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Fathering in rodents: Neurobiological substrates and consequences for offspring

Karen L. Bales [a,b,*], Wendy Saltzman [c]

[a] Department of Psychology, University of California, Davis, USA
[b] California National Primate Research Center, USA
[c] Department of Biology, University of California, Riverside, USA

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ABSTRACT

This article is part of a Special Issue "Parental Care".

Paternal care, though rare among mammals, is routinely displayed by several species of rodents. Here we review the neuroanatomical and hormonal bases of paternal behavior, as well as the behavioral and neuroendocrine consequences of paternal behavior for offspring. Fathering behavior is subserved by many of the same neural substrates which are also involved in maternal behavior (for example, the medial preoptic area of the hypothalamus). While gonadal hormones such as testosterone, estrogen, and progesterone, as well as hypothalamic neuropeptides such as oxytocin and vasopressin, and the pituitary hormone prolactin, are implicated in the activation of paternal behavior, there are significant gaps in our knowledge of their actions, as well as pronounced differences between species. Removal of the father in biparental species has long-lasting effects on behavior, as well as on these same neuroendocrine systems, in offspring. Finally, individual differences in paternal behavior can have similarly long-lasting, if more subtle, effects on offspring behavior. Future studies should examine similar outcome measures in multiple species, including both biparental species and closely related uniparental species. Careful phylogenetic analyses of the neuroendocrine systems presumably important to male parenting, as well as their patterns of gene expression, will also be important in establishing the next generation of hypotheses regarding the regulation of male parenting behavior.

Introduction

Male parenting behavior is rare among mammals and displayed mostly by socially monogamous species (Kleiman, 1977; Lukas and Clutton-Brock, 2013). The fact that fathering behavior is displayed by humans (Cabrera and Tamis-LeMonda, 2012), and that human paternal behavior is highly variable, has led to a keen interest in the hormonal and neural substrates of this behavior (Bales et al., 2011b; Saltzman and Ziegler, 2014), as well as its effects on offspring (Braun and Champagne, 2014). Rodent species have been particularly informative in this area, due to the ease of experimentation with them, but also to the relatively high number of biparental species in this order, including prairie voles (*Microtus ochrogaster*), mandarin voles (*Microtus mandarinus*), Mongolian gerbils (*Meriones unguiculatus*), California mice (*Peromyscus californicus*), Djungarian hamsters (*Phodopus campbelli*), and Octodon degus (*Octodon degus*). In this paper, we review the current understanding of the neuroanatomical and hormonal bases of paternal care in rodents. We also summarize what is known about the effects of fathering behavior on offspring, which has mostly been studied by removing fathers from the family group and, more rarely, by examining effects of individual variation in paternal behavior on offspring in intact groups.

Neuroanatomical basis of paternal behavior

The neural circuitry underlying maternal behavior has been studied extensively in the rat and provides a useful starting point for investigating the neuroanatomical basis of male parental care. Maternal behavior in Norway rats (*Rattus norvegicus*) is thought to be regulated largely by two opposing neural systems, both of which are activated in response to output from the main and accessory olfactory systems to the medial nucleus of the amygdala (MeA) (reviewed by Numan (2014); Numan and Insel (2003)). In the absence of specific hormonal and neurochemical inputs (estrogen, progesterone, oxytocin), MeA activity leads to activation of the anterior hypothalamus and ventromedial nucleus of the hypothalamus. These regions in turn project to the periaqueductal gray, which promotes aversion to pup stimuli as well as defensiveness and avoidance, thereby inhibiting the expression of maternal behavior. In contrast, in the hormonal milieu associated with late pregnancy

* Corresponding author at: Department of Psychology, One Shields Ave., University of California, Davis, CA 95616, USA.
E-mail address: klbales@ucdavis.edu (K.L. Bales).

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and parturition, stimulation of the MeA leads to activation of the bed nucleus of the stria terminalis (BST) and the medial preoptic area of the hypothalamus (MPOA), stimulating attraction to stimuli (primarily odors) from pups and promoting maternal behavior.

As in females, the brain region most consistently implicated in male parental behavior is the MPOA. Adult male Norway rats do not engage in spontaneous parental behavior but can be induced to behave paternally through continuous exposure to pups, as is also the case for virgin female rats (i.e., sensitization (Rosenblatt, 1967)). Several studies indicate that the MPOA is essential for this process in adult males. For example, Rosenblatt et al. (1996) found that radiofrequency lesions of the MPOA prevented sensitization in adult males, at least for the 13 days of pup exposure over which males were tested. Sturgis and Bridges (1997) used the neurotoxin NMA to lesion the MPOA in castrated adult males treated with estrogen and progesterone. In contrast to radiofrequency lesions, NMA selectively targets cell bodies, sparing fibers of passage. MPOA lesions in this study inhibited the expression of paternal behavior (i.e., retrieving and crouching over pups) in previously sensitized rats. Collectively, these findings indicate that the MPOA is important for the expression of several specific behavioral components of paternal care during both the initiation and maintenance of pup-induced paternal behavior in the adult male rat. In addition, the MPOA appears to be a critical site for estrogenic facilitation of rat paternal behavior (Rosenblatt and Ceus, 1998). Most recently, a series of studies in the uniparental laboratory house mouse found that galaninin-expressing neurons in the MPOA are essential for expression of paternal behavior (Z. Wu et al., 2014).

Because male rats do not show spontaneous infant care, this species is not a particularly appropriate model for studies of paternal behavior. In fact, Rosenblatt et al. (1996) refer to sensitization in male rats as maternal behavior, because in this species only females display parental behavior under natural conditions. In this context, it is notable that both biparental California mice and uniparental white-footed mice (*Peromyscus maniculatus*) show increases in Fos-ir in the MPOA in response to pups (Lambert et al., 2013). More recent studies, therefore, have focused on neural and endocrine influences on paternal behavior in biparental species, in which both parents provide infant care under natural conditions (Bales et al., 2011b); (Table 1). In rodents, most of these studies have focused on the biparental prairie vole and California mouse. In these species, as in female rodents and male rats, the MPOA is crucial for the expression of paternal behavior. Lee and Brown (2002, 2007) characterized pup-directed behavior in male California mice that underwent electrolytic lesions of the MPOA three days after the birth of their first litter. Over the subsequent 10 days of testing, lesioned males showed a slower onset of paternal behavior, as well as less time engaging in paternal behavior (retrieving, sniffing, licking, or crouching over pups), less time in proximity to pups, and longer latencies to retrieve pups, compared to sham-lesioned males. Consistent with these findings, several studies of Fos-immunoreactivity (Fos-ir), an index of neuronal activation, have found increased Fos expression in the MPOA following exposure of males to pups. California mouse fathers, but not virgins or males housed with primigravid females (females in their first pregnancy), had elevated Fos-ir in the MPOA following exposure to a foster pup, compared to fathers similarly exposed to a control object (De Jong et al., 2009); but see De Jong et al. (2010). In prairie voles, virgin males had increased MPOA Fos-ir following exposure to an unrelated pup compared to exposure to a novel object (Kirkpatrick et al., 1994b). (Please note that affiliative behavior toward an unrelated pup, also known as alloparenting, is a common behavior in prairie voles, especially in males.)

Several studies of biparental rodents provide evidence that the amygdala, in addition to the MPOA, is involved in paternal behavior. In California mice, lesions of the basolateral nucleus of the amygdala (BLA) had effects on parental behavior that were very similar to those of MPOA lesions (Lee and Brown, 2007). Specifically, new, first-time fathers with BLA lesions spent less time engaging in paternal behavior, licking pups, and in proximity to pups, as well as longer latencies to retrieve pups, compared to sham-lesioned males. In contrast, Kirkpatrick et al. (1994a) found that in young adult male prairie voles housed with ovariectomized females, electrolytic lesions of the BLA had no effect on responses to pups, whereas electrolytic lesions of the corticomedial amygdala or the MeA reduced males' contact time with pups. Immunohistochemical studies have further implicated the amygdala and the BST, considered part of the "extended amygdala" (Davis et al., 2010), in paternal behavior. Virgin male prairie voles exposed to a pup had higher Fos-ir in the MeA and medial BST, compared to males exposed to a control object (Kirkpatrick et al., 1994b), while in California mice exposed to a foster pup, fathers had significantly higher Fos-ir in both the medioventral and medial posteromedial amygdala, compared to virgin males (De Jong et al., 2009).

Not surprisingly, the olfactory bulbs also appear to play a critical role in rodent paternal behavior. This region has received little attention; however, bilaterally bulbectomized, virgin adult male prairie voles were significantly more likely to attack pups than were sham-lesioned males (Kirkpatrick et al., 1994c), suggesting that olfactory cues normally inhibit pup-directed aggression. In the same species, exposure to a pup elevated Fos-ir in the accessory olfactory bulbs, compared with exposure to a control object (Kirkpatrick et al., 1994b).

Immunohistochemical studies have identified several additional brain regions that might be associated with paternal care in biparental rodents. In California mouse fathers, exposure to a pup increased Fos-ir in the caudal dorsal raphe nucleus and the lateral habenula (De Jong et al., 2009, 2010), whereas in virgin male prairie voles, pup exposure elevated Fos-ir in the lateral septum, paraventricular nucleus of the thalamus, and nucleus reuniens of the thalamus (Kirkpatrick et al., 1994b). Virgin male California mice also exhibited elevated Fos-ir in the lateral septum when compared to either pup-exposed virgins or fathers (Lambert et al., 2011). The roles of these regions in paternal care, if any, are unknown.

In summary, findings from immunohistochemical and lesion studies suggest that paternal care in biparental rodents is associated with some of the same brain regions implicated in maternal care, including the olfactory bulbs, MeA, BST, and MPOA. The precise roles of these and other brain regions in both the initiation and maintenance of paternal behavior are not yet known, however, and the generalizability of these findings are not clear, as they come from only two cricetid rodents.

Intriguingly, recent studies have found that fatherhood influences neural plasticity in several rodent species. Lieberwirth and colleagues (Lieberwirth et al., 2013) used the cell-division marker bromodeoxyuridine (BrdU) to investigate neurogenesis in male prairie voles, and found that fatherhood reduced the survival of new cells in the amygdala, dentate gyrus, and hypothalamus, but not the main olfactory bulbs. In the California mouse, Glasper and colleagues (Glasper et al., 2011) found that fatherhood inhibited hippocampal neurogenesis in the California mouse. Lambert et al. (2011) found that biparental California mice had higher levels of nestin-ir in CA2 and CA3, while uniparental white-footed mice had higher glial fibrillary acid protein in dentate gyrus and hippocampal fissure (Lambert et al., 2011). They interpreted this as indicating higher neuroplasticity in the biparental species and higher glial plasticity in the uniparental species. Finally, a fascinating series of studies in the uniparental house mouse (*Mus*) indicated that interactions of adult male mice with their own pups stimulated neurogenesis in the father's subventricular zone and dentate gyrus under the influence of prolactin signaling (Mak et al., 2013; Mak and Weiss, 2010). Some of the new cells matured into olfactory interneurons in the olfactory bulb, where they responded preferentially to offspring odors and appeared to subserve later recognition of mature offspring. These results highlight potential differences in the role of pup cues in neurogenesis in males of different species, and may highlight differences between males of biparental and uniparental species;