Frontiers in Neuroendocrinology 35 (2015) 49–71

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Species, sex and individual differences in the vasotocin/vasopressin system: Relationship to neurochemical signaling in the social behavior neural network

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ARTICLE INFO

Article history:
Available online 4 August 2014

Keywords:
Oxytocin
Sociality
Aggression
Affiliation
Pair bonding
Communication
Testosterone
Estradiol
V1a
V1b

ABSTRACT

Arginine-vasotocin (AVT)/arginine vasopressin (AVP) are members of the AVP/oxytocin (OT) superfamily of peptides that are involved in the regulation of social behavior, social cognition and emotion. Comparative studies have revealed that AVT/AVP and their receptors are found throughout the "social behavior neural network (SBNN)" and display the properties expected from a signaling system that controls social behavior (i.e., species, sex and individual differences and modulation by gonadal hormones and social factors). Neurochemical signaling within the SBNN likely involves a complex combination of synaptic mechanisms that co-release multiple chemical signals (e.g., classical neurotransmitters and AVT/AVP as well as other peptides) and non-synaptic mechanisms (i.e., volume transmission). Crosstalk between AVP/OT peptides and receptors within the SBNN is likely. A better understanding of the functional properties of neurochemical signaling in the SBNN will allow for a more refined examination of the relationships between this peptide system and species, sex and individual differences in sociality.

1. Introduction

The arginine-vasotocin (AVT)/arginine-vasopressin (AVP) family of peptides regulates a variety of behavioral processes in a wide range of species. While the importance of AVT/AVP in reproductive behaviors was first discovered over 70 years ago, the role of these peptides in controlling non-reproductive social behavior is a more recent development (i.e., approximately 30 years ago) (Albers, 2012). AVT, AVP and a number of other structurally related peptides are part of a larger superfamily that includes various forms of oxytocin (OT) (for a review see Caldwell and Young, 2006). Because of the critical importance of these peptide systems in regulating social behavior, social cognition and emotion they have become a focus in the investigation of the basic mechanisms underlying a variety of psychiatric disorders. While this is a developing research area of great importance, the focus of the current review will be on the basic mechanisms underlying the role of AVT/AVP in sociality. The reader interested in the role of these peptides in translational and clinical research is referred to the large number of excellent recent reviews (Caldwell et al., 2008a; Insel, 2010; Rotzinger et al., 2010; Harony and Wagner, 2010; Neumann and Landgraf, 2012; Burkett and Young, 2012; Lukas and Neumann, 2013).

The AVP/OT peptide superfamily evolved more than 600 million years ago from an ancestral form of AVT through gene duplication (Acher and Chauvet, 1995). These peptides are often called nonapeptides because they are composed of nine amino acid residues. They have a highly conserved structure across vertebrates. For example, AVP and OT share seven of nine amino acid sequences, differing only in the third and eighth positions. AVT is found in fish, amphibians, reptiles and birds while AVP or AVP-like peptides (e.g., lysine-vasopressin) occur in mammals. There are a number of different OT-like peptides found in vertebrates; fish produce isotocin (IT) and amphibians, reptiles and birds produce mesotocin (MT). Even in mammals not all forms of OT are identical in structure (Lee et al., 2011). Although amino acid sequence differences exist across members of this peptide family, the structure of these peptides has been largely conserved during vertebrate evolution. The AVP/OT family of peptides is also found in a large number of invertebrate species such as mollusks, nematodes and arthropods (Gruber, 2014).

Abbreviations: AVP, arginine-vasopressin; AVT, arginine-vasotocin; GABA, gamma-aminobutyric acid; GAL, galanin; IT, isotocin; LH, lateral hypothalamus; LDCV, large dense-core vesicles; LHN, lateral habenular nucleus; LS, lateral septum; Me, medial amygdala; MPN, medial preoptic nucleus; MPOA, medial preoptic area; MT, mesotocin; OT, oxytocin; PAG, periaquaductal gray; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; SSV, small synaptic vesicles; VLH, ventrolateral hypothalamus; VMH, ventromedial hypothalamus.

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http://dx.doi.org/10.1016/j.yfrne.2014.07.001
0091-3022/

In mammals, four nonapeptide receptors have been identified: V1a, V1b, V2 and OT (Barberis and Tribollet, 1996; Caldwell and Young, 2006; Hasunuma et al., 2013). These receptors belong to the G protein-coupled receptor superfamily that have seven putative transmembrane domains and appear to be evolutionarily ancient. Interestingly, recent studies indicate that the original expression site of AVP/OT receptors may have been in the central nervous system and not peripheral tissues, as many have previously assumed (Yamashita and Kitano, 2013). V1a and OT receptors are robustly expressed in many regions of the mammalian brain. V1b receptors appear have a much more restricted distribution in the brain, although they are expressed prominently in the hippocampus and at lower levels in the hypothalamus and amygdala (Young et al., 2006). V2 receptors have also been reported in the adult and developing mammalian brain, but these findings are controversial and it seems unlikely that they play a significant role in regulating sociality (Hirasawa et al., 1994; Kato et al., 1995; Foletta et al., 2002; Vargas et al., 2009). The V1a-like receptor is the most widely distributed AVT/AVP receptor in the brains of vertebrates, and plays a critical role in the control of social behavior (e.g., Albers et al., 1986; Ferris et al., 1988). There is increasing evidence, however, that V1b receptors also play a role in the regulation of social behavior (see Stevenson and Caldwell (2012) for a review). Finally, it is possible that at least some of the effects of AVP- and OT-like peptides on social behavior might be the result of crosstalk between the canonical receptors.

Less is known about nonapeptide receptors in non-mammalian species, although receptors with similarity to mammalian nonapeptide receptors have been identified in all major vertebrate groups except reptiles (see Table 1). In fish, there are two V1a receptors, V1a1 and V1a2, as well as a V2 receptor and an IT receptor (Lema, 2010; Kline et al., 2011; Ocampo et al., 2012; Yamaguchi et al., 2012; Lema et al., 2012). V1a1, V1a2 and IT receptors are found in brain but V2 receptors are not (Lema, 2010). In newts (i.e., *Cynops pyrrhogaster*), three types of AVT receptors have been cloned and based on their structure they have been designated as V1a, V2 and V3/V1b receptors corresponding to the mammalian V1a, V2 and V1b receptors, respectively (Hasunuma et al., 2007). MT receptors have also been characterized and sequenced in amphibians (Akhundova et al., 1996; Kohno et al., 2003; Acharjee et al., 2004; Searcy et al., 2011). In birds, there are four nonapeptide receptors VT1–VT4 (Tan et al., 2000; Gubrij et al., 2005; Leung et al., 2011). The VT4, VT2, VT1, and VT3 avian receptors appear to be homologues of the mammalian V1a, V1b, V2 and OT receptors, respectively. Interestingly however, the V1b-like VT2 receptor has not been detected in avian brain, but the V2-like VT1 receptors is found in avian brain as well as the periphery. In summary, the nomenclature of vertebrate AVT/AVP receptors has become increasingly complex, perhaps unnecessarily. Despite some species differences, it would be useful to simplify this receptor nomenclature by adopting the mammalian designation for these receptors in birds. The situation, in amphibia and fish, however, appears to be more complex.

The focus of this review will be to examine the relationships between sociality and species, sex and individual differences in AVT/AVP systems. The plasticity in the expression of this signaling system, and in particular, how gonadal hormones and social experience can modulate its signaling capacity will be reviewed. Finally, how the complex interplay between AVP-like peptides and their receptors might control sociality by their actions in the "social behavior neural network" will be discussed.

Table 1
Nomenclature of vertebrate AVP/OT family of peptide receptors.

Mammals	V1a	V1b	V2	OT
Birds	VT4	VT2	VT1	VT3
Reptiles	–	–	–	–
Amphibia	V1a	V3/V1b	V2	MT
Fish	V1a1/V1a2	–	V2	IT

2. The "social behavior neural network"

There is a substantial amount of evidence that manipulation of peptides in the AVP/OT family can have dramatic and powerful effects on social behavior by acting within specific CNS sites. A full understanding of the neurobiology of social behavior, however, will require an understanding of the action of these peptides and their receptors across a complex neural network. The concept of a "social behavior neural network" (SBNN) has emerged relatively recently. Over the last 30 years, it has become clear that there is a large degree of overlap in the neural circuitry controlling different social behaviors. As originally proposed by Newman (1999), the SBNN is composed of neural groups or "nodes" including, but not limited to, the extended amygdala, LS, PAG, MPOA, VMH, and AH. Each node within the SBNN fulfills several criteria. They are reciprocally connected, all contain neurons with gonadal hormone receptors, and each has been identified as an important site of regulation or activation of more than one social behavior. Further, there is a substantial body of evidence that this network is involved in controlling a wide range of social behaviors including both offensive and defensive aggression, social recognition/memory, sex behavior, parental behavior and social communication (Albers et al., 2002; Caldwell et al., 2008a; Adkins-Regan, 2009; Albers, 2012; Bosch and Neumann, 2012; Goodson and Kingsbury, 2013). There is now evidence that social behavior neural networks also exist in non-mammalian vertebrates (Crews, 2003; Goodson, 2005; O'Connell and Hofmann, 2011). In fact, a comparative analysis across mammals, birds, reptiles, amphibians and teleost fish provides support for the proposition that there may be homologous nodes in the SBNN of these major vertebrate lineages and that these mechanisms are evolutionarily quite old. However, whether these non-mammalian networks are composed of a series of nodes that are homologous to those in mammals is controversial (for a review see Goodson and Kingsbury, 2013). The overarching hypothesis is that the diversity and complexity of different social behaviors across a wide range of species and individuals can be accounted for by variations in the functional interactions within and across the nodes of this highly conserved network. As such, social behaviors emerge from the entire network and not from its individual elements.

Given the diversity of the animals in which these networks are found, it seems almost certain that the specific nodes contained within the SBNN as well as their functional activity will vary across species. For example, studies in birds have revealed far more steroid hormone-induced modulation across nodes of the SBNN than that seen in mammals (Maney et al., 2008). It also seems likely that the criteria for establishing a structure as a node in the network will be re-considered (e.g., must all nodes have steroid receptors?). Certainly, when one considers the relative importance of different forms of sensory information in the expression of social behavior in different species, it is not at all surprising that there are going to be substantial differences in the structures providing sensory input. Because rodents rely heavily on olfactory information to guide their social behavior, the olfactory system is a key node in their SBNN. In contrast, in species such as birds and primates where visual cues guide social behavior, the structures mediating visual information will likely play a similar key role.

Nevertheless, the construct of the SBNN is a transformative way of looking at the neural mechanisms controlling social behavior when compared to previous approaches of studying the role of