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Neuropeptidergic regulation of affiliative behavior and social bonding in animals

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Abstract

Social relationships are essential for maintaining human mental health, yet little is known about the brain mechanisms involved in the development and maintenance of social bonds. Animal models are powerful tools for investigating the neurobiological mechanisms regulating the cognitive processes leading to the development of social relationships and for potentially extending our understanding of the human condition. In this review, we discuss the roles of the neuropeptides oxytocin and vasopressin in the regulation of social bonding as well as related social behaviors which culminate in the formation of social relationships in animal models. The formation of social bonds is a hierarchical process involving social motivation and approach, the processing of social stimuli and formation of social memories, and the social attachment itself. Oxytocin and vasopressin have been implicated in each of these processes. Specifically, these peptides facilitate social affiliation and parental nurturing behavior, are essential for social recognition in rodents, and are involved in the formation of selective mother–infant bonds in sheep and pair bonds in monogamous voles. The convergence of evidence from these animal studies makes oxytocin and vasopressin attractive candidates for the neural modulation of human social relationships as well as potential therapeutic targets for the treatment of psychiatric disorders associated with disruptions in social behavior, including autism.

Keywords: Vasopressin receptor; Oxytocin receptor; Social recognition; Social behavior; Pair bond; Autism; Neuropeptides

Introduction

Healthy social relationships are essential for proper mental health and many psychiatric disorders are associated with disruptions in social motivation and the ability to maintain social relationships (Bowlby, 1977; House et al., 1988; Kiecolt-Glaser and Newton, 2001; Monroe et al., 1986). Relationships among spouses, family, and friends are universally important across all human societies, yet little is known about the neurobiological mechanisms underlying the development and maintenance of such human relationships. Aside from a handful of postmortem studies and more recent functional imaging approaches, the neurobiology of human social behavior has been difficult to study. Fortunately, research using animal models has begun to provide insights into the social brain and the regulation of social relationships. Although the research in this field is far from complete, these animal models can serve to complement existing data on normal human social behavior and guide investigations of the neurobiology of pathological sociality, such as in autism spectrum disorders (see Bartz and Hollander, 2006).

The formation and maintenance of social relationships are a complex process that involves several levels of information processing in the brain. For both ease and clarity, animal models of social behavior have generally focused on a single level of processing at a time. Therefore, we have developed a simplified conceptual framework as a useful heuristic tool for understanding the neurobiology of social bonds, and we will follow that framework in this review. First, the organism must be motivated to approach and engage another individual. Next, the

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animal must be able to identify the individual based on social cues through the formation of social memories. Finally, given the appropriate conditions, a bond can form, leading to preferential interaction with that individual. Each of these conceptual levels engages different brain regions and neural circuits. Thus, neuropathology can occur at any level of this framework, with the resulting phenotype being a global impairment in the development of social relationships. This chapter will discuss the animal models developed for each of the three levels with a focus on the neuropeptides oxytocin and vasopressin as a preface to the following review, which will discuss translational implications relevant to these basic neuroscience discoveries (Bartz and Hollander, 2006).

Background

The neurohypophyseal hormones oxytocin and vasopressin play central roles in the regulation of affiliative behavior and social bonding in animals. Oxytocin is best known for its reproductive role in the peripheral circulation, particularly in contraction of the uterus during labor and ejection of milk during lactation (Burbach et al., 2006). Oxytocin is synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus (PVN and SON, respectively), which project to the neurohypophysis, or posterior pituitary, and release the peptide into the peripheral circulation. Oxytocin is also produced within the parvocellular neurons of the PVN, which project to limbic sites such as the hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens, and to mid- and hindbrain nuclei such as the locus coeruleus and nucleus of the tractus solitarius, as well as the spinal cord (Sofroniew, 1983). Oxytocin released within the brain itself is thought to regulate behavior by acting as a neurotransmitter/neuromodulator.

Vasopressin is a closely related peptide, also nine amino acids in length, best known for its actions as anti-diuretic hormone at V2 receptors in the kidney. It is thought that the genes for oxytocin and vasopressin emerged from the duplication of a single ancestral nonapeptide gene early in vertebrate evolution; they are highly conserved in structure and function across taxa. Like oxytocin, vasopressin is synthesized in magnocellular PVN and SON neurons and released from the posterior pituitary into the peripheral circulation. Vasopressin is also synthesized within parvocellular neurons in the PVN and suprachiasmatic nucleus as well as in extrahypothalamic neurons in the bed nucleus of the stria terminalis and medial amygdala (de Vries and Miller, 1998; De Vries and Panzica, 2006). These extrahypothalamic sources of vasopressin are androgen dependent and are the likely source of sexually dimorphic projections within the brain (de Vries and Miller, 1998).

Centrally released oxytocin and vasopressin have been implicated in the regulation of a wide range of social behaviors, some of which will be discussed in detail below. Oxytocin facilitates social motivation and approach behavior, including maternal nurturing behaviors (Burbach et al., 2006). Vasopressin regulates several male-typical social behaviors, including scent marking, aggression, and paternal care (Boyd et al., 1992; Delville et al., 1998; Ferris et al., 1990; Goodson and Bass, 2001; Wang et al., 1994). Both oxytocin and vasopressin are important for the formation or expression of social memories required for the discrimination of familiar individuals (Bielsky and Young, 2004). Both peptides are also involved in pair bond formation in monogamous prairie voles (Young and Wang, 2004). Thus, both oxytocin and vasopressin are heavily involved at each of the conceptual levels leading to social bonding: The initial approach and affiliation, the recognition of social cues required for individual recognition, and finally the formation of the bond itself. Each of these processes will be discussed separately below.

Social approach and motivation

The neurobiology of social approach and motivation can be studied by measuring the latency time to approach another individual and the amount of time spent in social contact. Here we discuss the role of oxytocin and vasopressin in three general animal models of social approach and motivation: parental behavior, infant–mother interactions, and adult affiliation. At this conceptual level, social motivation is primarily non-selective in nature. For example, maternal female rodents direct maternal nurturing to any pup, regardless as to whether they are their own.

Mother–infant care can be studied by examining the behavioral components of maternal care, which includes nest building, licking and grooming pups, and crouching over pups. Maternal nurturing behavior develops coincident with labor and parturition. Virgin female rats initially find pups aversive and will actively avoid them (reviewed in Fleming and Anderson, 1987). After parturition, rats find pups rewarding and can actually be trained to bar press to gain access to pups (Lee et al., 1999). Oxytocin originating from the PVN or SON may act on oxytocin receptors throughout the brain to promote maternal responsiveness. Lesions of the PVN result in a near complete loss of the brain oxytocinergic system (De Vries and Buijs, 1983), and a delay in the onset of maternal behavior in naïve rats (Insel and Harbaugh, 1989). Oxytocin injected intracerebroventricularly (i.c.v.) into virgin female rats induces maternal behavior (Pedersen et al., 1982). Similarly, i.c.v. oxytocin injected into both virgin and pregnant wild house mice also increases maternal behavior towards pups (McCarthy, 1990). In contrast, oxytocin receptor antagonists delivered to the ventricles delay the onset of maternal behavior in hormone-primed females (Fahrbach et al., 1985; van Leengoed et al., 1987). Finally, oxytocin receptor antagonists injected directly into the medial preoptic area (MPOA) and ventral tegmental area (VTA) inhibit maternal behavior (Pedersen et al., 1994).

Oxytocin and oxytocin receptor (OTR) levels in the brain are regulated by estrogen and progesterone followed by progesterone withdrawal (Amico et al., 1997; Bale et al., 1995). During pregnancy, when estrogen levels rise, OTR expression increases in the hypothalamus and MPOA (Young et al., 1997a). Treatment with estrogen also results in increased levels of OTR via estrogen receptor alpha activation (Breton and Zingg,