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Vasopressin: Behavioral roles of an ‘‘original’’ neuropeptide

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Abstract

Vasopressin (Avp) is mainly synthesized in the magnocellular cells of the hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) whose axons project to the posterior pituitary. Avp is then released into the blood stream upon appropriate stimulation (e.g., hemorrhage or dehydration) to act at the kidneys and blood vessels. The brain also contains several populations of smaller, parvocellular neurons whose projections remain within the brain. These populations are located within the PVN, bed nucleus of the stria terminalis (BNST), medial amygdala (MeA) and suprachiasmatic nucleus (SCN).

Since the 1950s, research examining the roles of Avp in the brain and periphery has intensified. The development of specific agonists and antagonists for Avp receptors has allowed for a better elucidation of its contributions to physiology and behavior. Anatomical, pharmacological and transgenic, including ‘‘knockout,’’ animal studies have implicated Avp in the regulation of various social behaviors across species.

Avp plays a prominent role in the regulation of aggression, generally of facilitating or promoting it. Affiliation and certain aspects of pair-bonding are also influenced by Avp. Memory, one of the first brain functions of Avp that was investigated, has been implicated especially strongly in social recognition. The roles of Avp in stress, anxiety, and depressive states are areas of active exploration. In this review, we concentrate on the scientific progress that has been made in understanding the role of Avp in regulating these and other behaviors across species. We also discuss the implications for human behavior.

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Abbreviations: ACTH, adrenocorticotropic hormone; AH, anterior hypothalamus; Avp, arginine vasopressin; ASD, autism spectrum disorders; BNST, bed nucleus of the stria terminalis; CNS, central nervous system; CSF, cerebrospinal fluid; Crh, corticotrophin releasing hormone; DDAVP, desmopressin; DEX, dexamethasone; HPA, hypothalamic–pituitary–adrenal; ir, immunoreactive; IGR, intergenic region; i.c.v., intracerebroventricular; i.p., intraperitoneal; KO, knockout, −/−; LS, lateral septum; MeA, medial amygdala; MPOA-AH, medial preoptic-anterior hypothalamic area; Oxt, oxytocin; Oxtr, oxytocin receptor; PVN, paraventricular nucleus; 5-HT, serotonin; SNPs, single nucleotide polymorphisms; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; Avpr1a, vasopressin 1a receptor; Avpr1b, vasopressin 1b receptor; Avpr2, vasopressin 2 receptor.

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1. Introduction

The neurohypophysial hormone arginine vasopressin (Avp) was originally detected by Oliver and Schäfer (1895) who demonstrated that extracts of the pituitary altered blood pressure. Subsequently, the antidiuretic properties of Avp were discovered (Farini, 1913; Vongraven, 1913). However, it was not until du Vigneaud (1952) isolated the peptide that specific activities could be ascribed. Following this finding, the nine amino acid sequence and structures of Avp (Turner et al., 1951; Acher and Chauvet, 1953; du Vigneaud et al., 1953a) and the related hormone oxytocin (Oxt) (Tuppy, 1953; du Vigneaud et al., 1953b) were elucidated, followed shortly by their synthesis (du Vigneaud et al., 1954a,b). In 1955, du Vigneaud won the Nobel Prize in chemistry due, in part, to his early descriptions and syntheses of Avp and Oxt.

Avp is mainly synthesized in the magnocellular cells of the hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) whose axons project to the posterior pituitary (Brownstein et al., 1980; Young and Gainer, 2003). Avp is then released into the blood stream upon appropriate stimulation (e.g., hemorrhage or dehydration) to act at the kidneys and blood vessels (Nishimura and Fan, 2003). The brain also contains several populations of smaller, parvocellular neurons whose projections remain within the brain. These populations are located within the PVN, bed nucleus of the stria terminalis (BNST), medial amygdala (MeA) and suprachiasmatic nucleus (SCN) (Buijs et al., 1978; De Vries and Buijs, 1983; De Vries et al., 1985). Other studies suggest that Avp may be more widely expressed in the brain but at significantly lower levels (Planas et al., 1995; Hallbeck et al., 1999).

Since the 1950s, research examining the roles of Avp in the brain and periphery has intensified. The development of specific agonists and antagonists for Avp receptors has allowed for a better elucidation of its contributions to physiology and behavior (Manning and Sawyer, 1991; Barberis et al., 1999; Serradeil-Le Gal et al., 2002a). Anatomical, pharmacological and transgenic, including "knockout," animal studies, have implicated Avp in the regulation of various social behaviors across species. Enough scientific progress has been made that we are now gaining a better understanding of Avp from its transcription to its regulation of behavior.

1.1. Structure and evolution of vasopressin

The Avp gene contains three exons and two introns (see Fig. 1). It is on the same chromosome as Oxt (chromosome 2 in mice and chromosome 20 in human), but oriented in the opposite transcriptional direction (Mohr et al., 1988; Hara et al., 1990), implying that these two genes were duplicated during evolutionary development. Avp peptide has a ring structure formed by a disulfide bridge and differs from Oxt at two amino acid residues (Hruby et al., 1990). The two genes are separated by an intergenic region (IGR) which is about 11 kbp in rat and human, and 3.6 kbp in the mouse (Gainer et al., 2001; Young and Gainer, 2003). Regulatory DNA sequences exist within conserved portions of the IGR (Gainer et al., 2001; Young and Gainer, 2003). The preprohormone consists of the signal peptide, the nonapeptide Avp, and the first nine amino acid residues of the neurophysin protein (encoded by first exon); the central part of the neurophysin (encoded by the second exon); and the C-terminal part of the neurophysin as well as a glycopeptide (encoded by the last exon) (Burbach et al., 2001; Young and Gainer, 2003). Avp is evolutionarily well conserved as even the primitive organism hydra expresses an Avp-like peptide (Grimmelikhuijzen and Spencer, 1984). The evolutionary progenitor of the vertebrate Avp, vasotocin, is found in birds and reptiles (Acher, 1990).

1.2. Pharmacology of the vasopressin receptors

There are three major receptor types for Avp: Avpr1a, Avpr1b, and Avpr2. The Avp receptors have seven transmembrane domains: Avpr1a and Avpr1b couple to $G_{\alpha q/11}$ GTP binding proteins, which along with $G_{\beta\lambda}$, activate phospholipase C activity whereas Avpr2 couples to Gs and acts through the cyclic AMP system (Michell et al., 1979; Jard et al., 1987). Although not confined to these tissues in the periphery, the Avpr1a is prominent in the liver, kidney and vasculature. The Avpr1b is prominent in the anterior pituitary in cells that make