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Functional Significance of Hormonal Changes in Mammalian Fathers

Wendy Saltzman[1,*] and **Toni E. Ziegler**[2]

[1]Department of Biology, University of California, Riverside

[2]Wisconsin National Primate Research Center, University of Wisconsin – Madison

Abstract

In the 5–10% of mammals in which both parents routinely provide infant care, fathers as well as mothers undergo systematic endocrine changes as they transition into parenthood. Although fatherhood-associated changes in such hormones and neuropeptides as prolactin, testosterone, glucocorticoids, vasopressin, and oxytocin have been characterised in only a small number of biparental rodents and primates, they appear to be more variable than corresponding changes in mothers, and experimental studies typically have not provided strong or consistent evidence that these endocrine shifts play causal roles in the activation of paternal care. Consequently, their functional significance remains unclear. We propose that endocrine changes in mammalian fathers may enable males to meet the species-specific demands of fatherhood by influencing diverse aspects of their behaviour and physiology, similar to many effects of hormones and neuropeptides in mothers. We review the evidence for such effects, focusing on recent studies investigating whether mammalian fathers in biparental species undergo systematic changes in 1) energetics and body composition, 2) neural plasticity, cognition, and sensory physiology, and 3) stress responsiveness and emotionality, all of which may be mediated by endocrine changes. The few published studies, based on a small number of rodent and primate species, suggest that hormonal and neuropeptide alterations in mammalian fathers might mediate shifts in paternal energy balance, body composition, and neural plasticity, but do not appear to have major effects on stress responsiveness or emotionality. Further research is needed on a wider variety of biparental mammals, under more naturalistic conditions, to more fully elucidate the functional significance of hormone and neuropeptide profiles of mammalian fatherhood and to clarify how fatherhood may trade off with, or perhaps enhance, aspects of organismal function in biparental mammals.

Keywords

Biparental care; Paternal behaviour; Energy balance; Stress; Anxiety; Nurogenesis

Introduction

During the transition to motherhood, female mammals undergo a series of hormonal changes that prepare the body and brain for the myriad challenges of parenting. These hormonal

[*]Corresponding author: Department of Biology, University of California, Riverside, Riverside, CA 92521, Phone: 951.827.6356, Fax: 951.827.4286, Saltzman@ucr.edu.

changes involve predictable fluctuations in circulating concentrations of steroids (e.g., oestrogens, progestagens, androgens, glucocorticoids) as well as peptides (e.g., prolactin and other lactogenic hormones, oxytocin, vasopressin, gonadotrophins). Functional effects of these endocrine changes fall into three broad categories. First, they directly regulate the physiological processes in the mother necessary for the production and maintenance of offspring – i.e., pregnancy, parturition and lactation – through actions on the reproductive tract and accessory tissues. During gestation, for example, oestrogen and progesterone act on the uterus to regulate endometrial morphology and function, and thereby play a critical role in maintaining the pregnancy, whereas during lactation, prolactin and oxytocin act on the mammary glands to stimulate the synthesis and release of milk (1–3). Second, the so-called maternal hormones directly stimulate maternal behaviour through actions on the central nervous system. Importantly, these actions involve the same hormones involved in the physiological regulation of pregnancy, parturition, and lactation. Thus, oestrogen, progesterone, prolactin, and oxytocin, among other hormones and neuropeptides, all act within the brain to activate or, in some cases, inhibit the expression of maternal behaviour (4). Third, these same hormones and neuropeptides can indirectly facilitate maternal care and/or maternal survival via a host of centrally and/or peripherally mediated effects. For example, pregnancy and lactation are accompanied by changes in maternal energy balance (5, 6), immune function (7), neural plasticity (8–10), cognition (8, 11, 12), sensory physiology (12, 13), emotional regulation (11), and stress responsiveness (11, 14), and these alterations have been hypothesised, or in some cases demonstrated, to be mediated by the endocrine profile of motherhood.

Although the vast majority of mammalian fathers play no systematic role in infant care, males in approximately 5–10% of mammalian genera routinely help to rear their young (15, 16). Paternal care appears to have evolved independently multiple times among mammals, and is thought to evolve under conditions in which males are more likely to increase the number of offspring fathered and/or the likelihood of offspring survival by assisting with infant care than by abandoning their mates and seeking additional mating opportunities (15,16, 17). The largest numbers of biparental mammals have been identified among the rodents, primates, and carnivores (15). Depending on the species, paternal care in mammals can entail a broad range of behaviours involved in transporting, defending, playing with, socializing, grooming, and warming offspring, and providing them with food, shelter, or other resources (15). In some species, fathers spend at least as much time interacting with their offspring as do mothers, and paternal care can have important consequences for the survival, growth, and development of young (16–18). Some components of paternal care may have considerable energetic costs (19) and may differ quantitatively and/or qualitatively from behaviour performed by nonbreeding males (17). In biparental mammals, therefore, the onset of fatherhood, like motherhood, can entail pronounced shifts in parents' behaviour and physiology.

Not surprisingly, then, fathers in biparental species, like mothers, undergo systematic endocrine changes in association with the onset of parenthood. These changes, in such hormones and neuropeptides as prolactin, testosterone, and vasopressin, have been characterised to a greater or lesser extent in a number of rodent and primate species; however, their functions are not well understood (4, 20). Obviously, these endocrine events

do not subserve obligatory changes in reproductive physiology comparable to pregnancy, parturition, and lactation in females (i.e., category 1, above). Therefore, their functional significance, if any, is likely to lie in either directly promoting paternal care (category 2) or indirectly facilitating paternal care or paternal survival through centrally and/or peripherally mediated effects that help fathers meet the demands of parenting (category 3). Over the last three decades, numerous investigators have used correlational or, less commonly, experimental approaches to evaluate possible effects of these fatherhood-induced endocrine changes on the expression of paternal behaviour (4, 20). Only in the last few years, however, have researchers begun to examine other possible effects of these hormonal and neurochemical changes as males undergo the transition to fatherhood. Thus, the extent to which the endocrine sequelae of fatherhood influence behaviour and physiology in fathers is still largely unknown.

In this paper we review the evidence – virtually all of which comes from rodents and primates – that suggests endocrine changes in mammalian fathers influence diverse aspects of fathers' behaviour and physiology. First, we briefly describe the hormone and neuropeptide changes that have been reported to occur in biparental mammalian fathers. We next summarise the evidence that these endocrine and neurochemical events of fatherhood play a causal role in the activation of paternal care, emphasizing results from experimental studies. We then review recent findings that suggest mammalian fathers in biparental species may undergo systematic changes in 1) energetics and body composition, 2) neural plasticity, cognition, and sensory physiology, and 3) stress responsiveness and emotionality, all of which are likely mediated by endocrine changes. Finally, we discuss the limitations and implications of these findings, as well as future directions for studying the physiological and behavioural consequences of parenthood for mammalian fathers.

Hormonal changes in biparental mammalian fathers

Males in a number of biparental mammals – specifically, several rodent and primate species – have been shown to undergo changing hormonal profiles during their mates' pregnancy and lactational periods. These changes appear to mimic the hormonal fluctuations that are occurring in their mates. Importantly, many of the endocrine changes in mammalian fathers are modulated by paternal experience (19, 21, 22). Hormonal changes in mammalian fathers have been reviewed elsewhere (e.g., (4, 20)) and therefore will be summarised only briefly here.

Prolactin

In biparental Mongolian gerbils (*Meriones unguiculatus*; (23), California mice (*Peromyscus californicus*; (24) and Djungarian hamsters (*Phodopus campbelli*; (25), circulating prolactin concentrations are significantly higher in fathers living with their mate and pups than in virgin males, newly mated males, and/or expectant fathers. Moreover, male Djungarian hamsters have increased prolactin receptor mRNA transcript levels in the choroid plexus of the hypothalamus during their mate's early postpartum period, indicating elevated prolactin activity in the brain during the period when males are interacting with pups (26).

Biparental male nonhuman primates also show increases in circulating or excreted prolactin levels during their mate's gestational period, and even more pronounced prolactin elevations during the postpartum period, when fathers are directly involved in caring for infants. The cotton-top tamarin (*Saguinus oedipus*) and common marmoset (*Callithrix jacchus*), cooperatively breeding, biparental, New World monkeys, both show elevated prolactin levels during their mate's pregnancy, with mid-gestational elevations and highest levels in the final month of pregnancy (tamarin: (27); marmoset: (28)). Once infants are born, fathers maintain significantly higher prolactin levels throughout the period of infant dependency than during the gestational phase (28, 29). Similarly, a recent study found that human fathers have significantly higher prolactin levels than other men (30).

Androgens

Testosterone generally shows a negative relationship with paternal care. In some biparental mammals, testosterone levels of expectant fathers rise across the mate's pregnancy (e.g., cotton-top tamarin: (22); Djungarian hamster: (25). Following the birth of infants, however, paternal testosterone concentrations drop precipitously in biparental primate fathers, including common marmosets (28), cotton-top tamarins (31), and humans (32). Similarly, rodent fathers undergo pronounced declines in testosterone levels following the birth of their pups (e.g., Mongolian gerbil: (23); Djungarian hamster:(25); California mouse:(33)).

Oestrogen and progesterone

Few studies have characterised changes in oestrogen signalling in mammalian fathers, and in the small number of species that have been studied, no consistent picture has emerged. In male Djungarian hamsters, serum oestradiol levels do not appear to change with paternal status (34), and oestrogen receptor alpha-immunoreactivity in several brain regions (medial preoptic area, bed nucleus of the stria terminalis (BNST), and medial amygdala) does not appear to differ between fathers and non-fathers (35). In contrast, mandarin vole (*M. mandarinus*) fathers have lower levels of oestrogen receptor alpha-immunoreactivity in the medial preoptic area and the BNST, and higher levels in the ventromedial hypothalamus, compared to non-fathers (36). Among the biparental primates, experienced, but not first-time, cotton-top tamarin fathers show significant increases in urinary oestrone and oestradiol concentrations in the final month of their mate's gestation (31), and black-tufted ear marmoset (*C. kuhlii*) fathers show significant but transient drops in urinary oestradiol concentrations following the birth of their infants (37).

Findings on progesterone, like those on oestrogen, are sparse and inconsistent. Male Djungarian hamsters show a significant increase in progesterone levels at the end of the mate's pregnancy (34), whereas progesterone levels in male California mice are significantly lower in fathers than in virgin males (33).

Glucocorticoids

Glucocorticoid (cortisol or corticosterone) levels rise during the mate's mid- to late gestational period in expectant fathers of several biparental mammals, including Djungarian hamsters (25), cotton-top tamarins (31), and humans (38). Glucocorticoid levels decline again shortly after parturition, however, so that studies of basal glucocorticoid

concentrations typically find no differences between fathers and non-breeding males (e.g., California mouse: (39, 40); prairie vole: (19); human: (41, 42)).

Vasopressin

Vasopressin in fathers has been studied most thoroughly in the prairie vole, with a strong emphasis on vasopressin signaling within the brain. In this species, new fathers have reduced densities of vasopressin-immunoreactive fibers in the lateral septum and lateral habenular nucleus compared to both sexually naïve males and males housed with late-pregnant mates; this finding appears to reflect increased synthesis and release of vasopressin from the BNST and medial amygdaloid nucleus following both copulation and parturition (43, 44). Prairie vole fathers (as well as mothers) also exhibit elevated vasopressin mRNA levels in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON) in the postpartum period compared to sexually naïve controls (45). In the California mouse, in contrast, vasopressin mRNA levels in the PVN do not differ between fathers and virgin males or males housed with tubally ligated females (46). In common marmosets, fathers have a greater abundance of vasopressin V1a receptors in the prefrontal cortex than males that have not sired offspring (47). Effects of fatherhood on vasopressin signalling therefore appear to differ across species and might be clarified by additional studies.

Oxytocin

Several studies have investigated changes in intracerebral oxytocin signalling or peripheral oxytocin concentrations in rodent fathers. In the facultatively biparental meadow vole, sexually and paternally experienced, paternally behaving males were found to have significantly higher oxytocin receptor binding in several brain regions (accessory olfactory nucleus, lateral septum, BNST, and lateral amygdala) than sexually and paternally inexperienced, non-paternally behaving males; however, it could not be determined, however, whether these neural differences were caused by differences in sexual activity, cohabitation with a female, and/or paternal experience (48). Similarly, fathers have increased numbers of oxytocin-immunoreactive fibers in the PVN and SON in biparental mandarin voles, compared to virgin males; however, similar effects were seen in non-fathers that were either exposed briefly to pups or housed with a female prior to parturition (36). Among biparental male prairie voles, in contrast, neither oxytocin gene expression in the hypothalamus nor oxytocin receptor binding in a number of brain regions was found to differ between sexually naïve males and new fathers (45). Male California mice exhibit elevated circulating oxytocin concentrations during the first half of their mate’s pregnancy, but oxytocin levels decline prior to parturition and remain low throughout the postpartum period (48); however, it is unclear whether circulating oxytocin levels reliably reflect levels in the brain (50). Thus, effects of fatherhood on the brain’s oxytocin system seem to be inconsistent across species, and where effects have been detected, they may correspond to cohabitation with a female rather than fatherhood *per se*.

In conclusion, whereas hormonal changes in mothers apparently evolved to subserve the physiological processes of gestation, parturition, and lactation, and thus appear to be broadly similar across eutherian mammals, hormonal changes in fathers are much less constrained. Not surprisingly, then, the endocrine profile of fatherhood is quite variable among the

handful of biparental mammals that have been studied in detail. Although fathers in all or most of the species studied show increases in prolactin and decreases in testosterone concentrations during the mate's perinatal period, changes in oestrogen, progesterone, vasopressin, and oxytocin signaling are less consistent.

Effects of hormonal changes in fathers on paternal behaviour

As described above, fathers in biparental mammalian species undergo species-specific changes in several hormone and neuropeptide systems as they prepare for and subsequently engage in paternal care. This has led to the hypothesis that these hormonal and neurochemical changes pay a role in the suppression of infanticidal behaviour and the activation of paternal behaviour (20, 51). Consequently, numerous studies have evaluated possible effects of these hormones and neuropeptides on males' behavioural responses to infants, often relying on correlational analyses of hormone-behaviour relationships (reviewed by (4, 20)). Here we briefly review the evidence that suggests endocrine profiles of fatherhood play a causal role in activating paternal care, focusing primarily on experimental studies.

Prolactin

In contrast to numerous studies demonstrating positive correlations between circulating prolactin levels and paternal behaviour, pharmacological experiments generally do not support a causal role of prolactin in the onset or maintenance of paternal care (20). Roberts et al. (52) found that treatment of common marmosets with the dopamine receptor agonist bromocriptine to suppress prolactin secretion reduced retrieval of infants; however, this study used parentally inexperienced animals, most of which were females, rather than fathers. In contrast, in a study using experienced marmoset fathers, suppression of prolactin secretion using the dopamine D2 receptor agonist cabergoline caused no changes in infant-care behaviours during observations made within the family context (53). A more recent, longitudinal study provides further insights into the role of prolactin in marmoset paternal behaviour. Ziegler et al. (28) tested experienced common marmoset fathers across three consecutive litters, during which each father underwent treatment, in randomised order, with cabergoline, human recombinant prolactin, or nothing. Neither of the prolactin manipulations significantly altered fathers' infant-carrying or other parenting behaviours within the family, but both significantly reduced fathers' responsiveness to infant distress calls when fathers were tested away from the family.

Studies in rodents, similar to those in marmosets, have failed to yield compelling evidence that prolactin influences paternal care in biparental species. Although prolactin has been shown to promote paternal behaviour in the uniparental rat (*Rattus norvegicus*) (54), no such effect was found in biparental Djungarian hamsters, in which treatment of first-time fathers with either cabergoline or bromocriptine did not alter fathers' pup-retrieval behaviour, or growth and survival of pups (55).

In conclusion, although prolactin is elevated in fathers of several biparental mammals and has been referred to as the "hormone of paternity" (56), findings from experimental studies provide little support for the hypothesis that prolactin plays a key role in activating paternal

behaviour in male mammals. Instead, the role of prolactin in fathers before and during periods of infant care may be more closely related to some of its other known functions, such as increasing food intake, stimulating neurogenesis, and reducing anxiety.

Testosterone and oestrogen

Although circulating or excreted testosterone levels correlate negatively with measures of paternal behaviour in several mammals (reviewed by (4, 20)), experimental studies indicate that effects of testosterone on paternal care differ markedly across species. In the Djungarian hamster (57) and in one study of prairie voles (58), for example, castration had no detectable effect on paternal behaviour, whereas castrated male Mongolian gerbils engaged in significantly more paternal behaviour than either castrated, testosterone-treated males or sham-castrated males (59). The opposite pattern has been found in another study of prairie voles (60) and in California mice (61), in which castration reduced and testosterone treatment restored paternal behaviour. In the California mouse, this effect is mediated by aromatization of testosterone to oestrogen within the brain: paternal behaviour of castrated, reproductively experienced males was restored by treatment with testosterone or oestrogen, but not by treatment with the non-aromatizable androgen dihydrotestosterone (62). Moreover, fathers had higher aromatase activity within the medial preoptic area of the brain – a region strongly implicated in paternal behaviour (63, 64) – than non-fathers (33). Thus, even though California mouse fathers have lower circulating concentrations of testosterone than nonfathers, they might have higher local concentrations of oestrogen within the brain.

Progesterone

In the uniparental house mouse (*Mus* spp.), progesterone signalling has been shown to promote infanticide and inhibit paternal behaviour in adult males (65, 66). Progesterone receptor knockout mice as well as mice treated with the progesterone receptor antagonist RU486 showed markedly reduced aggression toward pups and enhanced paternal behaviour, whereas progesterone treatment of wild-type males significantly increased aggression toward pups. To our knowledge, however, effects of progesterone on paternal care have not been tested in biparental mammals.

Glucocorticoids

Very few studies have examined effects of glucocorticoids on paternal care. To characterise effects of acute glucocorticoid elevations, Harris et al. (67) injected California mouse fathers with high doses of corticosterone and found neither short-term effects on paternal behaviour nor longer-term effects on pup survival or development. Similarly, in free-ranging, cooperatively breeding meerkats (*Suricata suricatta*), glucocorticoid injections had no effect on provisioning of pups or time spent in proximity to pups in non-breeding male alloparents (68). To determine effects of chronic stress, including chronic elevations of circulating corticosterone levels, on paternal care, Harris et al. (69) subjected California mouse fathers to a chronic variable stress paradigm for 7 days. Stressed fathers showed both significant elevations in corticosterone levels and subtle reductions in their interactions with their mate and pups compared to control fathers, but no differences were detected in pup survival or development. These findings suggest that neither acute nor chronic glucocorticoid elevations

have pronounced effects on parental or alloparental care males, but clearly, additional data are needed from other species.

Vasopressin

Both within and among species, paternal behaviour correlates with patterns of vasopressin-immunoreactivity and vasopressin binding, especially in the lateral septum and other parts of the "extended amygdala" (45, 48, 70, 71). Moreover, central infusion of vasopressin or vasopressin receptor antagonists promotes or inhibits paternal behaviour, respectively, in the biparental prairie vole (72) and in the facultatively biparental meadow vole (*M. pennsylvanicus*: (73)). Nonetheless, castration of male prairie voles virtually eliminates vasopressin-immunoreactivity in the lateral septum and lateral habenula but does not affect paternal behaviour, suggesting that vasopressin signalling in these areas is not essential for the expression of paternal care (58).

Oxytocin

Several experimental studies support a role of oxytocin in paternal behaviour. In humans, intranasal oxytocin treatment of fathers modulates several aspects of father-child interactions (74–76); however, the extent to which intranasally administered oxytocin enters the brain and gains access to oxytocin-responsive regions is unclear (50). In virgin male prairie voles, paternal behaviour is inhibited by combined treatment with a vasopressin receptor antagonist and an oxytocin receptor antagonist, but not either antagonist alone (77). Finally, in free-ranging meerkats, peripheral injections of oxytocin increased adults' feeding of pups and time spent in proximity to pups; however, this study included both breeding and non-breeding animals of both sexes, and, again, the extent to which oxytocin entered the brain is unknown (78). Further studies utilizing direct manipulation of intracerebral oxytocin signalling are needed in order to clarify the effects of the brain's oxytocin system on paternal behaviour.

In summary, experimental studies provide limited and inconsistent support for the hypothesis that the hormone and neuropeptide changes occurring in mammalian fathers are important in the expression of paternal behaviour. What, then, can we conclude about the functional significance of parenthood-associated hormonal and neurochemical alterations in biparental mammalian fathers? Although the answer is still far from clear, we explore several possibilities below, based on known effects of these same hormones and neuropeptides in mammalian mothers, and on observed morphological, physiological, neurobiological, and behavioural changes in fathers.

Effects of fatherhood on energy balance and body composition

Female mammals show a direct relationship between reproduction and energy balance (79). Pregnancy and lactation are energetically expensive; without access to adequate calories, females will either terminate reproductive attempts or continue them at the expense of self-maintenance (80, 81). Several hormones are involved in the energetics of pregnancy and induce coordinated adaptations to physiological functions in the mother. In particular, prolactin and placental lactogen appear to be involved in the leptin resistance that occurs

beginning at mid-pregnancy, and prolactin induces hyperphagia (82). Oestradiol increases energy utilization (83) but inhibits food intake (84), whereas progesterone increases food intake and body weight during pregnancy (85). During lactation, mild leptin resistance may persist, whereas sensitivity to ghrelin appears to increase, thereby stimulating hyperphagia (6, 86). Prolactin also acts centrally to stimulate hyperphagia during the lactational period, complemented by elevated basal levels of the orexigenic glucocorticoid hormones and low levels of the anorexigenic oestrogens (6). Thus, the endocrine changes in pregnancy and lactation provide signals to reset maternal homeostatic mechanisms, facilitating shifts in feeding behaviour and energy utilization to meet increased metabolic demands (6, 82).

Although males in biparental species obviously do not undergo pregnancy or lactation (with the exception of some species of fruit bats in which males lactate: (87)), hormonal changes in fathers nonetheless appear to interact with paternal homeostatic mechanisms, and males may show changes in body mass and body composition similar to those in their mates (Table 1). In two biparental primates, the common marmoset and the cotton-top tamarin, expectant fathers undergo significant weight gain, especially in the final month of the mate's gestation, concurrent with elevations in prolactin concentrations (88, 89). Fathers engage in infant care beginning shortly after parturition, including extensive carrying of multiple infants, and lose weight during the period of infant dependency (28, 90). Prolactin has been shown to limit weight loss in common marmoset fathers in the first few weeks postpartum: fathers treated with the dopamine D2 receptor agonist cabergoline in order to lower their circulating prolactin levels lost significantly more weight during the infant-care period than males given prolactin implants (28). It is possible, therefore, that prolactin has orexigenic effects in fathers providing infant care, as in pregnant and lactating mothers.

Similar to marmosets and tamarins, California mouse fathers show significant increases in body weight towards the end of their mate's pregnancy, followed by weight loss during the postpartum period (67). Prairie vole fathers also lose weight while caring for pups, and undergo a significant loss of subcutaneous fat and a significant decline in plasma leptin concentrations (19). These morphological and endocrine changes in prairie vole fathers are associated with an increased preference for sucrose solution over water and increased time spent feeding, but no change in physical activity levels (19).

In summary, findings from biparental monkeys and rodents demonstrate that fathers undergo systematic decreases in body weight and, in at least one species, reductions in subcutaneous fat and circulating leptin levels while rearing infants, suggesting that providing paternal care is energetically costly. Importantly, these findings were obtained from captive animals housed under non-challenging conditions, with ample food, comfortable ambient temperatures, and an absence of predators. Studies of biparental mammals living in natural or semi-natural environments would likely reveal even more pronounced energetic costs of fatherhood.

Effects of fatherhood on neural plasticity, cognition, and olfaction

Reproduction in female mammals governs plasticity in the brain. During pregnancy and lactation, mothers undergo molecular, electrophysiological, neurochemical, and

morphological changes in brain regions associated with the expression of maternal behaviour, as well as in regions involved in cognition, sensory processing, and emotional regulation (reviewed by (8–10, 12)). In recent years, particular interest has focused on effects of motherhood on neurogenesis. Neuronal proliferation in the dentate gyrus of the hippocampus declines during the early lactational period in rats, mice, and sheep, compared to control females, and this effect appears to be mediated by hormonal and/or neurochemical events, including reductions in oestrogen and elevations in glucocorticoid levels. In contrast, in the subventricular zone, which produces neurones that migrate to the olfactory bulb, proliferation of neurones is enhanced during both pregnancy and lactation in rats and mice, as a result of stimulatory effects of prolactin, but is suppressed in lactating ewes (10). Although the functional significance of these motherhood-induced changes in neural plasticity is not yet known, they have been proposed to mediate changes in cognition (e.g., spatial memory), sensory processes (e.g., olfactory recognition of offspring), and emotional regulation (e.g., anxiety reduction) in mothers, potentially enhancing mothers' ability to meet the demands of parenthood (8–10, 12).

In the past decade, a handful of studies have indicated that fatherhood, like motherhood, modulates plasticity in brain regions subserving cognitive, affective, and sensory functions (Table 2). Kozorovitskiy and colleagues (47) found that in the common marmoset, both first-time and experienced fathers had higher densities of dendritic spines on pyramidal neurones in the prefrontal cortex, a region involved in goal-directed behaviour, compared to age-matched males that had not sired offspring. The functional significance of this difference is not known.

More recently, two studies have examined possible effects of fatherhood on neural plasticity and cognition in the biparental California mouse, with contrasting results. Glasper and colleagues (91) injected the cell-division marker bromodeoxyuridine (BrdU) into adult males one week following the birth of the males' offspring, and euthanised the fathers three weeks later. Compared to control males, fathers had fewer BrdU-labelled cells and, specifically, fewer BrdU-labelled neurones, in the dentate gyrus, suggesting that fatherhood inhibits hippocampal neurogenesis; no differences were seen in the subventricular zone. The functional significance of this difference, if any, is not clear: no significant correlations were found between number of BrdU-labelled cells and measures of paternal behaviour, and performance in two hippocampus-dependent cognitive tests, the object-recognition test and the novelty-suppressed feeding test, did not differ between fathers and controls.

Franssen et al. (92) similarly investigated effects of fatherhood on hippocampal plasticity and function in California mice, comparing neural and cognitive measures among fathers, pup-naïve virgin males, and virgin males that had been exposed to a pup for 10 minutes on each of seven consecutive days. Fathers performed significantly better in a dry land maze than both pup-exposed and pup-naive virgins, whereas pup-exposed virgins performed significantly better than pup-naïve virgins. Fathers also showed increased exploratory behaviour in the maze and, subsequently, had enhanced Fos-immunoreactivity in the CA1, CA3, and dentate gyrus of the hippocampus, compared to one or both control groups. No differences were found between fathers and non-fathers, however, in markers of neural plasticity, including hippocampal expression of nestin (a marker of restructuring in mature

neurones), Ki-67 (a marker of cell proliferation), doublecortin (an index of the number of new neurones), or glial fibrillary acidic protein (a marker of glial responsiveness).

As in the California mouse, fatherhood has been found to modulate neural plasticity in the prairie vole. Lieberwirth et al. (93) injected male voles with BrdU daily for 14 days before assigning them to mixed-sex pairs, same-sex pairs, or individual housing. Voles were euthanised the day after the birth of the breeding males' second litters, and brains were analysed for BrdU labelling to characterise survival of new cells. Compared to one or both control groups, fathers had significantly *fewer* BrdU-labelled cells in the central, cortical, and medial amygdala, but not the basolateral amygdala. Fathers also had significantly fewer BrdU-labelled cells in the dentate gyrus as well as the ventromedial hypothalamus. No differences were found in the main olfactory bulbs. These results suggest that fatherhood reduces the survival of new cells in the amygdala, dentate gyrus, and hypothalamus of male prairie voles. These results could not be attributed simply to fathers' interactions with pups: in male prairie voles pair-housed with oestrogen-treated, ovariectomised females, neither acute (20 minutes on one day) nor chronic (20 minutes on each of 10 consecutive days) exposure to a pup altered survival of new cells in these brain regions (93) (see also (94)).

Finally, an elegant series of studies in the uniparental house mouse (*Mus*) indicates that interactions of an adult male mouse with its own pups stimulate neurogenesis in the father's subventricular zone and dentate gyrus under the influence of prolactin signalling (95). Some of the new cells mature into olfactory interneurones in the olfactory bulb, where they respond preferentially to offspring odors and appear to subserve recognition of mature offspring.

In sum, these findings indicate that several aspects of plasticity, including proliferation and survival of neurones, as well as neuronal morphology, can be altered by parental experience in male mammals. To date, the only documented functional consequence of this fatherhood-induced plasticity is olfactory recognition of offspring in male house mice (95). Clearly, additional work is needed to more fully characterise the effects of fatherhood on the paternal brain; the sensory, behavioural, and endocrine mechanisms mediating these effects; and the functional significance of fatherhood-induced neural plasticity for fathers' physiology and behaviour.

Effects of fatherhood on stress responsiveness and emotionality

In at least several mammalian species, mothers exhibit blunted hormonal, neural, and behavioural responses to stressors during late pregnancy and lactation (reviewed by (14, 96, 97)). Late-pregnant and lactating rats, for example, have reduced corticosterone and/or adrenocorticotrophic hormone responses to numerous psychological and physiological stressors, compared to virgin females. Pregnant and lactating rats also show attenuated stress-induced increases in corticotrophin-releasing hormone (CRH) mRNA, vasopressin mRNA, and c-fos mRNA expression in the PVN. The mechanisms underlying these reductions in hormonal and neural responsiveness during pregnancy and lactation are not fully understood; however, increased activity of the brain's prolactin and, to a lesser extent,

oxytocin systems and decreased noradrenergic stimulation of the PVN have been implicated (14, 97).

Pregnant and lactating rats, mice, and, arguably, women also exhibit reduced anxiety and fearfulness (97, 98). Compared to nulliparous females, for example, postpartum rats and/or mice show reduced acoustic startle responses, increased locomotion in the open field, increased time in the open arms of the elevated plus maze, increased time in the light compartment of a light/dark chamber, and reduced fleeing from an intruder. The mechanisms of decreased emotionality in mothers are not fully understood but, like reduced stress-responsiveness, are thought to involve intracerebral prolactin and oxytocin, which tend to have anxiolytic effects, as well as intracerebral CRH and vasopressin, which tend to be anxiogenic (97–99).

The function of diminished stress responsiveness and emotionality in mothers is not known. Hypotheses include protection of infants from exposure to high glucocorticoid levels through the placenta or breast milk (96, 97), protection of mothers from mood disorders (97, 98), and protection of maternal behaviour and/or lactation from stress-induced inhibition (14, 96, 99). Because fathers in biparental species, like mothers, presumably undergo selection to provide infant care under stressful circumstances, and because these fathers, like mothers, may undergo changes in prolactin, oxytocin, and vasopressin signalling with the onset of parenthood (4, 100), the question arises as to whether fathers, too, exhibit blunted stress responsiveness and reduced emotionality, compared to their non-breeding counterparts. This question has been addressed in recent studies using the California mouse and prairie vole (Table 3).

An acute stressor, handling plus 5-minute exposure to predator urine, elicited a marked elevation in plasma corticosterone concentrations in male California mice; however, the magnitude of this elevation did not differ between new fathers (housed with their pairmate and first litter of pups) and either virgin males (housed in with another male) or pair-housed, nonbreeding males (intact males housed with a tubally ligated female, (40); or vasectomised males housed with an intact female (39). These results were obtained whether the males were tested individually or with their cagemate(s) present. In a separate study, Fos expression in three brain regions associated with stress – the PVN, central nucleus of the amygdala, and BNST – did not differ between new fathers and either expectant fathers or virgin males, either under baseline conditions or after exposure to predator urine (101).

Fatherhood also does not appear to alter hormonal or neural responses to chronic stress in California mice. A 7-day chronic variable stress paradigm elicited a transient elevation in plasma corticosterone concentrations and an increase in vasopressin mRNA (but not CRH mRNA) expression in the PVN; however, these effects did not differ between new fathers, nonbreeding males pair-housed with a tubally ligated female, and virgin males pair-housed with another male (46).

On the other hand, two studies have found that California mouse fathers show attenuated behavioural responses to acute stressors, compared to non-fathers. Bardi et al. (102) found no differences in behavioural responses to 3-minute exposure to 2,5-dihydro-2,4,5-

trimethylthiazoline (TMT, a component of fox feces) among experienced fathers, virgin males with no previous exposure to pups, and virgin males that had been exposed to pups on three previous days. When tested in an open field containing a novel object, however, the three groups showed several significant differences in the patterning of behaviour, with fathers showing the lowest and pup-naïve virgins showing the highest numbers of interrupted grooming bouts, behavioural transitions, and changes in direction of locomotion (102). In contrast, Chauke et al. (101) found no differences among fathers, expectant fathers, paired virgins, and isolated virgins in behavioural responses in a novel-object test. Chauke et al. (101) did find, however, that in males tested with their familiar cagemates, 5-minute exposure to predator urine elicited acute changes in several behaviours in virgin males and nonbreeding males, but not in fathers. In the California mouse, therefore, mixed evidence suggests that fathers may show blunted behavioural responses to acute stressors, and this effect does not seem to depend upon the immediate presence of the fathers' mate and pups; however, no evidence to date indicates that California mouse fathers have attenuated hormonal or neural responses to acute or chronic stressors.

In contrast to California mice, prairie vole fathers may show *increased* anxiety-like behaviour, according to a recent study. Compared to virgin males housed in same-sex pairs and mated males housed with an ovariectomised, oestrogen-primed female, fathers spent significantly more time in the corners of an open field, and a significantly lower proportion of time in the open arms of the elevated plus maze (93). These differences were subtle, however, and most behavioural measures in both tests did not differ among groups, calling into question the biological significance of the effects. Prairie vole fathers also showed increased depression-like behaviour in the forced-swim test (i.e., shorter latency to immobility, more bouts of immobility, increased duration of immobility) compared to virgin males; however, these measures did not differ between fathers and non-breeding mated males, suggesting that depression-like behaviour was increased by pair-bonding or cohabitation with a female, rather than by fatherhood *per se*, (93).

Taken together, these results from California mice and prairie voles suggest that parenthood may not have pronounced effects on stress responsiveness or emotionality in fathers, in contrast to the well documented effects of pregnancy and lactation in mothers. Given that gestational and lactational hyporesponsiveness to stress have not been documented in female California mice (39) or prairie voles, this apparent difference between mothers and fathers might instead reflect differences among species. On the other hand, if gestational and lactational hyporesponsiveness to stress evolved as a mechanism to protect fetuses and pups from exposure to high levels of glucocorticoids via the placenta and mother's milk, then the lack of similar hyporesponsiveness in males would make sense, from a functional perspective. Studies of additional biparental species, including intraspecific comparisons of mothers and fathers, would be informative.

Conclusions

Behavioural endocrinologists have recognised for three decades that mammalian fathers can undergo systematic endocrine changes in association with infant care (29). These changes commonly appear to include shifts in circulating prolactin and testosterone levels, and may

additionally include changes in peripheral oestrogen, progesterone, and glucocorticoid concentrations, as well as in the intracerebral vasopressin and oxytocin systems. In recent years, however, it has become increasingly clear that the hormonal and neuropeptide profiles of fatherhood may be quite variable among species and might not play important, direct, causal roles in the expression of paternal behaviour (4, 20). Several investigators have therefore suggested that the hormonal and neurochemical sequelae of fatherhood in biparental mammals may indirectly facilitate paternal care and/or paternal survival through diverse actions on fathers' behaviour and physiology (e.g., (9, 103)); however, the study of such effects is still in its infancy.

The endocrine consequences of fatherhood, as well as their physiological and behavioural sequelae, are likely to differ within and among species, in association with the specific demands on fathers. These, in turn, may depend on such factors as ecological and demographic parameters – e.g., abundance and distribution of food, intensity of predation pressure, and availability of alloparents – as well as the quality, quantity, and energetic costs of infant care provided by fathers.

Several important caveats should be kept in mind when considering hormonal and neurochemical changes in mammalian fathers and their potential significance. First, our understanding of such effects comes almost entirely from only a small number of species, primarily several muroid rodents and callitrichid primates (i.e., marmosets and tamarins). Clearly, data are needed from a broader range of taxa, including the heavily biparental canids (15).

Second, hormonal correlates of fatherhood, as well as their possible physiological and behavioural consequences, have been studied almost exclusively in captive animals, which face few energetic demands such as finding food, thermoregulating, detecting or escaping from predators, defending a territory, or competing for mates. Studies of biparental mammals in natural or semi-natural environments would provide valuable insights into the physiological and behavioural impacts of parenthood on mammalian fathers.

In spite of these limitations, as reviewed above, recent evidence suggests that fathers in biparental mammalian species undergo systematic changes in body weight, body composition, and neurogenesis, all of which are likely to be mediated by hormonal profiles of fatherhood. The mechanisms, functional significance, and frequency in nature of these effects remain to be determined. Moreover, endocrine changes in biparental mammalian fathers are likely to effect additional physiological and behavioural alterations in such functions as thermoregulatory ability, osmoregulation (103), immune function (46), exercise physiology and performance ability. Characterizing such impacts of fatherhood on male mammals in biparental species would significantly enhance our understanding of male reproductive strategies as well as mammalian life histories, and poses an exciting challenge for behavioural endocrinology.

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Table 1

Effects of fatherhood on energy balance and body composition in males of biparental mammalian species.

Dependent Variable	Species	Effect of Fatherhood	Reference
Body mass	Common marmoset	Increase across mate's pregnancy, especially in final month; decrease during period of infant care	28, 88
Body mass	Cotton-top tamarin	Increase across mate's pregnancy, especially in final month; decrease during period of infant care	88–90
Body mass	California mouse	Increase during mate's pregnancy; decrease during period of infant care	67
Body mass, subcutaneous fat	Prairie vole	Decrease during period of infant care	19

Table 2

Effects of fatherhood on neural plasticity, cognition, and olfaction in males of biparental mammalian species.

Dependent Variable (Interpretation)	Species	Effect of Fatherhood	Reference
Density of dendritic spines on pyramidal neurones in prefrontal cortex (structural reorganization)	Common marmoset	Increase	47
BrdU[a]-labelled neurones in dentate gyrus (neurogenesis)	California mouse	Decrease	91
BrdU-labelled neurones in subventricular zone (neurogenesis)	California mouse	No effect	91
Performance in object-recognition test and novelty-suppressed feeding test (hippocampal function)	California mouse	No effect	91
Nestin, Ki-67, doublecortin, and glial fibrillary acidic protein in hippocampus (neural plasticity)	California mouse	No effect	92
Performance in dry land maze, exploratory behaviour in dry land maze (spatial learning)	California mouse	Increase	92
BrdU-labelled cells in amygala, dentate gyrus and ventromedial hypothalamus (neurogenesis)	Prairie vole	Increase	93
BrdU-labelled cells in main olfactory bulbs (neurogenesis)	Prairie vole	No effect	93
BrdU-labelled cells in subventricular zone and dentate gyrus (neurogenesis)	House mouse (uniparental)	Increase	95

[a]Bromodeoxyuridine

Table 3

Effects of fatherhood on responses to stressors and anxiety-like behavior in males of biparental mammalian species.

Stressor/Test (interpretation)	Dependent Variable	Species	Effect of Fatherhood	Reference
Handling + 5-minute exposure to predator urine (acute stress response)	Plasma corticosterone	California mouse	No effect	39, 40
Handling + 5-minute exposure to predator urine (acute stress response)	Fos in PVN[a] CeA[b], BNST[c]	California mouse	No effect	101
Handling + 5-minute exposure to predator urine (acute stress response)	Behavior	California mouse	Decrease	39
Novel-object test (neophobia)	Behavior	California mouse	No effect	101
Novel-object open-field test (anxiety-like behavior)	Disruptions in patterning of behavior	California mouse	Decrease	102
3-minute exposure to TMT[d] (acute stress response)	Behavior	California mouse	No effect	102
Chronic variable stress paradigm (chronic stress response)	Plasma corticosterone	California mouse	No effect	46, 69
Chronic variable stress paradigm (chronic stress response)	CRH[e] mRNA and AVP[f] mRNA in PVN	California mouse	No effect	46
Elevated plus maze (anxiety-like behavior)	Behavior	Prairie vole	Decreased ratio of time in open arms to total time in arms; no other significant differences	93
Open-field test (anxiety-like behavior)	Behavior	Prairie vole	Increased time in corners of open field; no other significant differences	93
Forced-swim test (depression-like behavior)	Behavior	Prairie vole	Increased latency to immobility, number of immobility bouts, and duration of immobility (in fathers and mated males)	93

[a] Paraventricular nucleus of hypothalamus

[b] Central nucleus of amygdala

[c] Bed nucleus of stria terminalis

[d] 2,5-dihydro-2,4,5-trimethylthiazoline (component of fox feces)

[e] Corticotropin-releasing hormone

[f] Vasopressin