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SPECIES DIFFERENCES IN BEHAVIOR AND CELL PROLIFERATION/SURVIVAL IN THE ADULT BRAINS OF FEMALE MEADOW AND PRAIRIE VOLES

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Abstract—Microtine rodents display diverse patterns of social organization and behaviors, and thus provide a useful model for studying the effects of the social environment on physiology and behavior. The current study compared the species differences and the effects of oxytocin (OT) on anxiety-like, social affiliation, and social recognition behaviors in female meadow voles (*Microtus pennsylvanicus*) and prairie voles (*Microtus ochrogaster*). Furthermore, cell proliferation and survival in the brains of adult female meadow and prairie voles were compared. We found that female meadow voles displayed a higher level of anxiety-like behavior but lower levels of social affiliation and social recognition compared to female prairie voles. In addition, meadow voles showed lower levels of cell proliferation (measured by Ki67 staining) and cell survival (measured by BrdU staining) in the ventromedial hypothalamus (VMH) and amygdala (AMY), but not the dentate gyrus of the hippocampus (DG), than prairie voles. Interestingly, the numbers of new cells in the VMH and AMY, but not DG, also correlated with anxiety-like, social affiliation, and social recognition behaviors in a brain region-specific manner. Finally, central OT treatment (200 ng/kg, icv) did not lead to changes in behavior or cell proliferation/survival in the brain. Together, these data indicate a potential role of cell proliferation/survival in selected brain areas on different behaviors between vole species with distinct life strategies.

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Abbreviations: AMY, amygdala; ANOVA, analysis of variance; BrdU, 5-bromo-2′-deoxyuridine; CSF, cerebrospinal fluid; DAB, 3′-diainobenzidine; DG, dentate gyrus of the hippocampus; Icv, intracerebroventricular; NGS, normal goat serum; OT, oxytocin; PBS, phosphate buffer saline; PBT, PBS with 0.5% Triton X-100; SVZ, subventricular zone; VMH, ventromedial hypothalamus.

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INTRODUCTION

Adult neurogenesis, the generation of new neurons from neural stem cells, has been documented primarily in two regions of the adult mammalian brain, the dentate gyrus of the hippocampus (DG) and the subventricular zone (SVZ) (Gross, 2000; Lieberwirth and Wang, 2012). Newly generated cells have also been reported in non-traditional neurogenic brain regions including the neocortex, cerebellum, amygdala (AMY), substantia nigra, striatum, and hypothalamus (Ming and Song, 2005; Martino et al., 2011; Crociara et al., 2013). Although we still know little about the functional relevance of adult neurogenesis (Kempermann et al., 2004), increasing evidence has shown that adult neurogenesis may play an important role in learning and memory (Shors et al., 2001; Dupret et al., 2007), social processing and responding (Feierstein et al., 2010; Lagace et al., 2010; Mak and Weiss, 2010; Oboti et al., 2011), and emotional behavior (Revest et al., 2009; Larsen and Grattan, 2010; Snyder et al., 2011). Studies have indicated that the distinct phases of adult neurogenesis in both traditional and non-traditional neurogenic brain regions are regulated by a variety of endogenous (e.g., neurotransmitters and hormones) and exogenous (e.g., voluntary physical exercise and enriched environment) factors (Fowler et al., 2008; Larsen and Grattan, 2010; Lucassen et al., 2010; Snyder et al., 2011). Recent studies have also shown that social interactions affect adult neurogenesis (Lucassen et al., 2010; Lieberwirth and Wang, 2012). For example, aversive social experience—such as agonistic interactions with dominant and aggressive conspecifics—reduces cell proliferation and survival in the adult brain in a variety of mammalian species (Gould et al., 1997; Westenbroek et al., 2004; Czeh et al., 2007; Thomas et al., 2007; Van Bokhoven et al., 2011; Lieberwirth and Wang, 2012; Pan et al., 2014). Conversely, positive social interactions among conspecifics, such as pheromonal exposure or sociosexual encounters facilitate adult neurogenesis across distinct brain regions (Mak et al., 2007; Ruscio et al., 2008; Furuta and Bridges, 2009; Corona et al., 2011).

Using a comparative approach, striking differences have been found in several types of social behaviors of

animals with different life strategies. For example, social species generally show high levels of prosocial behavior among individuals, social affiliation with mates/conspecifics, and bi-parental care for their offspring; whereas non-social species generally exhibit low levels of prosocial behavior and social affiliation, but high levels of aggression (Getz et al., 1981; McGuire and Novak, 1984; Oliveras and Novak, 1986; Bester-Meredith et al., 1999; Xu et al., 2010; Wang et al., 2013). Social behaviors are selected by evolution and are the result of precise adaptations in morphology, connectivity, and chemistry (Insel and Young, 2000). Therefore, such behavioral differences among species with different life strategies may reflect their adaptations to different evolutionary selection pressures and show their potential species differences in the central nervous system.

Oxytocin (OT) is a neurotransmitter that has received substantial attention due to its role in social behaviors. OT is primarily produced in the paraventricular and supraoptic nuclei of the hypothalamus and is involved in a wide variety of processes related to social behavior, including maternal behavior, trust, and pair-bond formation (Carter et al., 2008; Neumann, 2008; Young et al., 2008; Ross and Young, 2009; Anacker and Beery, 2013). Several comparative studies between social and non-social rodent species have shown that species differences in behaviors correlate with the OT system (Young et al., 2008; Anacker and Beery, 2013). For example, the immunoreactive (ir) expression or receptor distribution of OT differs between social and non-social rodent species (Insel and Shapiro, 1992; Beery et al., 2008; Xu et al., 2010; Wang et al., 2013). Moreover, genetic and pharmacological manipulations of the OT system in the brains of social and non-social rodents have shown that OT has differential effects in regulating social behaviors corresponding to the life strategy (Williams et al., 1994; Young et al., 2001; Olazabal and Young, 2006; Ross et al., 2009).

Microtine rodents display diverse social organizations and thus offer an excellent comparative model for studying the effects of the social environment on physiology and behavior (Young and Wang, 2004; Young et al., 2011). For example, prairie voles (*Microtus ochrogaster*) are a highly affiliative, socially monogamous species and members of the species form long-term bonds after mating (Getz and Hofmann, 1986; Carter and Getz, 1993). Pair-bonded males and females occupy a common nest and guard the territory against unfamiliar conspecifics, and both the male and female provide parental care of their offspring (Wilson, 1982; FitzGerald and Madison, 1983; McGuire and Novak, 1984; Gruder-Adams and Getz, 1985; Getz and Hofmann, 1986; Oliveras and Novak, 1986; Carter and Getz, 1993). In contrast, meadow voles (*Microtus pennsylvanicus*) are an asocial, promiscuous species and males and females neither form pair bonds nor share a nest after mating (Getz, 1972; Madison, 1978, 1980a,b). In this species, as it is common in other promiscuous mammals, only the mothers provide parental care (Wilson, 1982; McGuire and Novak, 1984; Gruder-Adams and Getz, 1985; Oliveras and Novak, 1986). It has been shown that the distribution patterns and regional densities of OT receptors in the brain differ between prairie and meadow voles (Insel and Shapiro, 1992; Smeltzer et al., 2006). Further, OT appears to play an important role in behaviors associated with social monogamy in prairie voles: central or site-specific (e.g., into the nucleus accumbens) OT treatment facilitates social contact and induces pair bond formation in female prairie voles (Williams et al., 1992, 1994; Insel and Hulihan, 1995; Cho et al., 1999; Liu and Wang, 2003) and these effects are blocked by concurrent administration of an OT receptor antagonist (Cho et al., 1999).

Recent studies have also shown that experimental alterations of the social environment significantly influence the rate of cell proliferation and survival in the vole brain (Smith et al., 2001; Fowler et al., 2002; Ormerod and Galea, 2003; Ormerod et al., 2004; Liu et al., 2007; Ruscio et al., 2008; Lieberwirth et al., 2012, 2013). For example, in the prairie vole, long-term chronic social isolation decreases the rate of cell proliferation in the DG and medial preoptic area (MPOA) and impairs cell survival in the AMY, DG, and ventromedial hypothalamus (VMH); whereas 48 h of cohabitation with a male results in a significant increase in SVZ cell proliferation in female prairie voles (Smith et al., 2001; Lieberwirth et al., 2012). However, few studies (e.g., Fowler et al., 2005) have examined the relationship between the animal's sociality and adult neurogenesis. Therefore, in the present study we compared female prairie and meadow voles and examined their differences in behaviors relevant to anxiety-like, affiliation, and social recognition behavior as well as compared cell proliferation and survival in the brain. In addition, because of the reported roles of OT on species-specific behaviors in voles (Young et al., 2011) and on cell proliferation and survival in rats (Leuner et al., 2012), we examined the effects of OT on behaviors and cell proliferation and survival.

EXPERIMENTAL PROCEDURES

Subjects

Subjects were sexually naïve female meadow and prairie voles that were the offspring of laboratory breeding colonies All voles were weaned at 21 days of age and housed in same sex sibling pairs in plastic cages (12 × 28 × 16 cm) containing cedar chip bedding with food and water *ad libitum*. It has been well-documented that, unlike traditional rodent species such as rats and mice, female voles are induced ovulators. They do not experience ovarian cycles and can only be induced into estrus by exposure to a conspecific, strange male or male-associated cues (Dluzen and Carter, 1979; Cohen-Parsons and Carter, 1987). In our experiments, we used sexually naïve females that were housed in same sex pairs in plastic cages located in the female-only colony rooms for each species. This experimental set-up was designed to prevent any potential effects of gonadal steroid hormones from affecting subject's behavior and cell proliferation/survival in the brain. The cages were maintained in a 14-L:10-D photoperiod (lights on at 0700)