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Neuropeptides and the social brain: potential rodent models of autism

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Abstract

Conducting basic scientific research on a complex psychiatric disorder, such as autism, is a challenging prospect. It is difficult to dissociate the fundamental neurological and psychological processes that are disturbed in autism and, therefore, it is a challenge to discover accurate and reliable animal models of the disease. Because of their role in animal models of social processing and social bonding, the neuropeptides oxytocin and vasopressin are strong candidates for dysregulation in autism. In this review, we discuss the current animal models which have investigated oxytocin and vasopressin systems in the brain and their effects on social behavior. For example, mice lacking the oxytocin gene have profound deficits in social processing and social recognition, as do rats lacking vasopressin or mice lacking the vasopressin V1a receptor (V1aR). In another rodent model, monogamous prairie voles are highly social and form strong pair bonds with their mates. Pair bonds can be facilitated or disrupted by perturbing the oxytocin and vasopressin systems. Non-monogamous vole species that do not pair bond have different oxytocin and V1aR distribution patterns in the brain than monogamous vole species. Potential ties from these rodent models to the human autistic condition are then discussed. Given the hallmark disturbances in social function, the study of animal models of social behavior may provide novel therapeutic targets for the treatment of autism.

Keywords: Vasopressin V1a receptor; Oxytocin receptor; Social memory; Knockout mice; Pair bond; Vole; Oxytocin; Vasopressin; Neuropeptides

1. Introduction

Given the complex nature of autism and autism spectrum disorders, it is difficult to comprehensively investigate the underlying neurobiology using only human patients. Much can be learned by studying the neurobiology of social behavior in animal models in parallel. Patients with autism exhibit global dysfunction in social interaction and social communication. Parents of autistic children commonly report that they do not demonstrate affection, prefer to stay isolated, and at times appear not to notice or recognize other people (Baird et al., 2003). Fortunately, several animal models of these deficits in social behavior exist that may provide insights into the underlying neuropathology. Here, we present studies using rodent models that suggest that the structurally related neuropeptides oxytocin and vasopressin may play a critical role in the processing of social cues, social recognition and social bonding. Based on these data, oxytocin, vasopressin and their respective brain receptors may be candidate genes and proteins that contribute to the social behavior deficits observed in autism.

Oxytocin and vasopressin are closely related neuropeptides synthesized in the paraventricular and supraoptic nucleus of the hypothalamus and are released into the bloodstream via axon terminals in the posterior pituitary. Both are members of a nine amino acid family of peptides which can be traced phylogenetically to invertebrates (Gainer and Wray, 1994). Ancestral forms have been implicated in species-typical reproductive and social behaviors, such as courtship display, sexual behavior, and social communication (Insel and Young, 2000; Goodson and Bass, 2001). Peripherally released oxytocin plays a role in parturition and lactation, while peripheral actions of vasopressin are primarily to maintain water balance and blood pressure. Centrally released oxytocin and vasopressin, on the other hand, are coordinated independently from peripheral release from the pituitary. Separate neuronal populations exist that synthesize oxytocin and vasopressin for central release,

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such as the parvocellular neurons in the PVN, as well as the medial amygdala and the bed nucleus of the stria terminalis (BnST) (De Vries and Buijs, 1983). Central actions of oxytocin and vasopressin include the regulation of maternal behavior and species-typical male behaviors ranging from courtship, territorial defense, and paternal care of young across many diverse species ranging from fish to mammals (Goodson and Bass, 2001). Although, central administration of peptides appears to have a stronger behavioral effect in rodents than peripheral administration, there are some behavioral effects observed with peripheral administration, suggesting that the circulating peptides can at least partially cross the blood-brain barrier.

In this review, we describe the role of oxytocin and vasopressin in animal models of two social behaviors: social recognition and social bonding. Human relationships rely on social interactions that include the ability to recognize other individuals, remember their personal qualities, and forge bonds with them. Social processing of interactions relies on face and voice recognition, which are processed differently in the brain than inanimate objects (Haxby et al., 2000). These general requirements are necessary across a spectrum of social interactions, from the casual meeting between acquaintances, to the mother–infant bond, to bonds between friends, family, and lovers. Given the central roles of oxytocin and vasopressin in social behavior across many species, they are ideal candidate systems to examine in relation to autism.

2. Social recognition and processing

Reciprocal and sustained social relationships require the ability to recognize a familiar conspecific. For all social animals, the ability to recognize familiar individuals is a necessity for functioning in society, and requires an additional level of processing for social cues. Patients with autism are thought to have a fundamental deficit in social reciprocity and communication, which conceivably could be due to deficits in social recognition or processing of social cues. Visual cues are the primary methods of recognition in humans, and clinical research suggests that children and adults with autism may have deficits in the cognitive processing of faces and facial cues. Langdell (1978) showed that autistic children can recognize faces of classmates; however, in contrast to normal children who attend to upper facial features, such as eyes, autistics attended to lower facial features. They also failed to show the "inversion effect," or the typical difficulty in recognizing inverted faces (Langdell, 1978). Although, patients with autism appear to identify faces normally at a basic object level (i.e., when asked to identify a face from a set of basic objects), they show impairments when asked to match unfamiliar faces on tests, such as on the Benton Face Recognition Test (BFRT) (Szatmari et al., 1990; Davies et al., 1994; Barton, 2003). These patients perform at the level of normal subjects when asked to recognize and match objects, such as buildings (Boucher and Lewis, 1992; Boucher et al., 1998). In addition to these studies of face matching and recognition, some studies have reported deficits in perceiving facial expression, age, and sex (Hobson, 1987; Tantam et al., 1989). Taken together, these studies suggest that autistic children might use an abnormal strategy for face recognition, such as processing faces in terms of their component parts like objects. This brings up the hypothesis that face processing in autistic patients may utilize different neural pathways in the brain, and helps to identify candidate brain regions and neurochemical systems that might reflect these abnormalities (Hobson et al., 1988).

Social recognition in rodents may represent an animal model for the neural processing of social stimuli and the deficits observed in autism. In contrast to human social recognition, which relies heavily on visual cues, rodents are dependent on olfactory cues. In the laboratory, social recognition in rodents is assessed by quantifying the duration of social investigation during subsequent exposures to the same individual. The behavioral assay is based on the phenomenon that rodents investigate novel objects (or unfamiliar individuals) longer than familiar objects and individuals. Thus, subsequent exposures to the same individual result in a significant decrease in the amount of time spent investigating that individual (Winslow, 2003). Vasopressin itself was first implicated in the 1960s in avoidance learning and memory (van Wimersma Greidanus et al., 1983). Since these early studies, considerable evidence has demonstrated the importance of vasopressin and oxytocin in other forms of complex memory, including social recognition paradigms.

Initial investigations into the social behaviors of the Brattelboro rats, a naturally occurring vasopressin-deficient mutant, demonstrated a total disruption of social recognition (van Wimersma Greidanus, 1982). Social memory in these animals was restored by retrodialyzing vasopressin into the lateral septum (Engelmann and Landgraf, 1994). Perpipheral, intracerebroventricular (i.c.v.) and intraseptal administration of the vasopressin V1a receptor (V1aR) antagonist have all been shown to block social recognition in normal rats (Dantzer et al., 1987). Likewise, intraseptal injection of V1aR antisense oligonucleotides also results in impaired social memory (Le Moal et al., 1987; Landgraf et al., 1995; Everts and Koolhaas, 1999). Furthermore, viral vector-mediated over-expression of V1aR specifically in the lateral septum can facilitate social recognition in normal rats by prolonging the duration of social memory (Landgraf et al., 2003).

Investigation of vasopressin in mice also points to a critical role in social memory. Transgenic male mice with a null mutation in the *V1aR* gene lack the ability to recognize a familiar conspecific, despite repeated exposures (Bielsky et al., 2004). This social deficit is not a result of a general olfactory deficiency, given the ability of these mice to habituate to a non-social stimulus. Furthermore, spatial learning and memory and sensorimotor processing are also normal in the V1aR knockout mice, suggesting that the deficit is specific