and is involved in complex behavioral and cognitive functions, such as sexual behavior (Smock et al., 1998), memory processes (Alescio-Lautier et al., 2000), pair-bond formation (Lim et al., 2004; Young et al., 1999; Young and Wang, 2004), fatherhood behavior (Kozorovitskiy et al., 2006), anxiety and depression (Bielsky et al., 2004; Holmes et al., 2003; Landgraf, 2005) and social recognition (Bielsky et al., 2004, 2005; Keverne and Curley, 2004; Winslow and Insel, 2004).

The present review will focus on the electrophysiological effects of vasopressin at the neuronal level. A large proportion of the experiments summarized here have been performed in *in vitro* systems, especially in brain and spinal cord slices of the rat. Data published up to about 2000 have been previously reviewed (Raggenbass, 2001), and will not re-reviewed here in their entirety.

2. Vasopressin as an activator of motoneurons

A pioneering study showed that vasopressin could directly enhance the excitability of spinal motoneurons (Suzue et al., 1981). Since then, the action of vasopressin on motoneurons has probably become the most thoroughly studied and best characterized effect of the peptide at the cellular level. During development, vasopressin V_{1A} receptors are abundantly expressed in brainstem and spinal motor nuclei (Barberis and Tribollet, 1996; Liu et al., 2003; Tribollet et al., 1991; Tribollet, 1992). By binding to these receptors, vasopressin exerts a powerful excitatory action on motoneurons of young rats and mice (Alberi et al., 1996; Liu et al., 2003; Ogier et al., 2006; Oz et al., 2001; Palouzier-Paulignan et al., 1994; Raggenbass et al., 1991; Rekling et al., 2000). In facial motoneurons, vasopressin acted by generating a sustained cationic inward current, which was tetrodotoxin-insensitive, voltage gated and modulated by extracellular Ca^{2+} (Alberi et al., 1993; Delmas et al., 1997; Raggenbass et al., 1991). In hypoglossal motoneurons, the vasopressin-evoked current persisted in the presence of blockade of potassium channels, and reversed in polarity around −15 mV, again suggesting the involvement of a cation conductance (Palouzier-Paulignan et al., 1994). By contrast, in spinal motoneurons located at the thoracolumbar level, the vasopressin-induced inward current appeared to arise predominantly through reduction of a potassium conductance (Oz et al., 2001). In pudendal motoneurons, located in the caudal lumbar spinal cord and involved in sexual and eliminative functions, multiple mechanisms were evidenced (Fig. 1). In some motoneurons, vasopressin acted by enhancing a nonselective cation conductance, whereas in some others it probably exerted a dual effect, enhancing a cation conductance and, concomitantly, suppressing a resting K^+ conductance (Ogier et al., 2006). Thus, the vasopressin-regulated conductances appear to vary among motoneuron types. The results described above, however, were obtained in young animals. It has been suggested that vasopressin-operated conductances may be developmentally regulated (Kolaj and Renaud, 1998). To fully investigate this issue, recordings from adult motoneurons would be required. Unfortunately, for reasons that are not entirely clear, adult mammalian motoneurons survive poorly *in vitro*. Despite various attempts, such as dissection in Na^+-free medium (Aghajanian and Rasmussen, 1989), co-culture with muscle cells (Gueritaud and Seyfritz, 1992), or adjunction of neurotrophic factors to culture media (Hanson et al., 1998), no efficient technology allowing the systematic survival of adult motoneurons *in vitro* is presently available.

Several important unsolved problems remain. (*i*) What is the exact nature of the cation channel and of the resting K^+ channel which are activated, respectively suppressed, following vasopressin binding to vasopressin V_{1A} receptors? (*ii*) What is the intracellular signaling pathway responsible for the excitatory action of vasopressin on motoneurons?