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SYMPOSIUM

Paternal Care in Biparental Rodents: Intra- and Inter-individual Variation

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Synopsis Parental care by fathers, although rare among mmmals, can be essential for the survival and normal development of offspring in biparental species. A growing body of research on biparental rodents has identified several developmental and experiential influences on paternal responsiveness. Some of these factors, such as pubertal maturation, interactions with pups, and cues from a pregnant mate, contribute to pronounced changes in paternal responsiveness across the course of the lifetime in individual males. Others, particularly intrauterine position during gestation and parental care received during postnatal development, can have long-term effects on paternal behavior and contribute to stable differences among individuals within a species. Focusing on five well-studied, biparental rodent species, we review the developmental and experiential factors that have been shown to influence paternal responsiveness, and consider their roles in generating both intra- and inter-individual variation. We also review hormones and neuropeptides that have been shown to modulate paternal care and discuss their potential contributions to behavioral differences within and between males. Finally, we discuss the possibility that vasopressinergic and possibly oxytocinergic signaling within the brain, modulated by gonadal steroid hormones, may represent the "final common pathway" mediating effects of developmental and experiential variables on intra- and inter-individual variation in paternal care.

Introduction

In all mammals, mothers invest heavily in producing and rearing their offspring. Fathers, in contrast, provide care for their young in only an estimated 5–10% of mammalian taxa (Kleiman and Malcolm 1981). Paternal care is often associated with social monogamy and can involve such behaviors as warming, feeding, protecting, retrieving, and grooming infants, depending on the species (Kleiman and Malcolm 1981). In these biparental mammals, fathers can make important and lasting contributions to the survival and development of their offspring, including effects on social, reproductive and aggressive behavior, neural development, endocrine function, emotionality, and cognition that persist into adulthood (reviewed in Braun and Champagne 2014; Bales and Saltzman 2016).

Not surprisingly, our understanding of the proximate basis of paternal care has lagged far behind that of maternal care. In recent years, however, considerable progress has been made in elucidating developmental, social, hormonal, and neural determinants of paternal behavior, primarily in biparental rodents. Much of this work has focused on determinants of within-animal changes in males' responses to pups across the lifespan: males of some species undergo

predictable changes in their behavioral responses to pups, transitioning, in some cases, between aggression, indifference, and nurturance at different life stages. More recently, attention has begun to focus on between-individual variation in pup responsiveness, addressing both its causes and consequences. While it is becoming apparent that behavioral differences among fathers can translate into long-term differences among their offspring, the environmental and organismal sources of these differences have, for the most part, not yet been addressed in an integrated manner.

In this article, we discuss proximate determinants of males' behavioral responses to pups in biparental rodents within the context of both intra- and inter-individual variation in paternal and allopaternal care. We begin by briefly reviewing findings on endocrine and neuroendocrine influences on paternal behavior. Next, we describe developmental and experiential influences, focusing first on determinants of longitudinal changes in males' responses to pups across the lifespan and second on sources of variation among individuals within a particular species. Finally, we examine the possibility that the brain's vasopressinergic systems, and possibly the oxytocinergic system, in association with gonadal steroid hormones, may represent a "final common pathway" mediating both within- and between-animal variation.

Several important points should be noted. First, we focus exclusively on naturally biparental rodents, in which fathers routinely provide care for their offspring; we do not include studies of uniparental rodents (e.g., *Rattus, Mus*) or other taxa, although findings from these groups might complement or extend those from biparental rodents. Second, although approximately 6% of rodent genera are estimated to perform biparental care (Kleiman and Malcolm 1981), paternal care has been studied in only a handful of these species, most notably the prairie vole (*Microtus ochrogaster*), mandarin vole (*M. mandarinus*), California mouse (*Peromyscus californicus*), Campbell's dwarf hamster (*Phodopus campbelli*), and Mongolian gerbil (*Meriones unguiculatus*). These species come from only two families (Cricetidae: prairie vole, mandarin vole, California mouse, Campbell's dwarf hamster; Muridae: Mongolian gerbil) and only one of the major rodent lineages (Fabre et al. 2012), and therefore may not be representative of biparental rodents in general.

Third, in spite of the relatively close phylogenetic relationships among these species, it should not be assumed that influences on and mechanisms underlying the expression of paternal behavior are consistent across taxa. Thus, we attempt to develop a general model of the proximate basis of paternal behavior that may be broadly applicable across taxa, while highlighting observed differences among species.

Fourth, although these five species are classified as biparental based on observations in both free-living and captive animals, mechanistic studies of paternal behavior have been performed almost exclusively under highly controlled laboratory conditions. Moreover, although some investigators characterize fathers' behavior toward their own pups in the context of the entire family, the most common experimental paradigm is to quantify behavior of a juvenile or adult male toward a single, experimentally presented, unrelated pup in the absence of other individuals or stimuli with which to interact. This paradigm is extremely useful for controlling and standardizing the physical and social environment during testing, but clearly is highly artificial and simplistic. Thus, these studies almost certainly underestimate the complexity and diversity of environmental influences on paternal behavior.

Fifth, although nurturant behavior by any male toward a non-descendant, immature conspecific should, technically, be referred to as "allopaternal behavior" or "allopaternal care," we use these phrases specifically to refer to nurturant or affiliative behavior performed toward conspecific pups by immature males, since alloparents in these species are likely to be juveniles. We use "paternal behavior" or "paternal care" to refer to such behavior by adult males, whether or not the male and the pup are related, to facilitate comparisons among animals in different reproductive conditions. Similarly, we use the terms "allopaternal responsiveness" and "paternal responsiveness" to refer to the propensity of an immature or adult male, respectively, to perform nurturant behavior towards pups.

Finally, it should be noted that different components of paternal or allopaternal behavior, such as huddling, licking/grooming, and retrieving a pup, may be influenced by somewhat different neural, endocrine, and experiential factors. Furthermore, although we discuss several studies that focus on infanticide, aggression toward pups should not be assumed to represent, at a mechanistic level, the inverse of parental care (Dulac et al. 2014).

Neuroendocrine influences on paternal behavior

Males in biparental mammalian species undergo systematic changes in hormonal and neuropeptide signaling during the transition to fatherhood, in association with pair formation, mating, cohabitation with a pregnant female, and/or exposure to

infants. Some of these changes differ across species, and their functional significance, including potential effects on paternal behavior, is generally unknown. Endocrine and neuroendocrine changes in fathers, as well as their possible functions, have been reviewed in detail recently (Saltzman and Ziegler 2014; Bales and Saltzman 2016). Therefore, we discuss them only briefly here, focusing primarily on experimental rather than correlational findings.

The anterior pituitary hormone prolactin has been referred to as "the hormone of paternity" (Schradin and Anzenberger 1999), as circulating or excreted levels are elevated in fathers of numerous biparental species and often correlate with males' expression of allopaternal or paternal behavior (Saltzman and Ziegler 2014; Hashemian et al. 2016). To our knowledge, however, prolactin has not been shown to have a causal influence on allopaternal or paternal care in any rodent species.

Circulating testosterone concentrations, on the other hand, are typically reduced in fathers and have been shown convincingly to influence the expression of paternal behavior; however, effects may differ both within and among species. In California mice, castration reduces and testosterone or estrogen replacement restores parental behavior (Trainor and Marler 2001, 2002). Similar results were found in virgin male Mongolian gerbils housed in same-sex groups (Martínez et al. 2015); however, virgin male gerbils housed with a lactating female showed the opposite pattern (Clark and Galef 1999). Studies of prairie voles have likewise yielded mixed results: castration either reduced (Wang and De Vries 1993) or did not alter (Lonstein and De Vries 1999) responses to pups in virgin males. Finally, castration did not alter paternal behavior in a study of Campbell's dwarf hamster fathers (Hume and Wynne-Edwards 2005).

The stimulatory effect of testosterone in California mice is mediated by aromatization of testosterone to estrogen in the brain (Trainor and Marler 2002). Few other studies have investigated effects of estrogen on allopaternal or paternal behavior in juvenile or adult males. In prairie voles, however, Cushing et al. (2008) found that experimentally increasing the expression of estrogen receptor α (ERα) in the medial amygdala (MeA) via a viral vector inhibited parental behavior in adult males, while increasing ERα expression in the bed nucleus of the stria terminalis (BNST) had no effect (Lei et al. 2010).

The neuropeptide vasopressin (AVP) has been strongly implicated in the expression of paternal behavior. Both within and among rodent species, paternal behavior correlates with patterns of AVP-immunoreactivity and AVP binding, particularly in the lateral septum (LS) and other parts of the extended amygdala (reviewed by Bales and Saltzman 2016). Moreover, central injection of AVP promotes paternal behavior whereas central infusion of AVP receptor antagonists has the opposite effect in both the obligately biparental prairie vole (Wang et al. 1994; but see Bales et al. 2004) and the facultatively biparental meadow vole (*M. pennsylvanicus*; Parker and Lee 2001). On the other hand, castration of male prairie voles virtually eliminates AVP-immunoreactivity in the LS and lateral habenular nucleus (LHN) but does not alter paternal behavior, indicating that AVP signaling in these areas is not essential for expression of paternal care (Lonstein and De Vries 1999).

Oxytocin, the "sister" neuropeptide of AVP, facilitates both maternal and allomaternal behavior in rodents (Bridges 2015; Kenkel et al. 2017). In contrast, little is known about effects of oxytocin on paternal and allopaternal care. Paternal behavior in adult virgin male prairie voles was inhibited by combined intracerebroventricular treatment with an AVP receptor antagonist and an oxytocin receptor antagonist, but not by either antagonist alone (Bales et al. 2004); however, the oxytocin receptor antagonist that was used was later found to more potently antagonize the AVP receptor than the oxytocin receptor (Kenkel et al., 2017), leaving the results of this study difficult to interpret. More recently, treatment with a different oxytocin receptor antagonist acutely inhibited parental behavior in adult male prairie voles in a dose-dependent manner (described in Kenkel et al. 2017).

Very few studies have addressed possible organizational effects of early-life hormone exposure on paternal behavior. In male prairie voles, however, exposure to androgens, estrogens and oxytocin during the postnatal period appears to be vital for expression of paternal behavior in adulthood (reviewed by Bales and Saltzman 2016).

Some or all of the hormones and neuropeptides thought to influence paternal behavior might also play key roles in determining within- and between-individual differences in paternal and allopaternal responsiveness. Therefore, in describing sources of variation in paternal and allopaternal care, below, we point out, where possible, hormonal and neuropeptide differences that correlate with—and might underlie—this variation (Fig. 1).

Within-animal changes in behavioral responses to pups

Age

Allopaternal or paternal responsiveness in biparental rodents is modulated by males' age and/or

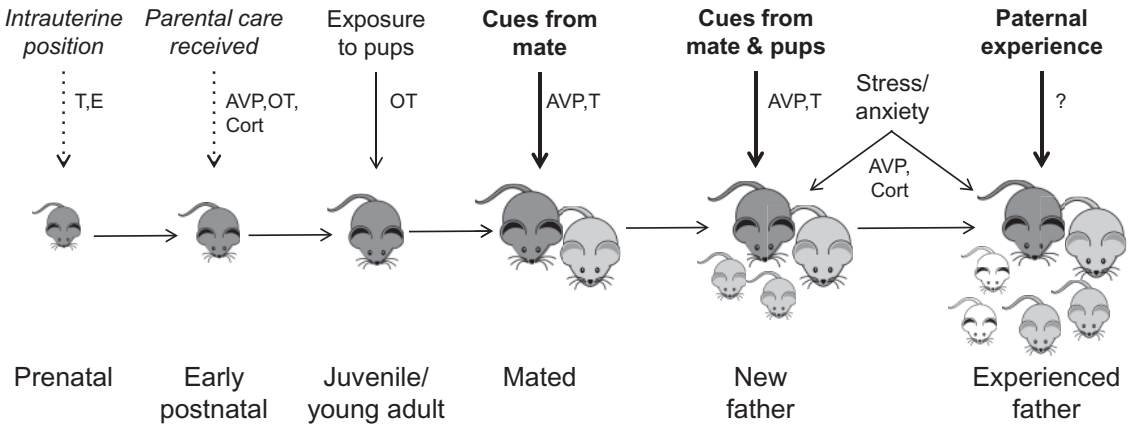

Fig. 1 Experiential effects on allopaternal and paternal responsiveness acting at different life stages in biparental rodents, as well as hormones and neuropeptides that have been implicated correlationally and/or experimentally. Bold text and thick arrows indicate cues or experiences routinely encountered during reproduction. Italicized text and dashed arrows indicate early-life influences that may differ across animals and contribute to stable inter-individual differences in (allo)paternal responsiveness. Non-italicized text and thin arrows indicate factors that might contribute to either intra- or inter-individual differences over a variable time span. T: testosterone; E: estrogen; AVP: vasopressin; OT: oxytocin; and Cort: corticosterone.

developmental stage (e.g., juvenile, adult) as well as reproductive status (e.g., sexually naïve, mated, father), with males typically showing (1) high levels of allopaternal care and little or no infanticide toward younger siblings or unfamiliar pups, as juveniles, (2) a decrease in nurturant responses to pups and, in some cases, increased rates of infanticide, as sexually naïve adults, and (3) pronounced paternal responsiveness and little or no infanticide toward either descendant or unrelated pups during cohabitation with a pregnant or lactating female. In male Mongolian gerbils, for example, (allo)paternal responsiveness, as measured by time spent with pups as well as preference for pups over an empty nest, declines from the age of weaning until young adulthood, and thereafter begins to increase again (Clark and Galef 2001), whereas infanticide toward unrelated pups shows the opposite pattern (Elwood 1980). Interestingly, testosterone levels follow roughly the same pattern across development as infanticide (Probst 1987), such that the peak in testosterone levels (~75 days of age) coincides with the peak in infanticide and the nadir in nurturant behavior toward pups (Clark and Galef 2001).

In prairie voles, males and females of all ages tend to behave affiliatively toward pups. Nonetheless, they, like Mongolian gerbils, exhibit a shift in behavioral responses to pups around the age of puberty: for virgin males and females combined, individuals older than 40 days both retrieve and attack unfamiliar pups more than do individuals 40 days and younger; testosterone levels in males rise at around 45 days of age (Roberts et al. 1999). In virgin male California mice, affiliative behavior toward unrelated pups declines across the juvenile period and remains low into adulthood (Gubernick and Laskin 1994); however, testosterone levels have not been characterized in young males across the pubertal period. In contrast to Mongolian gerbils, prairie voles, and California mice, sexually naïve male Campbell's dwarf hamsters do not show significant changes in affiliative behavior toward pups from the early postpubertal period to mid-adulthood (Gregg and Wynne-Edwards 2005; Vella et al. 2005). Again, however, hormonal changes across this period have not been characterized.

Cues from the mate

Males' responses to pups can be influenced dramatically by cues from or interactions with a female mate. Bamshad et al. (1994) compared behavioral responses to unfamiliar pups among male prairie voles 0, 2, 13 or 21 days after they were paired with an adult female, or 6 days following the birth of their first litter (approximately 30 days after pairing). Males' duration of time spent in paternal behavior toward an unfamiliar pup was positively correlated with length of cohabitation with a female, and males whose mates were in the late stages of pregnancy or early stages of lactation were markedly more likely than other males to behave paternally. Circulating testosterone concentrations did not differ among the groups of males, but AVP-immunoreactivity in the LS and LHN changed with duration of cohabitation: AVP-immunoreactivity in both regions declined significantly within 3 days after pair formation and increased gradually across the mate's pregnancy. In a separate study of prairie

voles, 3 days of cohabitation with a female elevated males' plasma testosterone levels and increased expression of AVP mRNA in the BNST, a likely source of AVP detected within fibers in the LS and LHN (Wang and De Vries 1993). Thus, the authors speculated that cohabitation with a female increases synthesis of AVP in the BNST and release of AVP in the LS and LHN, potentially leading to enhanced paternal responsiveness.

In Mongolian gerbils, similar to prairie voles, paternally inexperienced males show a sharp reduction in infanticide and an increase in paternal behavior toward an unrelated pup across the course of their mate's first pregnancy (Elwood 1977). The same pattern is seen in virgin male gerbils housed with a female during roughly the second half of her pregnancy (Clark et al. 2001). In expectant first-time fathers, this inhibition of infanticide appears to be mediated largely by physical and visual contact with the mate: males that were prevented from engaging in physical contact with their mate, especially those that were also prevented from seeing the mate, during the last few days of pregnancy were significantly more likely to kill an experimentally presented, unrelated pup than expectant fathers with full physical and sensory access to their mates (Elwood 1980). Olfactory cues from the pregnant mate, on the other hand, did not appear to play a role in the inhibition of infanticide in expectant fathers (Elwood and Ostermeyer 1984). Interestingly, experienced fathers, in contrast to first-time fathers, show pronounced paternal behavior toward unrelated pups whether or not the mate has been removed, indicating that experience with pups has a long-term facilitatory effect on the maintenance of paternal responsiveness (Elwood and Ostermeyer 1984). California mouse fathers whose mates have recently given birth to their first litter show more paternal behavior toward an unrelated pup than do age-matched virgin adult males housed with another male, whereas responses to pups do not differ markedly between new fathers and males whose mates are pregnant with their first litter (De Jong et al. 2009). Finally, in adult male mandarin voles, both mating/cohabitation with a female and fatherhood Increase expression of some components of paternal behavior (Song et al. 2010).

Cues from a mate can facilitate not only the onset but also the maintenance of paternal behavior. California mouse fathers housed with their mates tend to be highly paternal toward an unrelated pup 3 days after the birth of their litter, regardless of whether their own litter is removed on the day of birth or remains with the parents. On the other hand, fathers that are permanently separated from both their mate and pups on the day of parturition are much less likely to behave paternally toward an unrelated pup 3 days later, and more likely to commit infanticide, compared to males that remain with their mate (Gubernick and Alberts 1989). Thus, continuous exposure to the mate, but not to the pups, is important for the maintenance of paternal responsiveness in new fathers. Finally, paternal responsiveness is maintained in California mouse fathers that are housed without their mate and pups but are exposed to urine from their mate, indicating that chemosensory cues from the mate, but not necessarily from the pups, are important for the maintenance of paternal responsiveness in fathers during the early postpartum period (Gubernick 1990).

Previous exposure to pups

Interactions with younger siblings or unrelated pups, either during the juvenile period or in adulthood, may contribute to both intra- and inter-individual differences in (allo)paternal responsiveness in some biparental rodents. Virgin male prairie voles that have lived with younger siblings are significantly more likely to behave paternally to an unfamiliar pup than those that have no experience with younger siblings, although most males in both conditions behave paternally (Roberts et al. 1999). Similarly, in California mice, virgin males that have lived with their parents and younger siblings show high levels of paternal care toward an unrelated pup, compared to virgin males that have lived with only their parents and a littermate but no younger siblings, or with only a littermate (Gubernick and Laskin 1994). This effect is age-limited, however: nurturant behavior toward experimentally presented pups decreases from the young juvenile period to adulthood, and previous cohabitation with younger siblings does not affect pup-directed behavior in older juveniles or adults (Gubernick and Laskin 1994). In Mongolian gerbils, unlike both prairie voles and California mice, cohabitation with younger siblings does not appear to alter behavioral responses to pups in adult virgin males, in terms of frequency of infanticide (Elwood 1980; Saltzman et al. 2009); however, effects on parental behavior *per se* have not been evaluated.

Species also differ in whether repeated exposure to pups during adulthood facilitates the onset of paternal care. In a recent study of California mice, Horrell et al. (2017) found that adult virgin males with no previous exposure to pups engaged in less paternal behavior than new fathers, as observed in other studies, but that virgins' paternal responsiveness was

increased by repeated, brief (20-min) exposure to pups: after 2-3 exposures, virgin males' behavioral responses to pups did not differ from those of new fathers. In adult, virgin male mandarin voles, even a single, 10-min exposure to an unrelated pup increased paternal responsiveness to an unrelated pup 1 week later (Song et al. 2010). In contrast, repeated 10-min exposure to a pup did not reliably alter paternal behavior in adult virgin Campbell's dwarf hamsters, even after four exposures (Vella et al. 2005). Similar to dwarf hamsters, adult, virgin male prairie voles showed no change in parental behavior after 3 consecutive 20-min exposures to pups over 6 days (Kenkel et al. 2013).

Stress and anxiety

Age, cues from a mate, and experience with pups are predictable developmental factors that influence the expression of affiliative behavior toward pups over the life of an individual animal in several biparental rodent species. In contrast, affective factors, especially stress and anxiety, may exert more subtle and possibly more transient effects on males' responses to pups, and are likely to differ among individuals as a result of environmental and genetic influences. Thus, stress and anxiety could potentially contribute to both within- and between-animal differences in allopaternal and paternal care.

Maternal care by rodent mothers can be impaired by exposure to acute or chronic stressors or to experimental increases in corticosterone or corticotropin-releasing factor (e.g., Nephew and Bridges 2011; Klampfl et al. 2014; Pereira et al. 2015). Relatively little is known, however, about effects of stress or stress-related hormones or neuropeptides on allopaternal or paternal behavior, and in the few studies addressing this topic, results have mostly been fairly subtle.

Two studies have found that acute stress or acute increases in stress hormones can alter males' interactions with pups. Virgin male prairie voles tested with an unfamiliar pup for 10 min were more likely to behave paternally and spent more time engaged in paternal behavior if they underwent a swim stressor 45 min before exposure to the pup than if they did not. Moreover, males' circulating corticosterone concentrations immediately after interactions with the pup correlated negatively with the amount of time spent licking and grooming the pup (Bales et al. 2006). In contrast, California mouse fathers that underwent acute corticosterone treatment, which raised their circulating corticosterone to supraphysiological levels, were nominally slower to contact their own pups when tested in the absence of the mate, but no effects of corticosterone were seen on the frequency or duration of fathers' interactions with their offspring when tested either with or without the mate present (Harris et al. 2011).

Harris et al. (2013) evaluated effects of a 7-day chronic variable stress paradigm on paternal behavior of California mouse fathers beginning 1-3 days after the birth of their first litter. Despite the clear physiological effects of the stress paradigm (De Jong et al. 2013), effects on paternal behavior were modest. Most notably, upon being reunited with their mate and pups following acute exposure to a restraint stressor, fathers spent less time engaging in paternal behavior and grooming their female mate, compared to fathers that were removed from and returned to their families without being exposed to an additional stressor. Aside from these behavioral differences immediately following stressor exposure, only minor behavioral differences were observed between fathers in the chronic variable stress and control conditions. These results suggest that males increase pup- and mate-directed behaviors following a brief separation from their family (consistent with Bredy et al. 2004), but that stress can block this effect. Interestingly, chronically stressed fathers in the same study had increased levels of AVP mRNA in the paraventricular nucleus of the hypothalamus (PVN) compared to non-stressed fathers and also showed higher levels of autogrooming following stress. Both PVN expression of AVP and autogrooming are linked to anxiety in rodents (Ferré et al. 1995), suggesting that anxiety, as well as stress, might inhibit paternal behavior.

In addition to experimental studies, several correlational studies, mostly in California mice, provide evidence for links between paternal responsiveness and stress or anxiety. Latency of adult male California mice to approach a novel object (a measure of neophobia) was positively and significantly correlated with latency to perform paternal behavior toward an unfamiliar pup (Chauke et al. 2012). In the same species, Lambert et al. (2011) found a negative correlation between the total time that virgin males spent performing paternal behavior toward an unrelated pup and the expression of the immediate-early gene Fos in the PVN, a region strongly involved in the stress response, following a 10-min exposure to the pup. Finally, De Jong et al. (2012) found that latencies of adult virgin males to sniff an unfamiliar pup correlated positively with expression

of AVP mRNA in the PVN and negatively with urine marking in the center of a novel environment; both of these measures are considered indices of anxiety. Taken together, these findings suggest that paternal responsiveness may be inversely related to anxiety and stress-reactivity, at least in the short term.

Intriguingly, two studies have provided evidence that consumption of placenta by adult male California mice can reduce males' anxiety and increase their willingness to interact with pups. First, Perea-Rodriguez (2016) treated adult virgin males with either near-term placenta homogenized in oil or oil alone via oral gavage, and subsequently characterized behavioral and neural responses to a pup or novel object. Seven hours after treatment, males that had been administered placenta had lower latencies to approach both a novel object and a pup, as well as reduced Fos expression in the dorsal BNST following exposure to either stimulus. In a separate study, Perea-Rodriguez (2016) found that both virgin males and new fathers treated with placenta traveled longer distances in an open field 4 h after treatment, compared to control males treated with oil vehicle; distance traveled in an open field is considered an inverse measure of anxiety in rodents (Sestakova et al. 2013). As fathers from several biparental rodent species [Campbell's dwarf hamster (Jones and Wynne-Edwards 2000), California mouse (Lee and Brown 2002; Perea-Rodriguez and Saltzman 2014), prairie vole (K. L. Bales, personal communication.)] have been observed eating their mates' placentas, this behavior might reduce anxiety in new fathers and increase their willingness to interact with their newborn pups.

In sum, several findings from biparental rodents suggest that males—especially virgin males—with high levels of anxiety-related behavior or neuroendocrine correlates of anxiety may engage in less nurturant behavior toward unrelated pups, and that this behavior may be inhibited by acute or chronic stress as well as by the stress-related glucocorticoid hormones. These effects of stress and glucocorticoids have mainly been fairly subtle, however; to our knowledge, no studies have found marked effects of stress on either paternal care or infanticide. Thus, stress and anxiety might play a limited role in determining intra- and inter-individual differences in behavioral responses to pups in biparental rodents. Importantly, however, almost all of the studies on associations between paternal care and stress or anxiety have been performed in adult California mice; thus, the extent to which these findings can be generalized to other species or age classes is not known.

Between-animal differences in behavioral responses to pups

In the biparental rodents that have been studied, behavioral responses to pups may differ markedly among individual sexually naïve males as well as among individual fathers within a species. Although these differences are likely to arise in part from genetic influences, early-life experience can also contribute to long-term differences among individuals. To date, three important sources of inter-individual variation in paternal responsiveness have been identified: intrauterine position during gestation, parental care received during the pre-weaning period, and early-life handling.

Intrauterine position

Working with Mongolian gerbils, Clark et al. (1998) demonstrated that intrauterine position can influence males' behavioral responses to pups in adulthood, as well as potential hormonal mediators of paternal behavior. During the first 20 days following the birth of their first litter, fathers that had gestated between two sisters (2-F males) had significantly more contact with pups than fathers that had gestated between two brothers (2-M males). In addition, 2-M male gerbils had higher circulating testosterone levels in adulthood than 2-F males (Clark et al. 1992). Studies in other rodents indicate that differences in males' intrauterine position are associated with differences in exposure to androgens and estrogens during gestation (Vom Saal et al. 1983; Pei et al. 2006), as well as with differences in expression of androgen receptors and at least one steroidogenic enzyme, 5α-reductase, in peripheral reproductive organs (Nonneman et al. 1992; reviewed in Ryan and Vandenbergh 2002). Therefore, intrauterine position likely affects males' parental behavior in adulthood by modulating exposure to steroid hormones during both early development and adulthood. Effects of intrauterine position on paternal behavior have not, to our knowledge, been investigated in other species.

Parental care received

A second early-life influence on the expression of paternal care in biparental rodents is the quality and/or quantity of care that fathers received from their own parents (reviewed by Braun and Champagne 2014; Bales and Saltzman 2016). Broadly, males that were reared uniparentally (i.e., without their fathers present) subsequently perform less paternal care toward their own offspring than do males reared biparentally (i.e., by both parents).

In prairie voles, males raised by only their mothers spend significantly less time licking and grooming their own pups during the first 6 postpartum days than fathers that were raised by both parents (Ahern et al. 2011). On the other hand, virgin male prairie voles raised uniparentally show no differences in behavioral responses to pups, compared to virgins reared biparentally (Ahern and Young 2009). Importantly, prairie vole mothers engage in comparable levels of infant care whether rearing pups with or without a mate; consequently, pups reared by single mothers receive less total parental care than those raised by both parents (Ahern and Young 2009). Thus, effects of father absence on behavioral development in pups do not appear to be mediated by changes in maternal behavior. As in prairie voles, mandarin vole (Jia et al. 2011; Yu et al. 2015) and Mongolian gerbil (Gromov 2009, cited by Braun and Champagne 2014) fathers raised by only their mothers perform less paternal behavior toward their own offspring than do fathers that were raised by both parents.

Even among males raised by both parents, the early rearing environment can influence paternal care performed towards pups in adulthood. In a series of studies on the California mouse, Marler and colleagues have demonstrated that experimental manipulation of parental care received by young males can lead to long-term changes in these males' behavior toward their own offspring. Bester-Meredith and Marler (2003) compared paternal behavior of male California mice that were raised either by conspecific foster parents or by foster parents of a congeneric species, the white-footed mouse (*Peromyscus leucopus*), in which fathers provide little care of offspring. Male California mice reared by white-footed mouse pairs received fewer retrievals by their foster fathers and subsequently, as adults, spent less time retrieving their own pups, compared to males reared by *P. californicus* pairs. Across all groups of male offspring, AVP-immunoreactivity in the BNST correlated positively with paternal care performed toward their own pups; however, cross-fostering across species did not alter expression of AVP in any of the brain regions examined (BNST, MeA, PVN, supraoptic nucleus of the hypothalamus [SON]). In another cross-fostering study, male meadow voles raised by prairie vole foster parents received higher levels of parental care during pre-weaning development and subsequently performed more paternal behavior toward their own offspring, compared to male meadow voles raised by conspecific foster parents (McGuire 1988).

Gleason and Marler (2013) characterized paternal behavior performed by castrated and sham-castrated California mouse fathers and, subsequently, by their sons. When tested in their home cage with one of their pups, castrated fathers took significantly longer than intact fathers to approach and begin caring for their pups, and spent significantly less time huddling and grooming their pups. These differences were repeated in the subsequent generation: gonadally intact sons of castrated fathers spent significantly less time huddling and grooming their pups, and performed significantly more retrievals of pups, than sons of intact fathers. Although neural and endocrine measures were not characterized in the offspring in this study, another study in the same species found that sons of castrated males had lower AVP-immunoreactivity in the dorsal region of the BNST compared to sons of intact males, as well as higher AVP-immunoreactivity in the PVN (Frazier et al. 2006). Together, these studies suggest that individual differences in paternal behavior may be transmitted across generations, potentially mediated by changes in AVP signaling within the brain.

Perkeybile and colleagues (2013) compared allopaternal behavior in prairie voles that had received different patterns of care from their own parents. Offspring of "high-contact" parents experienced high total levels of contact with their parents but relatively low levels of contact with their fathers specifically, compared to offspring of "low-contact" parents. When tested with an unfamiliar pup shortly after weaning, sons of high-contact pairs engaged in more non-huddling contact with the pup than sons of low-contact pairs; no other behaviors differed reliably between the two groups. Cross-fostering studies demonstrated that this effect was mediated primarily by experiential, rather than genomic, transmission of behavior, as juvenile males' behavioral responses to a pup correlated with several components of parental behavior that they had received from their foster parents (Perkeybile et al. 2015). In addition, binding of AVP and oxytocin in the BNST of juvenile males correlated significantly or marginally, respectively, with several aspects of parental care received, as well as with AVP and oxytocin binding in their biological parents.

Taken together, these studies demonstrate that the quality and/or quantity of parental care that males receive during early development influences their behavioral responses to pups—both their own offspring and unrelated pups—in adulthood and the juvenile period, and that these differences in parenting style can be transmitted to the next generation. They also indicate that these developmental effects on paternal behavior are associated with, and

perhaps mediated by, changes in oxytocin and AVP signaling within the brain.

Early-life handling

Alloparental responsiveness in male prairie voles can be modulated by experimental handling during the early postnatal period. Bales et al. (2007) found that males who, along with their families, were manually removed from their cage during routine cage-changing in the first two postnatal days were more likely to perform alloparental behavior, and engaged in higher levels of alloparenting, when tested with an unrelated pup during the juvenile period, compared to males that, with their families, were removed from the cage in a plastic cup rather than by hand. Notably, pups were not touched directly in either handling paradigm: pups in the "manual" condition dangled from their mothers' nipples while the mother was lifted and moved to a new cage, and those in the "cup" condition were scooped into the cup before being transferred to a new cage. In a separate study, juvenile males that, with their families, had undergone the "manual" handling paradigm before postnatal Day 7 showed more alloparental behavior than males that had not undergone handling manipulation during this period (Bales et al. 2011).

Early handling in the latter study also altered binding of oxytocin in the BNST and density of oxytocin-containing cell bodies in the SON; however, effects of handling on oxytocin signaling did not correspond closely to effects on alloparental behavior. In contrast, early handling did not significantly alter AVP expression or AVP binding to V1a receptors in any of the five brain regions studied. Importantly, both mothers and fathers increased their pup-directed behaviors immediately after the handling manipulation on postnatal Day 1, suggesting that effects of handling on pups' behavioral and neuroendocrine development might have been mediated by effects on the parental care that they received (Bales et al. 2007, 2011).

Correlated variation in males' behavioral responses to pups and neuropeptide signaling

As described above, the mechanisms underlying developmental and environmental influences on (allo)paternal responsiveness include multiple, interacting endocrine and neuroendocrine systems and neural pathways. Nonetheless, AVP signaling within the brain, possibly modulated by gonadal steroids, appears to play a key role in mediating effects of the social environment on paternal behavior, as well as in perpetuating individual differences in paternal behavior across generations (see Fig. 1). Numerous correlational and experimental studies in the prairie vole, meadow vole, mandarin vole, and California mouse (reviewed by Frazier et al. 2006; Bales and Saltzman 2016; Perkeybile and Bales 2017) have implicated AVP, especially vasopressinergic projections from the MeA and BNST to the LS and LHN, in regulating paternal care. The experiments reviewed above further indicate that AVP signaling is altered by several experiential factors that simultaneously influence paternal behavior. In prairie voles, for example, interactions with a pregnant female both increase paternal behavior and alter AVP-immunoreactivity in adult males, such that high paternal responsiveness appears to be associated with increased synthesis of AVP in the MeA and BNST as well as increased release of AVP in the LS and LHN (Bamshad et al. 1994). In the same species, castration reduces and testosterone replacement increases paternal behavior as well as AVP expression in the MeA, BNST, LS and LHN (Wang and De Vries 1993; De Vries and Miller 1999). In California mice, low levels of paternal behavior in adult sons of castrated males are associated with low expression of AVP in the dorsal BNST (Frazier et al. 2006; Gleason and Marler 2013).

AVP expression in the brain has not, to our knowledge, been characterized in male rodents from known intrauterine positions; however, given that 2-M male gerbils, compared to 2-F males, are exposed to high prenatal and adult androgen levels and have low paternal responsiveness in adulthood, and given the pronounced effects of gonadal steroids on the BNST-MeA-LS-LHN AVP pathway (De Vries and Miller 1999), this system seems likely to be affected by intrauterine position. Increases in testosterone coincide with decreases in (allo)paternal behavior in virgin male Mongolian gerbils (Elwood 1980; Probst 1987; Clark and Galef 2001) and prairie voles (Roberts et al. 1999) suggest that maturational effects, too, could potentially be mediated by changes in AVP signaling. Finally, although prior experience with pups promotes (allo)paternal responsiveness in prairie voles (Roberts et al. 1999) and California mice (Gubernick and Laskin 1994), possible effects on testosterone and AVP signaling have not been examined, to our knowledge.

In addition to associations between paternal behavior and expression of AVP in the gonadal-steroid-dependent BNST-MeA-LS-LHN pathway, several studies have found negative associations between paternal behavior and expression of AVP or AVP mRNA in the PVN (prairie vole: Perkeybile et al. 2013, 2015; mandarin vole: Wang et al. 2014; California mouse:

Frazier et al. 2006; De Jong et al. 2012). PVN AVP can facilitate activation of the hypothalamic-pituitary-adrenal axis in response to stress and promotes anxiety-related and depression-like behavior (Caldwell et al. 2008). Correspondingly, in three of these studies, inter-individual differences in paternal behavior and PVN AVP expression were associated with differences in circulating corticosterone concentrations and/or anxiety-like behavior (Frazier et al. 2006; De Jong et al. 2012; Perkeybile et al. 2013, 2015).

Oxytocin, in addition to AVP, has been implicated in the activation of allopaternal and paternal behavior, especially in voles. To our knowledge, only two studies, both in prairie voles, have directly manipulated oxytocin signaling and evaluated effects on behavioral responses to pups. As described above, these studies found that an oxytocin receptor antagonist, either alone (Kenkel et al. 2017) or in conjunction with an AVP receptor antagonist (Bales et al. 2004), reduced the expression of paternal behavior in adult males.

Additionally, several correlational studies have found that differences among males in (allo)paternal responsiveness were associated with differences in oxytocin signaling. Mandarin vole fathers that were treated with cocaine for 4 days, followed by 24 h of withdrawal, spent less time in contact with and licking/grooming their own pups, and had fewer oxytocin- (and AVP)- immunoreactive neurons in the PVN, compared to control males treated with saline (Wang et al. 2014). In another study of mandarin voles, adult males that either had been previously exposed to an unrelated pup, had been mated with a female, or were new fathers showed more nurturant behavior toward an unrelated pup and had more oxytocin-immunoreactive neurons in the SON and/or PVN, compared to virgin males (Song et al. 2010). Among virgin male mandarin voles, individuals that exhibited high levels of paternal behavior toward unrelated pups also had high expression of oxytocin in the PVN and SON, compared to males that engaged in low levels of paternal behavior (Li et al. 2015). Similarly, in the facultatively biparental meadow vole, new fathers that behaved paternally when tested with one of their own pups had higher levels of oxytocin binding in the BNST, LS, lateral amygdala, and accessory olfactory nucleus, compared to sexually and parentally inexperienced males tested with an unfamiliar pup (Parker et al. 2001). On the other hand, effects of cross-fostering on alloparental behavior in juvenile male prairie voles were not accompanied by significant changes in expression of oxytocin receptors in any of the five brain regions examined (Perkeybile et al. 2015).

In summary, experimental and correlational studies have implicated both AVP and oxytocin in the regulation of paternal responsiveness in rodents. In particular, fairly strong evidence indicates that AVP may be an important determinant of both intra- and inter-individual differences in (allo)paternal care. Evidence for a role of oxytocin is less consistent; however, this difference might arise, in part, from the traditional focus on AVP as influencing prosocial behavior in males and oxytocin playing a comparable role in females (e.g., Lim and Young 2006). More studies are needed in order to further elucidate the specific effects of both neuropeptides on pup-directed behavior in male rodents, as well as their contributions to intra- and inter-individual variation.

Conclusions and future directions

The studies reviewed above indicate that allopaternal and paternal responsiveness in male rodents can be modulated by numerous developmental and environmental factors. Several of these, including age, experience with pups, and cues from a reproductive female, are relatively consistent across most individuals and can result in predictable changes in males' behavioral responses to pups across the life span, as males transition from juveniles to sexually naïve adults to mated males to fathers. Others, including stress and anxiety, are likely to be more variable over time and among individuals, and may have relatively short-term effects on behavioral responses to pups; longer-term effects are likely to occur as well but have not yet been investigated. Finally, environmental differences among males during early development, particularly intrauterine position and patterns of parental care received, can have persistent effects on paternal responsiveness, potentially leading to stable inter-individual differences in adults.

Both within- and between-individual differences in (allo)paternal responsiveness have been linked to differences in several hormonal and neuropeptide signaling systems, including androgens, estrogens, glucocorticoids, oxytocin, and AVP. Several lines of evidence, however, point to AVP as playing a particularly prominent role. AVP signaling within the sexually dimorphic BNST-MeA-LS-LHN pathway, which is positively influenced by testosterone, commonly shows a positive association with paternal responsiveness, whereas AVP activity within the PVN, associated with stress and anxiety, typically shows a negative correlation with paternal care. The similarity of these patterns across several rodent species suggests that at least some components of the

proximate regulation of paternal care have evolved by a common mechanism in biparental rodents, at least within the Muridae and Cricetidae.

The mechanisms by which early-life experience exerts long-term effects on (allo)paternal responsiveness and neuroendocrine activity are not yet known. In rats, patterns of maternal care affect behavioral and neuroendocrine function in offspring through epigenetic regulation of gene expression (Stolzenberg and Champagne 2016), and a similar mechanism is likely to subserve early-life effects of paternal behavior as well. Elucidation of the specific genes that may be epigenetically regulated by paternal care, as well of interactions between these persistent epigenetic effects and shorter-term experiential influences, will yield important insights into the transgenerational transmission of paternal behavior.

Finally, the functional significance of inter-individual variation in paternal care is not clear. Infant-directed behavior expressed by a father can influence the morphological, behavioral, endocrine, neuroendocrine, cognitive, and affective development of his young; however, whether this ultimately affects reproductive success for the father and/or his offspring is, for the most part, unknown. Under natural conditions, the expression and consequences of different patterns of allopaternal and paternal care may depend heavily on the environment. For example, high levels of nest attendance and contact with offspring might be beneficial in cold climates, in which these behaviors may be crucial for maintaining pups' body temperature, whereas lower levels of nest attendance might facilitate foraging and food intake by the father or alloparent, especially under conditions of limited or highly dispersed food resources. Integration of mechanistic laboratory experiments with studies of rodents living under naturalistic conditions will greatly advance our understanding of the sources and consequences of variation in paternal care.

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References

Ahern TH, Young LJ. 2009. The impact of early life family structure on adult social attachment, alloparental behavior, and the neuropeptide systems regulating affiliative behaviors in the monogamous prairie vole (*Microtus ochrogaster*). Front Behav Neurosci 3 published online (doi: 10.3389/neuro.08.017.2009).

Ahern TH, Hammock EA, Young LJ. 2011. Parental division of labor, coordination, and the effects of family structure on parenting in monogamous prairie voles (*Microtus ochrogaster*). Dev Psychobiol 53:118–31.

Bales KL, Boone E, Epperson P, Hoffman G, Carter CS. 2011. Are behavioral effects of early experience mediated by oxytocin? Front Psychiatr 2:24.

Bales KL, Kim AJ, Lewis-Reese AD, Carter CS. 2004. Both oxytocin and vasopressin may influence alloparental behavior in male prairie voles. Horm Behav 45:354–61.

Bales KL, Kramer KM, Lewis-Reese AD, Carter CS. 2006. Effects of stress on parental care are sexually dimorphic in prairie voles. Physiol Behav 87:424–9.

Bales KL, Lewis-Reese AD, Pfeifer LA, Kramer KM, Carter CS. 2007. Early experience affects the traits of monogamy in a sexually dimorphic manner. Dev Psychobiol 49:335–42.

Bales KL, Saltzman W. 2016. Fathering in rodents: Neurobiological substrates and consequences for offspring. Horm Behav 77:249–59.

Bamshad M, Novak MA, De Vries GJ. 1994. Cohabitation alters vasopressin innervation and paternal behavior in prairie voles (*Microtus ochrogaster*). Physiol Behav 56:751–8.

Bester-Meredith JK, Marler CA. 2003. Vasopressin and the transmission of paternal behavior across generations in mated, cross-fostered *Peromyscus* mice. Behav Neurosci 117:455–63.

Braun K, Champagne FA. 2014. Paternal influence son offspring development: behavioural and epigenetic pathways. J Neuroendocrinol 26:697–706.

Bredy TW, Lee AW, Meaney MJ, Brown RE. 2004. Effect of neonatal handling and paternal care on offspring cognitive development in the monogamous California mouse (*Peromyscus californicus*). Horm Behav 46:30–8.

Bridges RS. 2015. Neuroendocrine regulation of maternal behavior. Front Neuroendocrinol 36:178–96.

Caldwell HK, Lee H-J, Macbeth AH, Young WS. III. 2008. Vasopressin: behavioral roles of an "original" neuropeptide. Prog Neurobiol 84:1–24.

Chauke M, de Jong TR, Garland T Jr, Saltzman W. 2012. Paternal responsiveness is associated with, but not mediated by reduced neophobia in male California mice (*Peromyscus californicus*). Physiol Behav 107:65–75.

Clark MM, Galef BG Jr. 1999. A testosterone-mediated tradeoff between parental and sexual effort in male Mongolian gerbils (*Meriones unguiculatus*). J Comp Psychol 113:388–95.

Clark MM, Galef BG Jr. 2001. Age-related changes in paternal responses of gerbils parallel changes in their testosterone concentrations. Dev Psychobiol 39:179–87.

Clark MM, Liu C, Galef BG Jr. 2001. Effects of consanguinity, exposure to pregnant females, and stimulation from young on male gerbils' responses to pups. Dev Psychobiol 39:257–64.

Clark MM, Vom Saal FS, Galef BJ Jr. 1992. Intrauterine positions and testosterone levels of adult male gerbils are correlated. Physiol Behav 51:957–60.

Clark MM, Vonk JM, Galef BG. Jr. 1998. Intrauterine position, parenting, and nest-site attachment in male Mongolian gerbils. Dev Psychobiol 32:177–81.

Cushing BS, Perry A, Musatov S, Ogawa S, Papademetriou E. 2008. Estrogen receptors in the medial amygdala inhibit the expression of male prosocial behavior. J Neurosci 28:10399–403.

De Jong TR, Chauke M, Harris BN, Saltzman W. 2009. From here to paternity: neural correlates of the onset of paternal behavior in California mice (*Peromyscus californicus*). Horm Behav 56:220–31.

De Jong TR, Harris BN, Perea-Rodriguez JP, Saltzman W. 2013. Physiological and neuroendocrine responses to chronic variable stress in male California mice (*Peromyscus californicus*): influence of social environment and paternal state. Psychoneuroendocrinology 38:2023–33.

De Jong TR, Korosi A, Harris BN, Perea-Rodriguez JP, Saltzman W. 2012. Individual variation in paternal responses of virgin male California mice (*Peromyscus californicus*). Physiol Biochem Zool 85:740–51.

De Vries GJ, Miller MA. 1999. Anatomy and function of extrahypothalamic vasopressin systems in the brain. Prog Brain Res 199:3–20.

Dulac C, O'Connell LA, Wu Z. 2014. Neural control of maternal and paternal behaviors. Science 345:765–70.

Elwood RW. 1977. Changes in the responses of male and female gerbils *(Meriones unguiculatus*) toward test pups during the pregnancy of the female. Anim Behav 25:46–51.

Elwood RW. 1980. The development, inhibition and disinhibition of pup-cannibalism in the Mongolian gerbil. Anim Behav 28:1188–94.

Elwood RW, Ostermeyer MC. 1984. Infanticide by male and female Mongolian gerbils: ontogeny, causation, and function. In: Hausfater G, Hrdy SB, editors. Infanticide: comparative and evolutionary perspectives. NY: Aldine. p. 367–86.

Fabre P-H, Hautier L, Dimitrov D, Douzery EJP. 2012. A glimpse on the pattern of rodent diversification: a phylogenetic approach. BMC Evol Biol 12:88.

Ferré P, Fernández-Teruel A, Escorihuela RM, Driscoll P, Corda MG, Giorgi O, Tobeña A. 1995. Behavior of the Roman/Verh high- and low-avoidance rat lines in anxiety tests: relationship with defecation and self-grooming. Physiol Behav 58:1209–13.

Frazier CR, Trainor BC, Cravens CJ, Whitney TK, Marler CA. 2006. Paternal behavior influences development of aggression and vasopressin expression in male California mouse offspring. Horm Behav 50:699–707.

Gleason ED, Marler CA. 2013. Non-genomic transmission of paternal behaviour between fathers and sons in the monogamous and biparental California mouse. Proc Biol Sci 280 published online, (doi: 10.1098/rspb.2013.0824).

Gregg JK, Wynne-Edwards KE. 2005. Placentophagia in naïve adults, new fathers, and new mothers in the biparental dwarf hamster, *Phodopus campbelli*. Dev Psychobiol 47:179–88.

Gromov VS. 2009. Interactions of partners in family pairs, care of the offspring, and the role of tactile stimulation in formation of parental behavior of the Mongolian gerbil (*Meriones unguiculatus*) under laboratory conditions. Izv Akad Nauk Ser Biol 5:569–79.

Gubernick DJ. 1990. A maternal chemosignal maintains paternal behaviour in the biparental California mouse, *Peromyscus californicus*. Anim Behav 39:936–42.

Gubernick DJ, Alberts JR. 1989. Postpartum maintenance of paternal behaviour in the biparental California mouse, *Peromyscus californicus*. Anim Behav 37:656–64.

Gubernick DJ, Laskin B. 1994. Mechanisms influencing sibling care in the monogamous biparental California mouse, *Peromyscus californicus*. Anim Behav 48:1235–7.

Harris BN, Perea-Rodriguez JP, Saltzman W. 2011. Acute effects of corticosterone injection on paternal behavior in California mouse (*Peromyscus californicus*) fathers. Horm Behav 60:666–75.

Harris BN, de Jong TR, Yang V, Saltzman W. 2013. Chronic variable stress in fathers alters paternal and social behavior but not pup development in the biparental California mouse (*Peromyscus californicus*). Horm Behav 64:799–811.

Hashemian F, Shafigh F, Roohi E. 2016. Regulatory role of prolactin in paternal behavior in male parents: a narrative review. J Postgrad Med 62:182–7.

Horrell ND, Perea-Rodriguez JP, Harris BN, Saltzman W. 2017. Effects of repeated pup exposure on behavioral, neural, and adrenocortical responses to pups in male California mice (*Peromyscus californicus*). Horm Behav 90:56–63.

Hume JM, Wynne-Edwards KE. 2005. Castration reduces male testosterone, estradiol, and territorial aggression, but not paternal behavior in biparental dwarf hamsters (*Phodopus campbelli*). Horm Behav 48:303–10.

Jia R, Tai F, An S, Zhang X. 2011. Neonatal paternal deprivation or early deprivation reduces adult parental behavior and central estrogen receptor α expression in mandarin voles (*Microtus mandarinus*). Behav Brain Res 224:279–89.

Jones JS, Wynne-Edwards KE. 2000. Paternal hamsters mechanically assist the delivery, consume amniotic fluid and placenta, remove fetal membranes, and provide parental care during the birth process. Horm Behav 37:116–25.

Kenkel WM, Perkeybile AM, Carter CS. 2017. The neurobiological causes and effects of alloparenting. Dev Neurobiol 77:214–32.

Kenkel WM, Paredes J, Lewis GF, Yee JR, Pournajafi-Nazarloo H, Grippo AJ, Porges SW, Carter CS. 2013. Autonomic substrates of the response to pups in male prairie voles. PLoS One 8:e69965.

Klampfl SM, Brunton PJ, Bayerl DS, Bosch OJ. 2014. Hypoactivation of CRF receptors, predominantly type 2,

in the medial-posterior BNST is vital for adequate maternal behavior in lactating rats. J Neurosci 34:9665–76.
Kleiman DG, Malcolm JR. 1981. The evolution of male parental investment in mammals. In: Gubernick DJ, Klopfer PH, editors. Parental care in mammals. New York (NY): Plenum. p. 347–87.
Lambert KG, Franssen CL, Bardi M, Hampton JE, Hainley L, Karsner S, Tu EB, Hyer MM, Crockett A, Baranova A, et al. 2011. Characteristic neurobiological patterns differentiate paternal responsiveness in two *Peromyscus* species. Brain Behav Evol 77:159–75.
Lee AW, Brown RE. 2002. The presence of the male facilitates parturition in California mice (*Peromyscus californicus*). Can J Zool 80:926–33.
Lei K, Cushing BS, Musatov S, Ogawa S, Kramer KM. 2010. Estrogen receptor-α in the bed nucleus of the stria terminalis regulates social affiliation in male prairie voles (*Microtus ochrogaster*). PLos One 5:e8931.
Li Y, Lian Z, Wang B, Tai F, Wu R, Hao P, Qiao X. 2015. Natural variation in paternal behavior is associated with central estrogen receptor alpha and oxytocin levels. J Comp Physiol A 201:285–93.
Lim MM, Young LJ. 2006. Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Horm Behav 50:506–17.
Lonstein JS, De Vries GJ. 1999. Sex differences in the parental behaviour of adult virgin prairie voles: independence from gonadal hormones and vasopressin. J Neuroendocrinol 11:441–9.
Martínez A, Ramos G, Martínez-Torres M, Nicolás L, Carmona A, Cárdenas M, Luis J. 2015. Paternal behavior in the Mongolian gerbil (*Meriones unguiculatus*): estrogenic and androgenic regulation. Horm Behav 71:91–5.
McGuire B. 1988. Effects of cross-fostering on parental behavior of meadow voles (*Microtus pennsylvanicus*). J Mammal 69:332–41.
Nephew BC, Bridges RS. 2011. Effects of chronic social stress during lactation on maternal behavior and growth in rats. Stress 14:677–84.
Nonneman DJ, Ganjam VK, Welshons WV, Vom Saal FS. 1992. Intrauterine position effects on steroid metabolism and steroid receptors of reproductive organs in male mice. Biol Reprod 47:723–9.
Parker KJ, Lee TM. 2001. Central vasopressin administration regulates the onset of facultative paternal behavior in *Microtus pennsylvanicus* (meadow voles). Horm Behav 39:285–94.
Parker KJ, Kinney LF, Phillips KM, Lee TM. 2001. Paternal behavior is associated with central neurohormone receptor binding patters in meadow voles (*Microtus pennsylvanicus*). Behav Neurosci 115:1341–8.
Pei M, Matsuda K-I, Sakamoto H, Kawata M. 2006. Intrauterine proximity to male fetuses affects the morphology of the sexually dimorphic nucleus of the preoptic area in the adult rat brain. Eur J Neurosci 23:1234–40.
Perea-Rodriguez JP, Saltzman W. 2014. Differences in placentophagia in relation to male and female reproductive status in the California mouse (*Peromyscus californicus*). Dev Psychobiol 56:812–20.
Perea-Rodriguez JP. 2016. Placentophagia in the California mouse (*Peromyscus californicus*) and its potential role in the onset of male parental care [dissertation]. [Riverside (CA)]: University of California, Riverside.
Pereira AS, Giusti-Paiva A, Vilela FC. 2015. Central corticosterone disrupts behavioral and neuroendocrine responses during lactation. Neurosci Lett 606:88–93.
Perkeybile AM, Bales KL. 2017. Intergenerational transmission of sociality: the role of parents in shaping social behavior in monogamous and non-monogamous species. J Exp Biol 220:114–23.
Perkeybile AM, Griffin LL, Bales KL. 2013. Natural variation in early parental care correlates with social behaviors in adolescent prairie voles (*Microtus ochrogaster*). Front Behav Neurosci 7 published online (doi: 10.3389/fnbeh.2013.00021).
Perkeybile AM, Delaney-Busch N, Hartman S, Grimm KJ, Bales KL. 2015. Intergenerational transmission of alloparental behavior and oxytocin and vasoapressin receptor distribution in the praiarie vole. Front Behav Neurosci 9 published online, (doi: 10.3389/fnbeh.2015.00191).
Probst B. 1987. Developmental changes in the pituitary-gonadal axis in male Mongolian gerbils from birth to adulthood. Exp Clin Endocrinol 90:157–66.
Roberts RL, Miller AK, Taymans SE, Carater CS. 1999. Role of social and endocrine factors in alloparental behavior of prairie voles (*Microtus ochrogaster*). Can J Zool 76:1862–8.
Ryan BC, Vandenbergh JG. 2002. Intrauterine position effects. Neurosci Biobehav Rev 26:665.
Saltzman W, Ziegler TE. 2014. Functional significance of hormonal changes in mammalian fathers. J Neuroendocrinol 26:685–96. [PMC][10.1111/jne.12176] [25039657]
Saltzman W, Thinda S, Higgins AL, Matsumoto WR, Ahmed S, McGeehan L, Kolb EM. 2009. Effects of siblings on reproductive maturation and infanticidal behavior in cooperatively breeding Mongolian gerbils. Dev Psychobiol 51:60–72.
Schradin C, Anzenberger G. 1999. Prolactin, the hormone of paternity. New Physiol Sci 14:223–31.
Sestakova Puzserova A, Kluknavsky N, Bernatove I. 2013. Determination of motor activity and anxiety-related behaviour in rodents: methodological aspects and role of nitric oxide. Interdiscip Toxicol 6:126–35.
Song Z, Tai F, Yu C, Wu R, Zhang X, Broders H, He F, Guo R. 2010. Sexual or paternal experiences alter alloparental behavior and the central expression of ERα and OT in male mandarin voles (*Microtus mandarinus*). Behav Brain Res 214:290–300.
Stolzenberg DS, Champagne FA. 2016. Hormonal and non-hormonal bases of maternal behavior: the role of experience and epigenetic mechanisms. Horm Behav 77:204–10.
Trainor BC, Marler CA. 2001. Testosterone, paternal behavior, and aggression in the monogamous California mouse (*Peromyscus californicus*). Horm Behav 40:32–42.
Trainor BC, Marler CA. 2002. Testosterone promotes paternal behaviour in a monogamous mammal via conversion to oestrogen. Proc R Soc Lond B 269:823–9.
Vella ET, Evans CCD, Ng MWS, Wynne-Edwards KE. 2005. Ontogeny of the transition from killer to caregiver imn in dwarf hamsters (*Phodopus campbelli*) with biparental care. Dev Psychobiol 46:75–85.
Vom Saal FS, Grant WM, McMullen CW, Laves KS. 1983. High fetal estrogen concentrations: correlation with increased adult sexual activity and decreased aggression in male mice. Science 220:1306–9.

Wang Z, De Vries GJ. 1993. Testosterone effects on paternal behavior and vasopressin immunoreactive projections in prairie voles (*Microtus ochrogaster*). Brain Res 631:156–60.

Wang Z, Ferris CF, De Vries GJ. 1994. Role of septal vasopressin innervation in paternal behavior in prairie voles (*Microtus ochrogaster*). Proc Nat Acad Sci U S A 91:400–4.

Wang J, Taia F, Lai X. 2014. Cocaine withdrawal influences paternal behavior and associated central expression of vasopressin, oxytocin and tyrosine hydroxylase in mandarin voles. Neuropeptides 48:29–35.

Yu P, Zhang H, Li X, He F, Tai F. 2015. Early bi-parental separation or neonatal paternal deprivation in mandarin voles reduces adult offspring paternal behavior and alters serum corticosterone levels and neurochemistry. Horm Behav 73:8–14.