Review

Biological Psychiatry

Oxytocin Pathway Genes: Evolutionary Ancient System Impacting on Human Affiliation, Sociality, and Psychopathology

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ABSTRACT

Oxytocin (OT), a nonapeptide signaling molecule originating from an ancestral peptide, appears in different variants across all vertebrate and several invertebrate species. Throughout animal evolution, neuropeptidergic signaling has been adapted by organisms for regulating response to rapidly changing environments. The family of OT-like molecules affects both peripheral tissues implicated in reproduction, homeostasis, and energy balance, as well as neuromodulation of social behavior, stress regulation, and associative learning in species ranging from nematodes to humans. After describing the OT-signaling pathway, we review research on the three genes most extensively studied in humans: the OT receptor (*OXTR*), the structural gene for OT (*OXT*/neurophysin-I), and *CD38*. Consistent with the notion that sociality should be studied from the perspective of social life at the species level, we address human social functions in relation to OT-pathway genes, including parenting, empathy, and using social relationships to manage stress. We then describe associations between OT-pathway genes with psychopathologies involving social dysfunctions such as autism, depression, or schizophrenia. Human research particularly underscored the involvement of two *OXTR* single nucleotide polymorphisms (rs53576, rs2254298) with fewer studies focusing on other *OXTR* (rs7632287, rs1042778, rs2268494, rs2268490), *OXT* (rs2740210, rs4813627, rs4813625), and *CD38* (rs3796863, rs6449197) single nucleotide polymorphisms. Overall, studies provide evidence for the involvement of OT-pathway genes in human social functions but also suggest that factors such as gender, culture, and early environment often confound attempts to replicate first findings. We conclude by discussing epigenetics, conceptual implications within an evolutionary perspective, and future directions, especially the need to refine phenotypes, carefully characterize early environments, and integrate observations of social behavior across ecological contexts.

Keywords: CD38, Epigenetics, Genetics, OXT, OXTR, Oxytocin

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EVOLUTIONARY ASPECTS OF THE OXYTOCIN SIGNAL PATHWAY

Vasopressin (AVP) and oxytocin (OT)—two closely related nonapeptides—are ancient and conserved peptides dating back more than 600 million years (1). The AVP/OT family originates from an ancestral peptide anteceding protostomian and deuterostomian animals that appears in different variants in all vertebrates, including mammals (oxytocin/arginine-vasopressin), bony fish (isotocin/vasotocin), and other nonmammalian vertebrates (mesotocin/vasotocin), and several invertebrates, including echinoderms (echinotocin), mollusks (cephalotocin/lys-conopressin), annelids (annetocin/lys-conopressin), arthropods (inotocin/crustacean-VP), and nematodes (nematocin) (2,3). The AVP/OT family presumably evolved via gene duplication from the ancestral vasotocin peptide of jawed vertebrates (4); gene duplication is a common evolutionary pathway toward the adaptation of genes to new functions (5). Within the mammalian lineage, peptides vary by a single amino acid and their genes are found near each other on the same chromosome (6), and variants in this receptor are thought to account for species-selective recognition, ligand binding profiles, and activation of receptors (7).

Throughout animal evolutionary history, neuropeptidergic signaling has been adapted by organisms for regulating physiological and behavioral response to rapidly changing environments, and the OT molecule is critically involved in multiple life-sustaining social and nonsocial functions in species ranging from nematodes to humans (Figure 1). In invertebrates, OT is implicated in associative learning and sensory processing in nematodes and egg-laying behaviors in annelids. In nonmammalian vertebrates, OT analogues have been shown to modulate male courting behavior in lizards, long-term memory formation and vocal circuitry in fish, flocking behavior in birds, and reproduction-related behavior in toads. Finally, in mammalian vertebrates, the AVP/OT family affects both peripheral tissues implicated in reproduction, homeostasis, osmotic regulation, gustatory functions, and energy balance, as well as central neuromodulation of social behavior, stress regulation, and associative learning (8–10). Such wide-ranging roles for the OT

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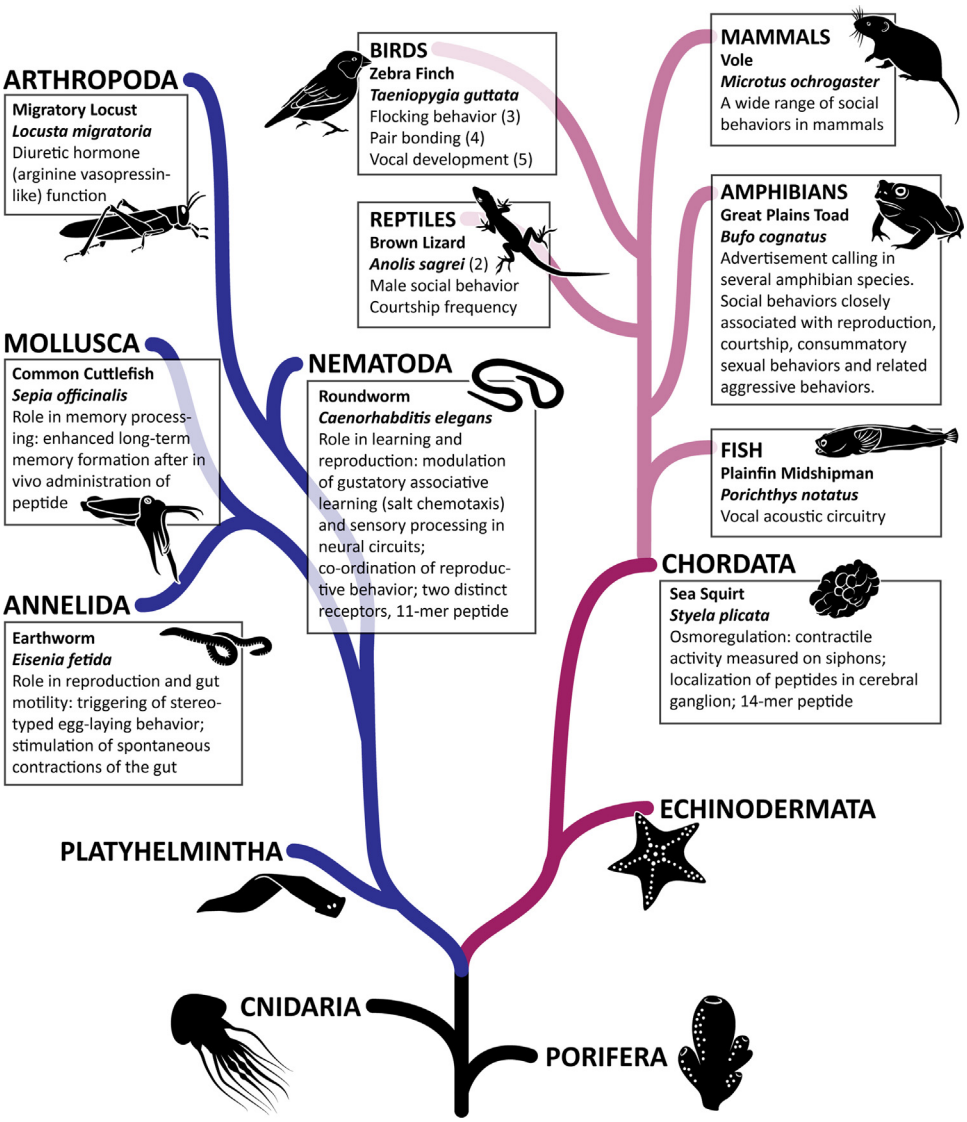

Figure 1. The role of oxytocin across animal evolution. The scheme illustrates the widespread distribution of oxytocin–vasopressin-like signaling system with roots deep in evolutionary time, attesting to the unique properties of such short peptides as information molecules both peripherally and in central nervous systems.

molecule across evolution demonstrates its critical importance for a variety of basic life functions. Moreover, these functions have been repurposed in diverse ways at the level of the species to underpin social life in ways that support the social organization of that species. Overall, the multipurpose species-specific OT system lends support to evolutionary perspectives theorizing that complex abilities co-opt basic ones and social functions are superimposed upon fundamental regulatory pathways (11).

Understanding how OT played a role in fine-tuning neuronal circuits for social behavior across evolution leading to the complexity of human social functions is a central challenge in the construction of a comprehensive theory for social neuroscience (12,13). Detecting commonalities in pleiotropic effects that describe the influence of a single gene on apparently nonrelated phenotypes may help define the underlying neurochemical pathways that buttress human-specific social traits (14). For instance, myoactivity—the stimulation of tissue contraction—is among the most conserved functions of OT (15). Myoactive effects of the OT family peptide on rhythmic-patterned behavior are observed in egg laying in invertebrates (16–19), stereotypical twisting in leeches (20), coordinated male mating behavior in nematodes (21), coupling of peptide secretion with light cycles in fish (22), and resonating with the repetitive-rhythmic synchronous exchange during human parent-infant interactions that introduce 3-month-olds into the social world and foreshadow human social competencies (23,24). The sequencing of such patterned motifs is coordinated by OT-like signaling between sets of cells in the simplest organisms, like *C. elegans,* that involve sexually dimorphic and nondimorphic neurons comprising both central and peripheral effects (3). Cells producing OT-related peptides are found in similar neurosecretory brain centers across species and taxa and are characterized by a typical molecular fingerprint (7,25). Gene regulatory features of the OT-type neuronal cell point to dual sensory-neurosecretory properties, suggesting that the ancient OT signaling system functioned to convert sensory inputs into online behavioral response supported by peptidergic secretion (3).