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Oxytocin receptor density is associated with male mating tactics and social monogamy

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ABSTRACT

Despite its well-described role in female affiliation, the influence of oxytocin on male pairbonding is largely unknown. However, recent human studies indicate that this nonapeptide has a potent influence on male behaviors commonly associated with monogamy. Here we investigated the distribution of oxytocin receptors (OTR) throughout the forebrain of the socially monogamous male prairie vole (*Microtus ochrogaster*). Because males vary in both sexual and spatial fidelity, we explored the extent to which OTR predicted monogamous or non-monogamous patterns of space use, mating success and sexual fidelity in free-living males. We found that monogamous males expressed higher OTR density in the nucleus accumbens than non-monogamous males, a result that mirrors species differences in voles with different mating systems. OTR density in the posterior portion of the insula predicted mating success. Finally, OTR in the hippocampus and septohippocampal nucleus, which are nuclei associated with spatial memory, predicted patterns of space use and reproductive success within mating tactics. Our data highlight the importance of oxytocin receptor in neural structures associated with pairbonding and socio-spatial memory in male mating tactics. The role of memory in mating systems is often neglected, despite the fact that mating tactics impose an inherently spatial challenge for animals. Identifying mechanisms responsible for relating information about the social world with mechanisms mediating pairbonding and mating tactics is crucial to fully appreciate the suite of factors driving mating systems. This article is part of a Special Issue entitled Oxytocin, Vasopressin, and Social Behavior.

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Introduction

Oxytocin (OT) is a mammalian hormone and neuromodulator that is closely associated with female behavior. Oxytocin induces labor, facilitates milk ejection during nursing, and mediates maternal behavior and mother–infant bonding (Gimpl and Fahrenholz, 2001). In mammals in which females form bonds with male mates, oxytocin is thought to have been co-opted to facilitate female bond formation with mating partners (Ross and Young, 2009). Oxytocin is released during vaginocervical stimulation or mating (Kendrick et al., 1986; Ross et al., 2009a; Sansone et al., 2002) and during human orgasm (Carmichael et al., 1987), presumably enhancing the association between an individual and the hedonic reward elicited by mating. While females of most mammalian species readily bond with and care for offspring, male parental care and social bonding are quite rare. Moreover, the neuroendocrine control over male attachment and paternal care in species for which these behaviors are important is often attributed to arginine vasopressin (AVP). For these reasons, oxytocin and vasopressin are considered prominent mechanisms governing mammalian monogamy and 'love' (Zeki, 2007). To some extent the two hormones have been distinctly associated with each sex, much in the way estrogens and androgens once were. As a result, the potential influence of OT in male monogamy is often neglected.

Monogamy is commonly characterized by selective affiliation with a mate, bi-parental care, and selective aggression in the form of territory, nest, and mate defense (Clutton-Brock, 1991; Kleiman, 1977). In this regard, prairie voles (*Microtus ochrogaster*) are great models of monogamy, and studies of this species have provided one of the best descriptions of mechanisms involved in mammalian monogamous behavior. Prairie voles establish long-term pairbonds in both the field (Getz and Hofmann, 1986; Getz et al., 1981, 1993) and laboratory (Oliveras and Novak, 1986; Solomon, 1993a,b; Thomas and Birney, 1979; Williams et al., 1992), and exhibit bi-parental care—with males contributing to all offspring needs except lactation (refs Op. cit.). Pairs are also territorial; there is minimal overlap with non-pair neighbors of both sexes, and males are selectively aggressive to intruders (Getz and Hofmann, 1986; McGuire and Getz, 1991, 1998, 2008; McGuire et al., 1990).

The influence of OT and AVP in prairie vole monogamy is most tightly associated with pairbonding and parental care (Carter et al.,

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1997; Winslow et al., 1993; Young et al., 1997), which are centrally mediated by the oxytocin receptor (OTR) and the vasopressin receptor subtype V1aR (refs Op. cit.). A growing body of work has led to the proposal that a 'pairbonding neural circuit' integrates the action of vasopressin and oxytocin with dopaminergic-mediated reward in mesolimbic structures to facilitate social bonds (Young and Wang, 2004; Young et al., 2005). This suggestion is strongly supported by experiments manipulating these nonapeptides or their receptors within several structures throughout the prairie vole forebrain (Carter and Keverne, 2002; Young and Wang, 2004; Young et al., 2005). For example, central infusion of OT or AVP facilitates partner preferences in both females and males, while antagonists for these peptides reduce the effects of OT or AVP on behavior in both sexes (Cho et al., 1999; Williams et al., 1994). However, these studies used antagonists to block the effects of exogenous nonapeptides. Central infusion of nonapeptide receptor antagonists targeting endogenous OT or AVP acting throughout the forebrain (Insel and Hulihan, 1995; Winslow et al., 1993), and structure-specific studies suggest that OT and AVP may have sex-specific effects on mammalian bonding. For instance, oxytocin receptor antagonists delivered to the prefrontal cortex (PFC) or nucleus accumbens (NAcc) block mating-induced partner preferences in females, but not males (Young et al., 2001). Blockade of V1aR in the ventral pallidum (VPall) inhibits the formation of partner preferences of males, but not females (Lim and Young, 2004). This has led to the belief that oxytocin mediates female bonding, while vasopressin mediates male bonding. This assumption has led to experiments focused on manipulating these hormones in either of the two sexes. For example, male prairie voles have been manipulated to over-express V1aR in the VPall (Pitkow et al., 2001), while females have been manipulated to over-express OTR in the NAcc (Ross et al., 2009b). In both cases the animals formed social preferences characteristic of pairbonds without the necessary step of mating. The role of septal AVP in males has further contributed to this divide considering that it has been closely associated with facilitating paternal care (Bamshad et al., 1993; Oliveras and Novak, 1986; Wang et al., 1994a,b; Wideman and Murphy, 1990), and it is both necessary and sufficient to induce male pairbonding (Liu et al., 2001). Although both OT and AVP antagonists delivered to the septum eliminated male pairbonds (Liu et al., 2001), it has been suggested that this effect may be more linked with its influence in social recognition than monogamous pairbonding per se (Young and Wang, 2004; Young et al., 2005).

It has been argued that the prairie vole pairbonding neural circuit may serve as a model for understanding human mechanisms of attachment and love. While human studies have been approached very differently than those focused on the prairie vole brain, an interesting point should be highlighted: OT clearly plays a role in human male attachment. It is generally agreed that trust is an important component of human relationships, and intranasal administration of OT in both genders facilitates trust (Baumgartner et al., 2008; Kosfeld et al., 2005; Zak et al., 2005). The influence of oxytocin in humans goes beyond trust; it facilitates recognition of faces (Rimmele et al., 2009; Savaskan et al., 2008), in-group social cohesion (De Dreu et al., 2011), and preemptive punishment toward outgroups (De Dreu et al., 2010), suggesting that it may influence a form of selective aggression in men. Furthermore, OT is increased during sexual arousal and released during orgasm in men, just as it is in women (Carmichael et al., 1987). Ironically, human studies suggest that the role of OT in male prairie vole monogamy may be underappreciated.

Hormone receptors are often the targets of selection and their distributions can reveal products of evolution (Ketterson and Nolan, 1992). Here we ask how patterns of OTR density relate to monogamous behavior in male prairie voles living in outdoor enclosures. Specifically we ask if oxytocin receptor expression predicts male mating tactics and paternity. Although we examined the distribution of oxytocin receptor expression throughout the male forebrain, we place a special focus on areas of the brain that are associated with pairbonding (e.g., NAcc and PFC). We were also particularly interested in neural structures involved in spatial or social memory (e.g., hippocampus and lateral septum) because our previous results indicated that socio-spatial memory structures expressing the vasopressin receptor, V1aR, were important predictors of the most successful male mating tactics (Ophir et al., 2008b).

Materials and methods

Test animals

In total, we used 48 male and 48 female prairie voles to investigate how individual differences in brain phenotype related to space use and sexual fidelity. The methods described below were in accordance with the guidelines set and approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Memphis (project number 0012). At weaning, we grouped all animals in same-sex sibling groups and maintained them under a 14:10 L:D cycle. Food and water were provided ad libitum and temperature was maintained at 21 ± 2 °C.

Animals were distributed into eight groups, each consisting of six nulliparous females and six adult, sexually mature males. All individuals were of similar age and weight and before introduction to field enclosures they were ear-tagged, weighed, and a tail clipping was taken. Further details on field and paternity methods can be found in Ophir et al. (2008a).

The study was conducted in four field enclosures located in Shelby Co. TN (for details see Mahady and Wolff, 2002; Ophir et al., 2007, 2008a). Each enclosure measured 20×30 m. Densities were within the range of natural densities reported elsewhere (Getz et al., 1993; Taitt and Krebs, 1985).

Radio telemetry and trapping

We outfitted each vole with a 1.9 g transmitter and collar (BD-2C, Holohil Systems Ltd.; Carp, Ontario) 2 days prior to introduction to the field. Animals were tracked with an LA12 Radio Telemetry Receiver (AVM Instruments Co, Ltd.; Livermore, CA) to within 1 m of their actual location.

To initiate a trial, we placed all twelve animals (six females and six males) in an enclosure. At the start of each trial, animals were standardized for age and body mass across enclosures. We ran a series of four trial blocks each consisting of two simultaneous trials over the breeding season.

Telemetry readings were taken twice daily for at minimum of 12 days, varying time of day and enclosure order. We began trapping and removing animals from the enclosure on day 18. By initiating trapping on this schedule we ensured that no females would give birth before trapping (gestation is 21 days), enabling us to know the identity of mothers with 100% confidence and increasing our ability to assign paternity to embryos. We collected tissue from all animals and the embryos for genetic parentage analysis. Further details are reported in Ophir et al. (2008a).

Home range size, space use, and pair determination

We used RANGES V (Anatrack Ltd.; Dorset, UK) to estimate the size of each core home range by calculating minimum convex polygons (MCP) with 75% fixes from the assembled X and Y coordinates. We focused on the central 75% of data points to estimate the core home ranges without resorting to more complex statistical kernel methods (Row and Blouin-Demers, 2006; White and Garrott, 1990; see Ophir et al., 2008a for more discussion). From these MCPs, we calculated the percent of home-range overlap between pairs of