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Hormones and Behavior 46 (2004) 30–38
Hormones and Behavior
www.elsevier.com/locate/yhbeh

Effect of neonatal handling and paternal care on offspring cognitive development in the monogamous California mouse (*Peromyscus californicus*)

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Received 10 February 2003; revised 1 May 2003; accepted 23 September 2003
Available online 24 May 2004

Abstract

In the laboratory rat and mouse, neonatal handling enhances hippocampal-dependent learning in adulthood, an effect mediated by changes in maternal behavior toward the handled young. In the present study, we examined the interaction between neonatal handling and biparental care during the early postnatal period and its effect on cognitive function in adult California mice (*Peromyscus californicus*). We characterized the parental behavior of handled and nonhandled father-present and father-absent families over the first 15 days of life. We then assessed cognitive performance of male and female offspring in the Barnes maze and object recognition test after they were 60 days of age. We found that the amount of licking and grooming received by pups was decreased in father-absent families. By postnatal days 12–15, licking and grooming in handled, father-absent families were equivalent to that of nonhandled, father-present families. Handling enhanced novel object recognition in father-present male mice with no effect in females. In the nonhandled group, the presence of the father had no effect on object recognition learning in male or female mice. Handling also enhanced spatial learning in the Barnes maze. In nonhandled families, the presence of the father appeared to have no effect on spatial learning in the male offspring. Interestingly, spatial learning in nonhandled, father-absent, female offspring was similar to that of handled animals. The average amount of licking and grooming received by pups was negatively correlated with the average number of errors made on the first day of reversal training in the Barnes maze. These data support previous findings that neonatal handling facilitates learning and memory in adulthood, suggest that under certain environmental conditions, there is a sex difference in the response of pups to paternal care, and further demonstrate the importance of active parental investment for offspring cognitive development.

Keywords: Biparental; Handling; Paternal; Barnes maze; Object recognition

Introduction

The effects of early life experience such as neonatal handling and maternal deprivation on the developing hippocampus may be responsible for individual differences in cognitive function in adulthood. For example, neonatal handling enhances cognition and delays age-related learning impairments, while maternal deprivation in infancy diminishes cognitive functioning and exacerbates age-related learning impairments (Meaney et al., 1988, 1991; Oitzl et al., 2000; Tang, 2001). The effects of early handling and maternal deprivation on behavioral development are mediated by changes in maternal behavior toward the young (D'Amato et al., 1998; Levine, 1967; Liu et al., 1997; Smotherman et al., 1977; Villescas et al., 1977). Tactile stimulation derived from maternal licking and grooming of the young appears to be a critical factor for hippocampal development. In rats, the offspring of mothers that show increased licking and grooming exhibit enhanced spatial and nonspatial learning and memory (Bredy et al., 2003; Liu et al., 2000). Further, individual variation in maternal care contributes to differences in cognitive development in humans and primates, as well as rodents (Bornstein, 1985; Liu et al., 2000; Ruddy and Bornstein, 1982; Tamaroff et al., 1986; Zaharia et al., 1996).

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0018-506X/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.yhbeh.2003.09.017

While much is known about the influence of maternal care on pup development, very little is known about the contribution of paternal care toward offspring neural and behavioral development. The California mouse (*Peromyscus californicus*) is a biparental rodent that is well suited for the study of the effects of biparental care on offspring development. *P. californicus* is exclusively monogamous in the wild, has persistent pair bonding, and a high level of paternal investment (Dudley, 1974a; Gubernick and Alberts, 1987). Further, male *P. californicus* displays all the components of parental behavior shown by mothers (huddling, licking and grooming, carrying and retrieving), with the exception of arched-back nursing and lactation (Dudley, 1974b; Gubernick and Alberts, 1987). In the wild, the presence of the male is crucial for offspring survival, and in the laboratory, the presence of the male enhances reproductive success and offspring survival when parents are required to forage for food (Cantoni and Brown, 1997; Gubernick and Teferi, 2000; McInroy et al., 2000; Wright and Brown, 2002). Moreover, *P. californicus* pups reared with both parents receive almost twice as much parental licking and grooming as pups reared with the mother alone (Wright and Brown, 2002). The evidence suggests that paternal investment is a direct process whereby the male actively contributes to offspring viability (Cantoni and Brown, 1997; Gubernick and Teferi, 2000; Wright and Brown, 2002).

Over the past four decades, Levines' (1967) neonatal handling model has provided much information on the effects of early environmental experience on neural development. Confirmation that the effects of handling are mediated, in part, by changes in maternal care has led to a greater understanding of the importance of the mother–infant interaction early in life. With this knowledge of early experience and maternal care effects in mind, we have begun to explore the importance of biparental care for offspring development. There are several reasons for returning to the handling model and combining it with the biparental care concept: (1) there is little information on the direct effects of handling on cognitive development in both males and females; hence, our aim was to extend the handling literature to include a new model species, *P. californicus*; (2) until now, the importance of paternal care for offspring development has received little attention since it cannot be examined in the rat; and (3) by using a manipulation that is known to increase maternal behavior toward the young, we sought to extend the literature to include the effect of increased biparental care (as well as the effect of handling induced increases in maternal care in the absence of the father), eventually moving toward elucidating and confirming the neural mechanisms mediating the influence of biparental care on offspring brain development.

Maternal licking and grooming contributes to offspring cognitive development in rats and mice (Bredy et al., 2003; Liu et al., 2000; Zaharia et al., 1996), and *P. californicus* pups receive additional licking and grooming from the father (Wright and Brown, 2002). Therefore, this study was designed to examine the interactions between neonatal handling, and biparental behavior during the early postnatal period and their effects on cognitive function in adult *P. californicus*. We characterized the parental behavior of handled and nonhandled biparental and father-absent family units over days 3–15 of life. We then assessed cognitive performance of male and female offspring in the Barnes maze and object recognition test after they were 60 days of age. We chose the Barnes maze because it is hippocampal-dependent and, while providing similar information about spatial learning, is a less stressful alternative to the Morris water maze (McLay et al., 1999; Poe et al., 2000). We used the object recognition test, although there is some controversy as to whether this task is hippocampal dependent, because it is a nonspatial, associative memory task that relies heavily on an animals' initial reactivity to novelty (Mumby et al., 2002; Rampon et al., 2000; Renner et al., 1992). These tests were used because, as previously mentioned, there is little information on the effect of neonatal handling on spatial and nonspatial learning and memory in rodents.

In the present study, we addressed the following questions: (1) What is the effect of neonatal handling on parental care in *P. californicus*? We expected that neonatal handling would increase parental licking and grooming toward the young from birth to weaning; (2) What is the effect of neonatal handling and paternal care on offspring spatial and nonspatial learning and memory in adulthood? If paternal behavior contributes to cognitive development, then pups reared without their father will be licked and groomed less often in infancy and exhibit poorer learning and memory in adulthood; and (3) Are there gender differences in offspring cognitive development in response to handling and paternal care? We hypothesized that male and female *P. californicus* would show a comparable response to handling and/or the absence of paternal care, given that in rats, postnatal handling delays age-related learning impairment in both sexes (Meaney et al., 1988, 1991).

Materials and methods

Postnatal environment (handling paradigm)

Forty *P. californicus* breeding pairs were established in our colony at Dalhousie University. The mice were housed in standard Plexiglas cages with pine bedding, on a 16:8 reversed light–dark cycle with lights off at 0900, at a temperature of 22 °C, and fed laboratory rodent chow (Agribrand #5001) and water ad libitum. At birth, litters (2–3 pups/litter) were randomly assigned to one of four groups with 10 litters/group (nonhandled father-present, handled father-present, nonhandled father-absent, and handled father-absent). The handling procedure was conducted