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PATERNAL DEPRIVATION AFFECTS SOCIAL BEHAVIORS AND NEUROCHEMICAL SYSTEMS IN THE OFFSPRING OF SOCIALLY MONOGAMOUS PRAIRIE VOLES

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Abstract—Early life experiences, particularly the experience with parents, are crucial to phenotypic outcomes in both humans and animals. Although the effects of maternal deprivation on offspring well-being have been studied, paternal deprivation (PD) has received little attention despite documented associations between father absence and children health problems in humans. In the present study, we utilized the socially monogamous prairie vole (*Microtus ochrogaster*), which displays male–female pair bonding and bi-parental care, to examine the effects of PD on adult behaviors and neurochemical expression in the hippocampus. Male and female subjects were randomly assigned into one of two experimental groups that grew up with both the mother and father (MF) or with the mother-only (MO, to generate PD experience). Our data show that MO subjects received less parental licking/grooming and carrying and were left alone in the nest more frequently than MF subjects. At adulthood (~75 days of age), MO subjects displayed increased social affiliation (SOA) toward a conspecific compared to MF subjects, but the two groups did not differ in social recognition (SOR) and anxiety-like behavior. Interestingly, MO subjects showed consistent increases in both gene and protein expression of the brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) as well as the levels of total histone 3 and histone 3 acetylation in the hippocampus compared to MF subjects. Further, PD experience increased glucocorticoid receptor beta (GRβ) protein expression in the hippocampus of females as well as increased corticotrophin receptor 2 (CRHR2) protein expression in the hippocampus of males, but decreased CRHR2 mRNA in both sexes. Together, our data suggest that PD has a long-lasting, behavior-specific effect on SOA and alters hippocampal neurochemical systems in the vole brain. The functional role of such altered neurochemical systems in social behaviors and the potential involvement of epigenetic events should be further studied.

Key words: parental behavior, social affiliation, hippocampus, BDNF, oxytocin, CRH, epigenetics.

INTRODUCTION

Variations in parental environment during development can affect adult phenotype in profound ways (Heim et al., 2002; Repetti et al., 2002; O'Donnell et al., 2014; Samek et al., 2015). In humans, for example, childhood family environments characterized by high conflict and low quality attachments are associated with vulnerability to social and emotional processing deficits (Repetti et al., 2002) as well as an increase in the risk for developing psychopathology in adulthood (Bifulco et al., 1991; Brown and Anderson, 1991; Felitti et al., 1998; Heim et al., 2002; Yam et al., 2015). It has been shown that father absence is a risk factor for a host of negative outcomes such as the development of depressive symptoms and externalizing behaviors (Culpin et al., 2013; McLanahan et al., 2013). In contrast, increased maternal responsiveness is associated with an increase in infant development including social, emotional, and cognitive competence (Landry et al., 2006). Therefore, early parental environment predicts susceptibility and resiliency to adult psychopathology (Smith and Prior, 1995; O'Donnell et al., 2014). Studies using functional magnetic resonance imaging (fMRI) have elucidated some of the brain regions, including the hippocampus as well as the cingulate and prefrontal cortices, that are affected by early childhood adversity (Brooks et al., 2014; Elton et al., 2014; Sripada et al., 2014; Jensen et al., 2015). However, the neurochemical systems that are affected by early life perturbations are less known due to the inherent difficulty of human studies.

Animal models demonstrating the effects of early life experience on adult outcome have shown high predictive and face validity, and have provided insights into neural mechanisms. Studies in rats and mice have shown that prenatal stress or maternal separation results in increased anxiety- and depressive-like

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Abbreviations: BDNF, brain-derived neurotrophic factor; CRH, corticotrophin releasing hormone; CRHR1, corticotrophin releasing hormone receptor 1; CRHR2, corticotrophin releasing hormone receptor 2; EPM, elevated plus maze; fMRI, functional magnetic resonance imaging; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GR, glucocorticoid receptor; GRα, glucocorticoid receptor alpha; GRβ, glucocorticoid receptor beta; H3ace, histone 3 acetylation; H3K9ace, histone 3 acetylation at lysine 9; H3total, total histone 3; HPA, hypothalamic pituitary adrenal; MF, mother and father; MO, mother only; NADH, nicotinamide adenine dinucleotide dehydrogenase; OXTR, oxytocin receptor; PB, parental behavior; PD, paternal deprivation; PND, postnatal day; SOA, social affiliation; SOR, social recognition; TrkB, tropomyosin receptor kinase B; TrkBFL, tropomyosin receptor kinase B full length; TrkBt, tropomyosin receptor kinase B truncated; V1aR, vasopressin 1a receptor.

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behaviors in the adult offspring, as well as an increased neuroendocrine response to stress with a host of neurochemicals acting in brain regions involved in stress responses (Plotsky and Meaney, 1993; Pryce and Feldon, 2003; Daniels et al., 2004; Binder et al., 2011; Barbosa Neto et al., 2012). Notably, alterations in neurochemicals involved in plasticity and gene expression have been found in the hippocampus (Suri et al., 2013; Nishi et al., 2014; Sousa et al., 2014; Shin et al., 2016) – a brain region important for learning and memory as well as for the regulation of stress responses via interactions with the hypothalamic pituitary adrenal (HPA) axis (Kim et al., 2015). For example, maternal separation is associated with alterations in the expression of neurotrophic factors in the hippocampus of offspring, including brain derived neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB), as well as altered performance in hippocampal-dependent cognitive tasks (Marco et al., 2013; Suri et al., 2013; Hill et al., 2014). Furthermore, adult offspring of rat dams that received more maternal licking/grooming during development displayed higher levels of maternal licking/grooming toward their own offspring but lower levels of anxiety-like behaviors, stress-induced circulating corticosterone, and glucocorticoid receptor (GR) expression in the hippocampus, compared to ones that received less maternal licking/grooming during development (Liu et al., 1997; Francis et al., 1999). Interestingly, epigenetic events have been implicated in mediating the effects of maternal environment on hippocampal neurochemical expression and associated behaviors in the adult offspring (Fish et al., 2004; Champagne et al., 2006; Pan et al., 2014; Wang et al., 2014).

While data from animal studies have revealed new knowledge regarding the effects of maternal environment on adult outcome and the underlying neurochemical mechanisms, the effects of paternal deprivation (PD) are less studied. In humans, paternal care is related to adult well-being and PD has been found to be associated with a variety of negative outcomes (McLanahan et al., 2013). Additionally, according to reports from the U.S Census Bureau and Center for Disease Control, the number of children living in father absent homes is prevalent and increasing in the United States and this corresponds to less paternal–offspring contact (U. S. Census Bureau, 2012; Jones and Mosher, 2013). Considering that PD is prevalent and increasing in our society, it is imperative to understand the neural mechanisms underlying the negative association between early father absence and adult well-being for the prevention and treatment of related psychopathologies. While common laboratory rats and mice cannot serve as appropriate models as they do not naturally display paternal behavior, the emergence of the socially monogamous prairie vole (*Microtus ochrogaster*) model has provided an opportunity to study male parental behavior (PB) and its effects on offspring cognitive and behavioral functions as well as the underlying neurochemical mechanisms.

The prairie vole is a rodent species that displays behavioral features of social monogamy including long-term bonding between opposite-sex mates (pair bonding) (Williams et al., 1992; Getz and Carter, 1996; Lim et al., 2004), and thus has been established as an animal model to study the neurochemical regulation of social attachment (Carter et al., 1995; Young et al., 1998). Prairie vole fathers contribute to the care of their young, displaying the full range of maternal behaviors with the exception of nursing (Wang and Novak, 1992; Wang and Insel, 1996). Furthermore, PD affects the behavior of prairie vole offspring: reducing the display of alloparental behavior by juveniles toward their younger siblings (Wang and Novak, 1994) and impairing their ability to form a pair bond in adulthood (Ahern and Young, 2009; Ahern et al., 2011). In the present study, we aimed to characterize the behavioral and neurobiological consequences of PD in prairie voles. We compared adult male and female voles that grew up with or without a father, and examined their social and anxiety-like behaviors as well as the gene expression of several neurochemicals in the hippocampus that have been implicated in regulating stress resiliency and memory deficits in response to stressful life experience. We hypothesized that in the absence of early paternal experience, voles would show altered social and anxiety-like behaviors associated with alterations in hippocampal neurochemical systems.

EXPERIMENTAL PROCEDURES

Experimental animals

All animals used in our experiments were prairie voles (*M. ochrogaster*) produced by a breeding colony housed at Florida State University. Animals had *ad libitum* access to food and water, and cages were maintained on a 14:10 light:dark cycle with lights on at 0700. Subjects were the offspring of adult male and female prairie voles that were paired at the beginning of the experiment and were sexually naïve upon pairing. Paired animals were housed in large polycarbonate cages (45 × 22 × 20 cm) lined with cedar chip bedding and two cotton nestlets were provided for nest identification. Fifteen pairs gave birth to 56 offspring subjects over a period of five days. Upon litter birth (postnatal day 1: PND1), fathers remained with the female partners in the home cages (n = 8 pairs) or were permanently removed from the home cages (n = 7 pairs). Thus, subjects were either housed with both a mother and father (MF; n = 31) or mother only to create PD experience (MO; n = 25) from PND1 until PND21. Notably, during litter births we removed the father from every other litter so that the treatment groups were created in a counterbalanced manner. At weaning (PND21), subjects were weighed and housed until adulthood with a same sex conspecific that went through the same experimental treatment. Subjects were assigned identification numbers and half of the subjects were ear-punched to distinguish them from their cage mates. All experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee at Florida State University.

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