Neuroscience and Biobehavioral Reviews 76 (2017) 87–98

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

# Oxytocin and vasopressin neural networks: Implications for social behavioral diversity and translational neuroscience

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ARTICLE INFO

*Article history:*
Received 4 August 2016
Received in revised form
15 December 2016
Accepted 25 January 2017

*Keywords:*
Social behavior network
Social decision-making network
Salience
Valence
Social behavior
Social cognition
Neuropeptides
Functional connectivity
Functional coupling
Autism spectrum disorders
Social attachment
Pair bonding
Oxtr
Avpr1a

ABSTRACT

Oxytocin- and vasopressin-related systems are present in invertebrate and vertebrate bilaterian animals, including humans, and exhibit conserved neuroanatomical and functional properties. In vertebrates, these systems innervate conserved neural networks that regulate social learning and behavior, including conspecific recognition, social attachment, and parental behavior. Individual and species-level variation in central organization of oxytocin and vasopressin systems has been linked to individual and species variation in social learning and behavior. In humans, genetic polymorphisms in the genes encoding oxytocin and vasopressin peptides and/or their respective target receptors have been associated with individual variation in social recognition, social attachment phenotypes, parental behavior, and psychiatric phenotypes such as autism. Here we describe both conserved and variable features of central oxytocin and vasopressin systems in the context of social behavioral diversity, with a particular focus on neural networks that modulate social learning, behavior, and salience of sociosensory stimuli during species-typical social contexts.

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**Contents**



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http://dx.doi.org/10.1016/j.neubiorev.2017.01.034
0149-7634/Published by Elsevier Ltd.

## 1. Introduction

In nature, many forms of social perception, learning, and behavior vary at the individual and species level. Major research efforts have identified conserved neural systems that regulate these processes across species. For example, homologues of the mammalian oxytocin (OT) and arginine vasopressin (AVP) neuropeptides and their respective target receptors (for clarity, homologous neuropeptides and target receptors in invertebrates and non-mammalian vertebrates will hereafter be referred to as "OT/AVP-like") modulate social and reproductive behaviors across bilaterian animals—including social behavior, social cognition, and psychiatric phenotypes such as autism spectrum disorder (ASD) in humans (Donaldson and Young, 2008). Here we review anatomical and functional properties of central OT/AVP-like networks and tie them to individual and species diversity in social learning and behavior.

## 2. OT/AVP-like neurons

OT/AVP-like neurons exhibit a conserved transcriptional architecture (Donaldson and Young, 2008). In annelid worms and zebrafishes, these neurons express common cell-type specific transcription factors, microRNAs, and opsin genes, suggesting common evolutionary origins (likely as neurosecretory cells) (Tessmar-Raible et al., 2007). In vertebrates, transcription of the genes encoding OT/AVP-like proneuropeptides is regulated by strongly conserved *cis*-regulatory mechanisms, such that transgenically integrated OT-like (isotocin) and AVP-like (vasotocin) gene regulatory constructs from puffer fish are faithfully transcribed in mammalian OT and AVP neurons, respectively (Gilligan et al., 2003; Murphy et al., 1998; Venkatesh et al., 1997). Despite these conserved transcriptional features, genetic variation in the *OXT/AVP* gene region may contribute to individual variation in social cognition and behavior. For example, polymorphisms in *OXT* (the gene encoding OT) have been associated with individual variation in maternal care, postpartum depression, and attachment anxiety in humans (Jonas et al., 2013; Love et al., 2012; Mileva-Seitz et al., 2013).

In vertebrates, OT- and AVP-like peptides are predominantly synthesized in hypothalamic neurons and can be released centrally and peripherally through the posterior pituitary (Lee et al., 2009). It was long thought that magnocellular OT/AVP-like neurons project exclusively to the posterior pituitary, while smaller parvocellular neurons project widely throughout brain. However, magnocellular OT- and/or AVP-like neurons in fishes, birds, and mammals also project to forebrain targets (Godwin and Thompson, 2012; Goodson and Kabelik, 2009; Knobloch et al., 2012; Mahoney et al., 1990; Ross et al., 2009a; Saito et al., 2004), revealing a conserved organization by which peripheral and central OT/AVP-like release may be coupled in vertebrates. AVP-like neurons, although predominantly localized within the hypothalamus, often populate extrahypothalamic sites (e.g. medial amygdala, bed nucleus of stria terminals) in a species-, sex-, and experience-dependent manner (Albers, 2015). Although specific OT- and AVP-like neuronal populations have been implicated in a variety of social behaviors, their functional features are beyond the scope of this review and are described elsewhere (Kelly and Goodson, 2014).

## 3. OT/AVP-like peptide release

OT- and AVP-like peptides are stored in large dense core vesicles (LDCVs) distributed throughout the soma, dendrites, and axons of OT- and AVP-like neurons. These LDCVs are exocytosed in response to increased concentrations of intracellular $Ca^{2+}$ (Stoop, 2012). A variety of osmotic, reproductive, and social stimuli have been shown to elicit OT and AVP release (Lee et al., 2009). For example, OT and AVP are released centrally during parturition, aggressive interaction, and social defeat in rats and/or sheep (Veenema and Neumann, 2008). OT is also released during mating and suckling (Veenema and Neumann, 2008), and in response to more subtle social stimuli including vocalizations (Seltzer et al., 2010), eye contact (Nagasawa et al., 2015), and touch (Okabe et al., 2015).

Somatodendritic exocytosis of LDCVs allows OT/AVP-like peptides to diffuse to hypothalamic and possibly extrahypothalamic sites (Ludwig et al., 2002). In mammals, like other vertebrate lineages, dendritic innervation of the third ventricle may also allow OT/AVP release directly into the ventricular circulation (Fig. 1) (Knobloch and Grinevich, 2014). In addition to dendritic release, OT/AVP-like peptides can be released focally from axons innervating extrahypothalamic brain regions, allowing for more rapid modulation of behavior (Knobloch et al., 2012; Oettl et al., 2016). In some instances, these multiple release mechanisms—volume diffusion through the extracellular space, widespread circulation through the ventricular system, and focal release into extrahypothalamic regions—are thought to occur simultaneously and interact to modulate neural networks in a multimodal fashion (Landgraf and Neumann, 2004; Ross and Young, 2009).

Importantly, OT/AVP release can be uncoupled from depolarization entirely. For example, α-MSH can activate melanocortin 4 receptors (MC4Rs) expressed on OT neurons, triggering mobilization of intracellular $Ca^{2+}$ stores and somatodendritic OT release, thereby increasing local OT concentrations without depolarization or axonal release (Ludwig and Leng, 2006). MC4R agonists have been proposed as an alternative pharmacological strategy for targeting the OT system in psychiatric disorders such as ASD (Young and Barrett, 2015). Similarly, CD38 is a transmembrane protein expressed in OT neurons that contributes to mobilization of intracellular $Ca^{2+}$ stores, triggering OT secretion without depolarization (Higashida et al., 2012; Young, 2007). In mice, CD38 regulates OT-dependent social memory and maternal behavior; in humans, genetic polymorphisms in the CD38 gene are associated with individual variation in parental behavior and ASD phenotypes, suggesting a conserved role for this pathway in social function across rodents and humans (Feldman et al., 2016, 2012; Higashida, 2016; Higashida et al., 2012; Jin et al., 2007).

OT/AVP-like neurons co-express OT/AVP-like receptors in both invertebrates and mammals, suggesting autocrine regulation of these neurons has been strongly conserved (Berlove and Piekut, 1990; Gillard et al., 2007; van Kesteren et al., 1995). In mammals, OT/AVP binding to autoreceptors "primes" the neuron into a more excitable state for up to an hour, augmenting somatodendritic OT/AVP release in response to depolarization or osmotic stimuli (Brussaard, 1995; Dayanithi et al., 2000; Gillard et al., 2007; Ludwig and Leng, 2006; Ludwig et al., 2002; Sabatier et al., 2004). Other signaling mechanisms may also prime OT/AVP-like neurons. For example, melanotan II, a MC4R agonist, potentiates OT release in the striatum following a physiological stimulus and facilitates OT-dependent behaviors (Modi et al., 2015).

It is unclear whether OT/AVP-like neuropeptides act as synaptic neurotransmitters themselves. Electrophysiological and behavioral effects following evoked axonal OT release in forebrain regions occur relatively slowly (on the order of 2–20 s), suggesting that axonal OT release may occur non-synaptically through periaxonal or *en passant* exocytosis of LDCVs (Fig. 1) (Hokfelt, 1991; Knobloch and Grinevich, 2014). Further, OT terminals in the striatum originating from magnocellular neurons are typically devoid of LDCVs, consistent with *en passant* OT release from unmyelinated axons (Ross et al., 2009a).

In rodents, hypothalamic OT and AVP neurons predominantly express VGLUT2, suggesting that depolarization of these neurons