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Review article

Neuropeptide diversity and the regulation of social behavior in New World primates

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ABSTRACT

Oxytocin (OT) and vasopressin (AVP) are important hypothalamic neuropeptides that regulate peripheral physiology, and have emerged as important modulators of brain function, particularly in the social realm. OT structure and the genes that ultimately determine structure are highly conserved among diverse eutherian mammals, but recent discoveries have identified surprising variability in OT and peptide structure in New World monkeys (NWM), with five new OT variants identified to date. This review explores these new findings in light of comparative OT/AVP ligand evolution, documents coevolutionary changes in the oxytocin and vasopressin receptors (OTR and V1aR), and highlights the distribution of neuropeptidergic neurons and receptors in the primate brain. Finally, the behavioral consequences of OT and AVP in regulating NWM sociality are summarized, demonstrating important neuromodulatory effects of these compounds and OT ligand-specific influences in certain social domains.

Contents

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1. Introduction

Oxytocin (OT), a nine amino acid neuropeptide hormone, has been characterized by some (Lee et al., 2009), not completely tongue-in-cheek, as "the Great Facilitator of Life". For eutherian (placental) mammals, this characterization appears apt. OT is a critical mediator for two of the fundamental defining reproductive characteristics of eutherian mammals: placental birth and lactation. Further, OT has been shown to be critical in the formation and maintenance of mother–infant bonds in mammals (Rilling and Young, 2014), a social process that further enhances the likelihood of offspring survivorship and hence reproductive success. There is also a growing interest in OT and the related neurohypophyseal nonapetide arginine vasopressin (AVP) and their analogues in the regulation of social behavior beyond the maternal context, including social attachments among adults, social cognition, and aggression (Albers, 2015; Caldwell and Young, 2006; Donaldson and Young, 2008; Goodson, 2008; Insel, 2010; Kelly and Goodson, 2014) and more complex human social traits, including social dysfunction (Feldman et al., 2016; Grinevich et al., 2015; LoParo and Waldman, 2014).

OT and AVP have important regulatory and modulatory roles in a host of processes. These nine amino acid peptides are synthesized primarily in magnocellular neurosecretory neurons in the paraventricular and supraoptic nuclei of the hypothalamus. The peripheral neuroendocrine effects of OT and AVP are mediated by the release of neuropeptides into peripheral circulation from the posterior pituitary (Kiss and Mikkelsen, 2005; Waite et al., 2014). Central effects of these modulatory neuropeptides are produced via projections to a host of forebrain regions that have high expression of OT and AVP receptors (Ludwig and Leng, 2006; Stoop, 2012, 2014). Both neuropeptides provide significant input to nuclei in the Social Brain Network (Newman, 1999). Oxytocinergic signaling impacts nuclei that are important in the regulation of attachment, parental care, reward, emotional intelligence, and social memory, and vasopressinergic signaling affects nodes in the network that regulate aggression, attachment, social memory, and parental care (Albers, 2015; Donaldson and Young, 2008; Kelly and Goodson, 2014) via both direct neuronal signaling and through volume transmission (Fuxe et al., 2012).

Until recently, every review on nonapeptide evolution and structure has indicated, almost axiomatically, that oxytocin structure is absolutely conserved (i.e., identical) in all species of eutherian mammals. This statement has been made in the earlier literature (see, for example: Acher et al., 1994; Donaldson and Young, 2008; Insel, 2010; Lee et al., 2009) and even as recently as 2014 (Gruber, 2014). A similar claim has been made for AVP in eutherian mammals (with a few notable and documented exceptions; see Section 3.2). A recent review on the molecular genetics of the nucleotide sequences coding for the mature OT and AVP peptides in eutherian mammals lends credence to this perspective. Wallis (2012) conducted a comparative assessment of the 27 nucleotides in the oxytocin (*OXT*) and the arginine-vasopressin (*AVP*) genes that specifically code for the nine OT and AVP amino acids, and quantified the degree of conservation of structure in these molecules via dN/dS ratios (the number of nonsynonymous nucleotide substitutions relative to the number of synonymous substitutions). Ratios of less than 1.0 implies stabilizing selection for protein structure, while ratios of greater than 1.0 imply positive selection for diverse nucleotide sequences (Yang, 2007). dN/dS for eutherian *OXT* is strikingly low: 0.009. The absence of significant mutations in the *OXT* gene in eutherians is not surprising, given that structural alterations in the neuropeptide have the potential to fundamentally modify ligand binding properties with its cell membrane-bound receptor, and subsequently alter the modulatory effects of OT on cell signaling. Altering these biochemical processes could thereby disrupt the critical roles of oxytocin in mediating both peripheral and central processes associated with mammalian reproduction. Although eutherian mammals express three variants of AVP-like molecules (Wallis, 2012), dN/dS ratios for the ligand-coding region of *AVP* are also remarkably low (0.005), again suggesting extreme conservation of AVP ligand structure across eutherian mammals.

The present review will explore emerging discoveries in nonapeptide biology in the New World monkeys (NWM) of South and Central America, nested within the broader comparative biology of nonapeptide structure and function. We will summarize very recent developments characterizing the genomic coding regions for OT and AVP demonstrating that while AVP structure is conserved within this group of primates (as it is in most eutherian mammals), OT structure is highly variable in this group, with six variants identified to date. These findings challenge the common consensus of strict evolutionary conservation of OT within eutherian mammals. Further, social monogamy is a rare mating system among mammals (estimated between 3% and 9% of mammalian species; (Kleiman, 1977; Lukas and Clutton-Brock, 2013). However, the incidence of social monogamy among NWM, in various forms, is exceptionally high – more than 62% of the 117 species in this primate group are classified as socially monogamous (Lukas and Clutton-Brock, 2013). It has not escaped our attention, then, that the one mammalian taxon in which social monogamy is the norm among species also represents the only mammalian taxon where there multiple documented mutations in the *OXT* gene. This exposition on ligand variation in NWM is followed by a corresponding genomic analysis of receptors for OT (*OXTR*) and AVP (*AVPR1A*) within this group, in which a strong coevolutionary relationship between ligand and receptor variation is demonstrated, and we discuss the potential functional consequences of this variation for ligand–receptor binding and subsequent cell signaling. Third, the potential relevance of neuropeptide ligand and receptor variation for behavioral profiles is explored by reviewing the status of OT and AVP signaling systems in the brain, including the source and projections of OT and AVP synthesizing neurons, and the distribution of neuropeptide receptors in the primate forebrain. Finally, we review the important role of neuropeptides in modulating sociality in NWM, based on studies that explore correlations between neuropeptides and social behavior, and those that manipulate neuropeptide function using receptor agonists and antagonists.

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