The neuroendocrinology of primate maternal behavior

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ABSTRACT

In nonhuman primates and humans, similar to other mammals, hormones are not strictly necessary for the expression of maternal behavior, but nevertheless influence variation in maternal responsiveness and parental behavior both within and between individuals. A growing number of correlational and experimental studies have indicated that high circulating estrogen concentrations during pregnancy increase maternal motivation and responsiveness to infant stimuli, while effects of prepartum or postpartum estrogens and progestogens on maternal behavior are less clear. Prolactin is thought to play a role in promoting paternal and alloparental care in primates, but little is known about the relationship between this hormone and maternal behavior. High circulating cortisol levels appear to enhance arousal and responsiveness to infant stimuli in young, relatively inexperienced female primates, but interfere with the expression of maternal behavior in older and more experienced mothers. Among neuropeptides and neurotransmitters, preliminary evidence indicates that oxytocin and endogenous opioids affect maternal attachment to infants, including maintenance of contact, grooming, and responses to separation. Brain serotonin affects anxiety and impulsivity, which in turn may affect maternal behaviors such as infant retrieval or rejection of infants' attempts to make contact with the mother. Although our understanding of the neuroendocrine correlates of primate maternal behavior has grown substantially in the last two decades, very little is known about the mechanisms underlying these effects, e.g., the extent to which these mechanisms may involve changes in perception, emotion, or cognition.

1. Introduction

The laboratory rat has traditionally been the animal model of choice for research on the neuroendocrinology of maternal behavior, as maternal behavior in this species is predictably elicited and easily quantified, and modern invasive techniques for the manipulation and measurement of neuroendocrine variables can be used in this species (e.g., Bridges, 1990). For similar reasons, and with the additional advantage of having a large brain, the sheep has also been a favorite animal model for research in this area (e.g., Keverne and Kendrick, 1994). Studies of the neural and endocrine regulation of maternal behavior in rats and sheep have produced largely converging findings, leading to generalizations concerning the regulation of maternal behavior in mammals (Pryce, 1992; Numan and Insel, 2003).

Until the mid- to late 1980s, virtually no research was conducted on the neuroendocrinology of maternal behavior in primates. In part,

this absence of research reflected the belief that maternal behavior in nonhuman primates and humans is learned early in life and later reinforced by experience acquired through reproduction (e.g., Keverne, 1996). Experiments with rhesus monkeys (*Macaca mulatta*) conducted in the 1950s and 1960s showed that socially deprived females displayed neglectful or abusive parenting with their first offspring, suggesting that opportunities to observe maternal behavior exhibited by other individuals and direct experience with one's own mother were necessary for the acquisition and expression of competent maternal care (Harlow and Seay, 1966; Ruppenthal et al., 1976). The abnormal behavior of socially deprived monkeys, however, was more likely the result of brain alterations induced by traumatic early experience and highly artificial laboratory housing conditions than of learning deficits (Maestripieri and Carroll, 1998a). Since the notion that maternal behavior is learned was consistent with the behaviorist paradigm, which dominated research in psychology for many decades, the "learning" interpretation of social-deprivation experiments went unchallenged for many years. The complementary assumption that maternal behavior in nonhuman primates and humans was largely emancipated from hormonal and other biological influences also went unchallenged for a long time (e.g., Coe, 1990; Keverne, 1996).

Studies of monkeys and humans in the late 1980s and 1990s, however, began to provide evidence that although hormones are not necessary for the expression of primate maternal behavior, they

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nevertheless may influence it (Pryce et al., 1988, 1993; Maestripieri and Wallen, 1995; Maestripieri and Zehr, 1998). This is similar to what occurs in rodents, in which virgin females can be induced to express maternal motivation and behavior simply through gradual and repeated exposure to pups, a process known as sensitization (Numan and Insel, 2003). Studies with nonhuman primates and humans conducted in the past two decades have shown that hormones can influence the motivation to interact with infants and the quality of parental behavior, not only in females, but in males as well.

Because primates are generally characterized by long lifespans, slow life histories, and long periods of immature development, experience with infants gathered during the juvenile period can play a more significant role in the acquisition of primate parenting skills than in animals with short lifespans such as many rodents (e.g., Pryce, 1996). Female primates typically produce one infant at a time, and rarely twins, and invest heavily in each offspring, compared to other animals. Maternal investment in primates involves not only nutritional investment but also transport, protection, and transfer of social skills that are crucial for survival and success in a complex social environment. The importance of maternal investment in primates and the high cost of replacing a lost infant are other evolutionary reasons why experience is expected to play an important role in the acquisition and refinement of mothering skills. The same reasons, however, may also explain why parental motivation and behavior are not fully emancipated from hormonal influences: it would be too risky to do so. For example, a female primate who, for some reason, missed the opportunity to acquire experience with infants during the juvenile period and, as a result, lacked the motivation or the skills to take care of her own offspring, would pay a very high price. Hormones (including prenatal hormonal exposure) and neuropeptides increase the likelihood that females are motivated to interact with infants, thus gaining opportunities for learning, and also to maintain close contact with newborn offspring and meet their basic needs. Hormone and neuropeptide differences between individuals, and hormone and neuropeptide changes across ages and reproductive conditions, also ensure that levels of maternal motivation and maternal behavior are tailored to stable individual characteristics and are expressed at appropriate times in one's lifespan.

In this review article, we first address some of the considerations and caveats that should be kept in mind when interpreting findings on the neuroendocrinology of primate maternal behavior. Next, we briefly describe general patterns of maternal behavior in primates, highlighting major similarities and differences among taxa. We then review and examine the evidence that each of the major hormones, neuropeptides, and neutrotransmitters that have been implicated in the regulation of maternal behavior in nonprimate mammals – gonadal steroids, lactogenic hormones, oxytocin, hypothalamic-pituitary-adrenal (HPA) axis hormones, endogenous opioids, and serotonin – influences maternal behavior in nonhuman primates and humans. We conclude with a brief summary and a discussion of future research directions.

2. Considerations and caveats

The growing number of studies on the neuroendocrinology of parental behavior in primates, including humans, has increased our understanding both of normative parenting within species and of variation among species and among individuals. Most studies to date, however, have been correlational and have been conducted with relatively non-invasive measures of endocrine function. Experimental studies manipulating hormonal or neuropeptide signaling or investigating the effects of hormones, neuropeptides, or neurotransmitters in the central nervous system are still rare in primates. In addition, most of the available data come from a few species or taxonomic families within the primate order (e.g., humans, great apes, macaques,

baboons, marmosets and tamarins), while virtually no data are available for prosimians, tarsiers, many cercopithecine, colobine, and cebid monkeys, gibbons and siamangs. Therefore, caution is necessary in generalizing the findings of these studies to all primates. Furthermore, most studies to date have involved captive primate populations, and very few have been conducted in the field. Because the ecological and social environment can modulate the influence of hormones on behavior, more studies of wild primates are necessary to ensure that research findings and conclusions have broad ecological validity.

Another important consideration in interpreting findings on neuroendocrine influences on maternal behavior is the endocrine methodology used. Studies of endocrine and neuroendocrine function in primates have traditionally utilized measures of circulating (plasma or serum) hormone concentrations. More recently, however, methods for characterizing excreted (urinary or fecal) hormone levels have been applied to a wide variety of species, while central concentrations of hormones, neuropeptides, monoamine neurotransmitters or their metabolites have occasionally been determined, either in cerebrospinal fluid (CSF) or in brain tissue. Each of these approaches has both advantages and drawbacks (see Harper and Austad, 2000; Bardi et al., 2003a). For example, measures of hormone levels in the peripheral circulation can provide an accurate indication of the hormone concentrations to which tissues are exposed at a precise point in time, but, for many hormones, are highly sensitive to acute perturbation. Thus, capture and sampling procedures can alter hormone levels, as well as behavioral and reproductive outcomes. In addition, circulating levels of many hormones undergo pronounced circadian and ultradian rhythms, potentially introducing substantial variability into hormone measures.

Fecal and urinary hormone levels, in contrast, provide non-invasive, time-integrated measures of hormone concentrations present in the body over a period of hours. Therefore, these measures are often useful for assessing differences in baseline hormone levels among individuals or within individuals across different conditions, but generally do not provide a useful measure of acute changes in hormone levels. Moreover, species may differ in their metabolic pathways and excretion patterns for specific hormones (e.g., which metabolites are excreted, relative rates of excretion in urine vs. feces, time course of excretion). Thus, proper use and interpretation of urinary or fecal hormone measures requires extensive biochemical and physiological validation, to ensure that the hormone or metabolite being assayed and the medium in which it is measured are biologically relevant (e.g., Ziegler et al., 1996a; Harper and Austad, 2000; Touma et al., 2003). Finally, some hormones, neuropeptides, and neurotransmitters, such as oxytocin, corticotropin-releasing hormone, and serotonin, are released both peripherally and within the brain, and do not readily cross the blood–brain barrier. Consequently, circulating or excreted concentrations of these substances may not accurately reflect central levels and may bear little relevance to the regulation of behavior. In these cases, characterization of hormone, neuropeptide, or neurotransmitter concentrations within the brain or CSF may be necessary; however, such approaches require relatively invasive or even terminal procedures, precluding their use in many primate studies.

Several additional caveats should be kept in mind when interpreting data on hormone–behavior interactions (Pfaff et al., 2004; Nelson, 2005). First, the biological effects of a hormone (or neuropeptide/neurotransmitter) are determined not only by concentrations of the hormone itself, but also by numbers and affinities of hormone receptors, and, for steroid hormones, by circulating concentrations of carrier proteins and availability of nuclear co-activator or co-repressor proteins. However, these variables are rarely evaluated in studies of primates. Second, many hormone–behavior relationships are not manifest as linear correlations. Instead, the relationship is often curvilinear so that, for example, hormones may have clear effects on behavior at low concentrations, but not at high

concentrations. Alternatively, threshold effects may occur, so that only low levels of hormone are required for normative expression of the behavior. Third, release of numerous hormones and neuropeptides can be altered by behavior or social stimuli, complicating interpretation of correlations between hormone or neuropeptide levels and behavioral measures.

Finally, it should be kept in mind that hormones do not "cause" behavior, but instead alter the probability that a particular behavior or set of behaviors will be expressed under certain conditions (Pfaff et al., 2004; Nelson, 2005). These effects may be mediated either by direct actions on the neural circuitry underlying the behavior or by indirect effects involving, for example, sensory or motor systems, cognition, emotionality, arousal, metabolism, or activity of other neuroendocrine systems. With respect to primate maternal behavior, for example, a particular hormone may alter the likelihood that a female will respond to an infant emitting distress vocalizations by approaching and retrieving the infant. In theory, such an effect could involve actions on the auditory system, on cognitive, arousal- or stress-related responses to the infant's vocalizations, or on brain regions directly mediating infant-retrieval behavior. While our understanding of the neuroendocrine correlates of and influences on primate maternal behavior has grown substantially in the last two decades, as summarized below, essentially nothing is known of the mechanisms underlying these effects.

3. Maternal behavior in primates

Maternal behavior can be defined broadly as any pattern of a mother's behavior that appears to enhance her offspring's survival and reproductive success. Interspecific differences in patterns of maternal behavior in primates are generally associated with differences in life styles and life histories, and in social, mating, and reproductive systems. Many species of prosimians are small-bodied, nocturnal, and solitary; in these species, infants are often parked in a nest while the mother is foraging. Maternal behavior during brief visits to the nest mainly includes nursing and grooming (e.g., Nicolson, 1991). Diurnal primates such as most of the New World monkeys, the Old World monkeys, and the apes typically have larger bodies and longer lifespans, and often live in groups. In these primates, infants are not parked in nests but must be carried for weeks, months, or even years after birth (Nicolson, 1991). In New World monkeys belonging to the family Callitrichidae (marmosets and tamarins), females usually produce twins, and infants are carried not only by their mothers but by adult males and older siblings as well. In these cooperatively breeding species, most daughters delay or suppress their reproduction and help their mothers take care of their younger siblings. When two females do breed in the same group, however, breeding females may kill one another's infants, especially during the late stages of pregnancy (Digby et al., 2007; Saltzman et al., 2009).

Most other primate species live in either one-male groups with polygynous mating systems, or in large, multi-male, multi-female groups in which both males and females mate promiscuously. In these species, fathers or other adult males typically do not contribute to parental care through extensive infant carrying; instead, their main role is protection of infants and their mothers from external threats, including the risk of infanticide posed by other adult males (Nicolson, 1991). Mothers raise their offspring mainly on their own, although in some species of colobine monkeys, other females carry infants for short periods of time. Maintenance of contact with infants for extensive periods of time is a major component of maternal behavior: mothers nurse their infants on demand, and therefore almost continuously, during the early postnatal period, and also carry them on their chest over long distances. Mothers also groom their infants extensively, which functions both to maintain hygiene and to strengthen social bonds. To protect infants from predators and potentially dangerous conspecifics, mothers often prevent infants from breaking contact by restraining them. Mothers also, however,

encourage their infants to walk independently at appropriate times, and during these times, they maintain close proximity to infants, are highly vigilant of their surroundings, and retrieve them at the first sign of potential danger (Maestripieri and Call, 1996).

Weaning is a gradual process that begins shortly after birth and that may take months or years to be completed, depending on the length of interbirth intervals in different individuals and species. Although infants contribute to their own weaning, mothers facilitate and accelerate this process by gradually increasing the frequency with which they reject their infants' attempts to make contact, gain access to their nipple, and suckle. In the great apes, mothers additionally facilitate their infants' transition from milk to solid food by sharing solid food with them. Finally, in many species of primates, mothers facilitate the social development of their infants and their integration in the group by influencing their social partner preferences and acquisition of dominance rank through supportive interventions in their offspring's conflicts with other group members (Nicolson, 1991).

Although mothers in many species of primates support and invest in their offspring for much of the offspring's lives, studies of the neuroendocrinology of maternal behavior typically focus on the periods of pregnancy and early lactation, i.e. the periods in which the influence of reproductive hormones and neuropeptides (e.g., estrogens, progestogens, prolactin and oxytocin) is likely to be strongest. Other hormones, neuropeptides, and neurotransmitters that are less strictly linked to reproduction (e.g., cortisol, corticotropin-releasing hormone, endogenous opioids and serotonin), however, can potentially influence maternal interactions with infants at any time. For the purposes of this review article, we make a distinction between maternal responsiveness, which we define as behavioral responsiveness to infant visual, auditory, or olfactory stimuli, and maternal behavior. Maternal responsiveness can be assessed before the onset of reproduction (e.g. during the juvenile period or prior to conception), during pregnancy, or during lactation. It can be measured experimentally, for example by measuring responses to pictures of infants or to recordings of infant vocalizations in the laboratory, or by quantifying female interest in and interactions with other females' infants in a group-living setting. As for maternal behavior, we focus on infant-directed activities that enhance infant survival during the pre-weaning lactation period, therefore excluding behaviors that contribute to the infant's development and reproduction after weaning.

4. Estrogens and progestogens

A common motif in behavioral endocrinology is the coordinated regulation by particular hormones of both specific physiological processes and the behaviors associated with those processes, with hormones exerting complementary effects in the periphery and in the brain. For example, aldosterone acts both on the kidneys to increase sodium reabsorption and in the brain to stimulate sodium ingestion, while androgens act on the testes and male reproductive tract to promote fertility and reproductive performance, as well as in the brain to stimulate libido (Pfaff et al., 2004; Nelson, 2005). Not surprisingly, therefore, the endocrine events governing female reproduction – particularly pregnancy, parturition, and lactation – have also been found to play key roles in activating the onset of maternal behavior in a number of mammalian species.

Among the most conspicuous hormonal changes occurring during female reproduction are the dramatic and predictable fluctuations in circulating concentrations of the sex steroids. These hormones are secreted by the gonads, as well as the adrenal cortex and placenta, and act on target tissues throughout the body, including the brain. In primates, both estrogens and progestogens typically are elevated during much of pregnancy, especially the latter half; however, species differ considerably in the exact patterning of these elevations, the specific steroids secreted, and the circulating concentrations of those steroids (reviewed by Albrecht and Pepe, 1998; see also Saltzman et al., 2010).

Sex steroids usually remain low and acyclic during the lactational period, in association with lactational anovulation (e.g., moustached tamarin, *Saguinus mystax*: Löttker et al., 2004; white-faced saki, *Pithecia pithecia*: Shideler et al., 1994; tufted capuchin, *Cebus apella*: Recabarren et al., 2000; rhesus macaque: Ördög et al., 1998; Japanese macaque, *Macaca fuscata*: Kondo et al., 2003; chimpanzee, *Pan troglodytes*: Shimizu et al., 2003). Exceptions to this pattern, however, are found in species that undergo postpartum ovulation and conception (e.g., common marmoset, *Callithrix jacchus*: Kholkute, 1984; cotton-top tamarin, *Saguinus oedipus*: Ziegler et al., 1987).

Estrogens and progestogens are well known to modulate the onset of maternal behavior in nonprimate mammals (reviewed by González-Mariscal and Poindron, 2002; Numan and Insel, 2003). In many nonprimate species, maternal circulating estrogen concentrations are high during the second half of pregnancy, while progesterone concentrations drop sharply several days before parturition. This pattern of high estrogen levels against a background of declining progesterone levels plays a critical role in the onset of maternal behavior in new mothers in several species, including rats and rabbits, whereas both estrogen and progesterone may facilitate maternal behavior in sheep. Both correlational and experimental studies indicate that in primates, too, the onset of maternal behavior may be influenced by estrogens and possibly progestogens.

Female primates in some species show increasing interest in infants across the course of pregnancy, and this pattern appears to be linked to changes in maternal sex steroid levels. For example, female pigtail macaques (*Macaca nemestrina*) showed increasing rates of interactions with other females' infants as their pregnancies progressed, and their rates of infant-handling during the last trimester of pregnancy were significantly and strongly correlated with circulating estradiol concentrations and ratios of circulating estradiol:progesterone levels, but not with progesterone concentrations alone (Maestripieri and Wallen, 1995; Maestripieri and Zehr, 1998). Similarly, in pregnant olive baboons (*Papio hamadryas anubis*), females' rates of interactions (both affiliative and aggressive) with unrelated infants were modestly but significantly correlated with urinary concentrations of estrogen metabolites (estrone conjugates, E_1C) (Ramirez et al., 2004). Moreover, treatment of ovariectomized female rhesus macaques with estradiol significantly increased their rates of infant-handling, confirming that estrogen, in particular, enhances maternal responsiveness (Maestripieri and Zehr, 1998).

Additional evidence that sex steroids influence maternal motivation, especially during late pregnancy, comes from an innovative series of studies by Pryce et al. (1993), in which an operant-conditioning paradigm was used to assess maternal responsiveness in female common marmosets. Marmosets were trained to press a bar in order to simultaneously (1) gain visual access to a replica of an infant marmoset and (2) turn off an audio recording of infant distress vocalizations. Rates of bar-pressing by primigravid (first-time pregnant) females were higher during late pregnancy and the early postpartum period than during early to mid-pregnancy. Furthermore, bar-pressing by nulliparous, reproductively suppressed females was increased by an exogenous estradiol and progesterone treatment regimen that mimicked the endocrine milieu of late pregnancy. While this study clearly demonstrates that sex steroids can influence females' responses to infant-related stimuli, it does not indicate the precise nature of those responses. Pregnant common marmosets may often kill other females' infants, and this infanticidal tendency appears to peak during late pregnancy, when females' attraction to and tolerance of unrelated infants has also been found to decline (Saltzman and Abbott, 2005; Digby and Saltzman, 2009). Thus, it is possible that in this species, estrogen and/or progestogen profiles of late pregnancy actually inhibit, rather than enhance, maternal motivation.

In addition to these studies demonstrating short-term effects of sex steroids on maternal responsiveness in macaques, baboons, and marmosets, several correlational studies have investigated the relationship between prepartum maternal estrogen and progestogen levels and subsequent postpartum maternal behavior; however, no clear pattern has emerged. Pryce et al. (1988) found that urinary estradiol concentrations in late pregnancy reliably predicted maternal behavior and infant survival in female red-bellied tamarins (*Saguinus labiatus*). "Good" mothers – i.e., those whose infants survived to at least one week of age – had significantly higher urinary estradiol concentrations during the last week of pregnancy, and higher rates of licking/cleaning, carrying, and nursing their infants during the first 2 h postpartum, than "poor" mothers, whose infants died within the first week after birth. Moreover, "good" mothers maintained stable urinary estradiol concentrations across the last 4–5 weeks of pregnancy, whereas "poor" mothers had declining urinary estradiol levels during this period. Prepartum estrogen levels have also been found to correlate positively with "good" maternal behavior in Japanese macaques: fecal E_1C concentrations, as well as the ratio of fecal E_1C to progesterone conjugates (pregnanediol-glucuronide, PdG), during the last four weeks of pregnancy were negatively correlated with rates of maternal rejection during the first 12 weeks postpartum (Bardi et al., 2003b). Finally, patterns of change in maternal sex steroid levels across pregnancy have been found to predict human mothers' postpartum feelings of attachment to their infants: women who reported high levels of attachment to their infant during the early postpartum period experienced increases in the ratio of circulating estradiol to progesterone levels from early to late pregnancy, whereas those who reported low levels of attachment underwent declines in the estradiol:progesterone ratio during the same time period (Fleming et al., 1997a).

In other studies, however, prepartum sex steroid levels have been found to have opposite relationships, or no relationship, to postpartum maternal behavior. In multiparous black tufted-ear marmosets (*Callithrix kuhlii*), for example, females' prepartum urinary estradiol concentrations were negatively correlated with maternal behavior and infant survival: individual mothers engaged in lower rates of infant-carrying and experienced lower infant survival rates following pregnancies in which they had high urinary estradiol levels than following pregnancies in which they had low urinary estradiol levels (Fite and French, 2000). In the closely related common marmoset, on the other hand, Pryce et al. (1995) found no significant correlations between urinary estradiol and progestogen (hydroxypregnanolone) levels in the last 50 days of pregnancy and postpartum maternal behaviors of primiparous females. Similarly, urinary concentrations of E_1C and PdG during the last few weeks of pregnancy did not reliably predict postpartum maternal behavior in western lowland gorillas (*Gorilla gorilla gorilla*) (Bahr et al., 2001) or baboons (Bardi et al., 2004).

Finally, several studies have examined relationships between postpartum maternal sex steroid levels and postpartum maternal behavior or maternal attitudes in humans and nonhuman primates. In striking contrast to the findings on prepartum sex steroid levels and maternal responsiveness, circulating or excreted concentrations of estrogens and progestogens in lactating females showed few or no significant correlations with measures of maternal behavior in black tufted-ear marmosets (Fite and French, 2000), baboons (Bardi et al., 2004), rhesus macaques (Maestripieri and Megna, 2000), gorillas (Bahr et al., 2001), and women (Fleming et al., 1987, 1997a).

In conclusion, a combination of correlational and experimental studies has indicated that sex steroids can influence females' responsiveness to infants in a variety of anthropoid primate species. In particular, high circulating estrogen concentrations during pregnancy appear to increase maternal responsiveness, and this effect may largely account for the increasing interest in infants seen in many primate females during pregnancy. On the other hand, effects of prepartum estrogen and progestogen on subsequent patterns of maternal behavior following parturition are less clear, with little consistency across studies, while postpartum sex steroid levels show little or no relationship to maternal behavior.

Importantly, although estrogens and progestogens can modulate maternal responsiveness, these hormones clearly are not essential for the expression of maternal responsiveness or maternal behavior in primates. In many primate species, prepubertal females (and, in some cases, males) show pronounced interest in infants (Ziegler, 2000). In rhesus macaques, nulliparous, ovariectomized females exhibited some, albeit low levels of, interest in unrelated infants (Maestripieri and Zehr, 1998), and multiparous, ovariectomized or menopausal females showed intense maternal responses to infants (Holman and Goy, 1995). Furthermore, humans of both sexes can engage in high levels of maternal-like behavior, independent of reproductive or hormonal status (Numan and Insel, 2003). In the anthropoid primates, therefore, the sex steroids are most appropriately viewed as having modulatory, rather than activational, effects on maternal behavior.

5. Prolactin and placental lactogen

Prolactin is a protein hormone secreted by the anterior pituitary gland into the general circulation. In addition to its best-known function, stimulation of lactation, prolactin has numerous physiological and behavioral effects, including roles in metabolism, growth, and, in some taxa, parental behavior (Ben-Jonathan et al., 2008). Prolactin is able to cross the blood–brain barrier via a receptor-mediated transport mechanism in the choroid plexus, thereby entering the CSF and, presumably, gaining access to neural tissue (Belchetz et al., 1982; Numan and Insel, 2003; Grattan and Kokay, 2008). Additionally, studies in rodents indicate that prolactin is produced locally within the brain, especially in a number of hypothalamic regions (Numan and Insel, 2003; Grattan and Kokay, 2008). Another lactogenic hormone, placental lactogen (also referred to as chorionic somato-mammotropin), is secreted by the primate placenta, activates prolactin receptors, and exerts somatotropic as well as lactogenic effects during pregnancy (Grattan, 2002; Saltzman et al., 2010). Thus, prolactin from both adenohypophyseal and neural sources, as well as placental lactogen, can potentially act on the brain to affect the central control of maternal behavior. Importantly, primates and rodents show numerous differences in the control and distribution of lactogenic hormone synthesis and secretion, as well as in the functions of these hormones (Ben-Jonathan et al., 2008); therefore, extrapolations from rodents (and other taxa) to primates should be made with caution.

Maternal circulating concentrations of prolactin and placental lactogen increase during pregnancy in primates, and prolactin levels remain elevated during at least the initial stages of lactation (e.g., common marmoset: Moro et al., 1995; Bolivian squirrel monkey, *Saimiri boliviensis*: Diamond et al., 1987; chimpanzee: Reyes et al., 1975; human: Hill et al., 1999). Prolactin receptor expression in the brain has not been characterized in primates, but in rats, prolactin receptor numbers within the brain – particularly in the choroid plexus, hypothalamus, and preoptic area – increase during pregnancy and lactation, presumably under the influence of prolactin itself, placental lactogen, and gonadal steroids (Grattan, 2002). Prolactin release from the pituitary and within the brain is stimulated by estrogen; however, short-term elevations in circulating prolactin levels are also stimulated by nipple stimulation and other cues from infants (Hill et al., 1999; Roberts et al., 2001b).

Prolactin and placental lactogen have been implicated strongly in stimulating maternal behavior in rodents and rabbits. In rats, numerous studies have demonstrated that prolactin synergizes with estrogen to accelerate the onset of maternal behavior, an effect that may be mediated, at least in part, by reductions in anxiety and neophobia (Numan and Insel, 2003). In contrast, prolactin has not been shown to play a significant role in the onset of maternal behavior in ewes; however, relatively few studies have been performed, so that firm conclusions cannot yet be drawn.

Essentially nothing is known about the role of lactogenic hormones in primate maternal behavior. Only two studies have evaluated possible associations between prolactin and maternal behavior in primate mothers, and in both, plasma prolactin levels did not correlate significantly with measures of maternal behavior in multiparous, lactating females (common marmoset: Saltzman and Abbott, 2005; rhesus macaque: Maestripieri et al., 2009). These findings are not surprising, however, in view of the dynamic patterning of prolactin secretion in lactating females, with acute elevations occurring in response to suckling bouts (Hill et al., 1999). No investigators, to our knowledge, have experimentally manipulated circulating or central prolactin or placental lactogen signaling in primates and evaluated the effects on maternal behavior. Clearly, an understanding of the role of lactogenic hormones in primate maternal behavior awaits further investigations, ideally involving manipulations of central signaling pathways.

In contrast to the paucity of studies on prolactin and maternal behavior in primate mothers, numerous investigators have evaluated a possible role of prolactin in promoting paternal and alloparental care in primates (reviewed by Ziegler, 2000; Schradin and Anzenberger, 2002; Fernandez-Duque et al., 2009). Circulating or urinary prolactin concentrations are often elevated in fathers in biparental species, and in nonbreeding alloparents, as compared to other adult males and nonbreeders (e.g., common marmoset: Dixson and George, 1982; Schradin et al., 2003; cotton-top tamarin: Ziegler et al., 1996b; coppery titi monkey, *Callicebus cupreus:* Schradin et al., 2003; squirrel monkey, *Saimiri sciureus*: Soltis et al., 2005), and may correlate with responsiveness to infants (e.g., common marmoset: Dixson and George, 1982; human: Storey et al., 2000; Fleming et al., 2002; Gordon et al., 2010) or prior experience with infants (cotton-top tamarin: Ziegler et al., 1996b; human: Fleming et al., 2002). Pharmacological reduction of circulating prolactin levels significantly reduced infant-carrying by nonbreeding male and female common marmosets (Roberts et al., 2001a), whereas experimental manipulations of prolactin in common marmoset and cotton-top tamarin fathers did not produce the expected changes in paternal behavior (Almond et al., 2006; Ziegler et al., 2009). Thus, correlations between prolactin and infant-care behaviors in primate fathers, and possibly in alloparents, are likely to reflect stimulation of prolactin secretion by infant-related cues, rather than activation of infant care by prolactin.

6. Oxytocin

Oxytocin is a nonapeptide synthesized primarily in two hypothalamic nuclei, the paraventricular nucleus (PVN) and the supraoptic nucleus (SON). Magnocellular oxytocinergic neurons from these nuclei project to the posterior pituitary, where oxytocin is stored in axon terminals and subsequently secreted into the general circulation. The major physiological functions of this neuropeptide are stimulation of myometrial contractions during parturition and stimulation of milk letdown during lactation; correspondingly, the major stimuli eliciting oxytocin release from the posterior pituitary are uterine contractions and suckling (Leng et al., 2005, 2008).

In addition to the neurohypophyseal oxytocin system, oxytocin is released within the brain, both from parvocellular neurons originating in the PVN and from dendrites of magnocellular PVN neurons (Leng et al., 2008; Lee et al., 2009). Intracerebral oxytocin in mammals appears to act as a neuromodulator to promote social bonding and affiliation, modulate sexual behavior, and reduce stress-responsiveness and anxiety (Numan and Insel, 2003; Leng et al, 2008; Neumann, 2008; Lee et al., 2009). Expression of oxytocin and its receptors in the brain and in the periphery is upregulated by high levels of estrogen in combination with progesterone withdrawal (Numan and Insel, 2003). In sheep and rats, both central and peripheral oxytocin levels rise during the peripartum period, but the two systems may be controlled independently of one another (Keverne and Kendrick, 1994; Numan

and Insel, 2003; Leng et al., 2008). Moreover, oxytocin does not readily cross the blood–brain barrier in adult mammals; consequently, oxytocin levels in the peripheral circulation may not correlate well with those in the brain and are unlikely to influence behavior through direct actions on the brain (Leng et al., 2008; Neumann, 2008).

Compelling evidence indicates that intracerebral oxytocin is important in the expression of maternal behavior in both sheep and rodents (reviewed by Kendrick et al., 1997; Numan and Insel, 2003). In parturient ewes, oxytocin release within the brain plays a key role in activating the onset of maternal behavior, particularly in reducing ewes' rejection of unfamiliar lambs and facilitating the formation of a selective mother–infant bond. In rats, similarly, intracerebral oxytocin has been implicated in mediating females' transition from aversion towards pups to attraction, thereby facilitating the onset of maternal behavior in new mothers.

Few studies have evaluated a possible role of oxytocin in primate maternal behavior. In free-ranging rhesus macaques, plasma oxytocin concentrations of multiparous, lactating females, following capture and overnight cage-housing, showed a strong, significant, positive correlation with measures of "maternal warmth", based on frequencies of nursing and grooming of the infant over the previous weeks or months (Maestripieri et al., 2009). In women, mothers whose plasma oxytocin levels increased from early to mid/late pregnancy (in a single blood sample at each time point) reported significantly higher levels of attachment to their fetuses than those whose oxytocin levels decreased or remained stable across the same time period; however, attachment to the fetus was not related to absolute oxytocin concentrations at either time point (Levine et al., 2007). Moreover, women's plasma oxytocin concentrations during both early pregnancy and the early postpartum period showed significant positive correlations with maternal behavior (Feldman et al., 2007). These correlational findings in macaques and women must be interpreted cautiously, however, in view of the possible dissociation between peripheral and central oxytocin concentrations, the failure of peripheral oxytocin to penetrate into the brain, and the acute effects of suckling bouts on circulating oxytocin levels (Leng et al., 2005; Neumann, 2008).

Further evidence that oxytocin may promote maternal responsiveness in primates comes from two pilot studies in which central oxytocin signaling was manipulated in a small number of nulliparous, adult female rhesus macaques. Holman and Goy (1995) found that infusion of oxytocin into the cerebral ventricles of two female rhesus monkeys appeared to increase their interest in and affiliative behavior towards infants, whereas peripheral administration of an oxytocin receptor antagonist that was found to accumulate in the brain appeared to have opposite effects in a single female (Boccia et al., 2007). Thus, in primates, as in nonprimate mammals, oxytocin may act within the brain to facilitate the onset of maternal behavior; however, this conclusion must remain tentative until additional, larger-scale experimental studies are performed.

7. Hypothalamic-pituitary-adrenal axis hormones

Stress, both chronic and acute, is thought to interfere with maternal behavior in primates. In nonhuman primates, anxiety and psychosocial or environmental stressors, such as crowding, receipt of aggression, and lack of social support, can increase the risk of infant abuse (Reite and Caine, 1983; Troisi and D'Amato, 1994; Maestripieri, 1994; Maestripieri and Carroll, 1998a,b). In women, similarly, such stressors as poverty, domestic violence, sexual assault, natural disasters, and lack of social support are often associated with impaired maternal behavior and increased abusive behavior (e.g., Kotch et al., 1995; Brockington, 1996; Banyard et al., 2003; Tolan et al., 2006; Taylor et al., 2009). The neuroendocrine mechanisms by which stress disrupts maternal behavior are not known but are likely to involve the hormones of the HPA axis.

The HPA axis plays key roles in governing metabolism, as well as in regulating physiological and behavioral responses to stress (reviewed by Sapolsky et al., 2000; Charmandari et al., 2005). Stress stimulates release of the neuropeptide corticotropin-releasing hormone (CRH; also known as corticotropin-releasing factor, CRF) from the PVN of the hypothalamus. CRH enters the hypothalamic-hypophyseal portal circulation and subsequently stimulates the anterior pituitary to synthesize and secrete adrenocorticotropic hormone (ACTH) and related peptides (e.g., β-lipotropic hormone and β-endorphin) from their common precursor molecule, proopiomelanocortin. ACTH, in turn, stimulates the zona fasciculata of the adrenal cortex to secrete glucocorticoids (e.g., cortisol in primates and corticosterone in many rodents). Glucocorticoids act on target cells throughout the body, including numerous brain regions, to regulate metabolism and to modulate physiological and behavioral preparations for and responses to stressors. CRH, in addition to its neuroendocrine function, acts within a number of brain regions to mediate behavioral, emotional, and autonomic responses to stress. Thus, both CRH and glucocorticoids, as well as β-endorphin and other endogenous opioids, can potentially modulate maternal behavior, especially under stressful conditions. Here we examine the evidence for modulation of primate maternal behavior by cortisol and CRH; we consider the endogenous opioids separately (see Section 8), because their behavioral effects are likely to be mediated by opioid release within the brain rather than from the pituitary, and therefore may be regulated independently of the HPA axis.

Circulating glucocorticoid concentrations in females vary with reproductive state. In primates, baseline cortisol levels rise during pregnancy, especially the second half (e.g., common marmoset: Tardif et al., 2005; cotton-top tamarin: Ziegler et al., 1995; mandrill, *Mandrillus sphinx*: Setchell et al., 2008; human: Lindsay and Nieman, 2005). Maternal cortisol levels during lactation are typically lower than those during pregnancy, but can be similar to, somewhat higher than, or lower than those of nonpregnant, nonlactating females (e.g., golden lion tamarin, *Leontopithecus rosalia*: Bales et al., 2005; mandrill: Setchell et al., 2008; Japanese macaque: Kondo et al., 2003; rhesus macaque: Maestripieri et al., 2008; Hoffman et al., 2010; chacma baboon, *Papio hamadryas ursinus*: Weingrill et al., 2004; western lowland gorilla: Bahr et al., 1988; human: Altemus et al., 1995, Butte et al., 1999). Effects of lactation on HPA reactivity to stress in primates are inconsistent. Although some studies have reported that breastfeeding women exhibit lower cortisol responses to acute stress than nonlactating women (e.g., Altemus et al., 1995), others have found no differences (e.g., Altemus et al., 2001). Among nonhuman primates, plasma cortisol and ACTH responses to acute stress did not differ between lactating and nonlactating, nonpregnant female common marmosets (Saltzman et al., 2008), whereas lactating female rhesus macaques had larger plasma cortisol elevations in response to stress than nonlactating, nonpregnant females (Maestripieri et al., 2008; Hoffman et al., 2010).

Effects of glucocorticoid hormones on maternal behavior have received relatively little attention in nonprimate mammals. A recent series of experiments in rats (Rees et al., 2004, 2006; Graham et al., 2006), however, has indicated that glucocorticoids can either promote or inhibit maternal behavior, depending on the female's reproductive status. In lactating rats, adrenalectomy decreased and corticosterone replacement restored licking of pups, time spent in the nest, and maternal memory (Rees et al., 2004; Graham et al., 2006). Conversely, in virgin females displaying pup-induced maternal behavior (i.e., sensitization), adrenalectomy increased licking of pups and time spent crouching over pups, whereas corticosterone replacement had opposite effects (Rees et al., 2006).

As with other hormones, data on possible effects of glucocorticoids on primate maternal behavior come almost exclusively from correlational studies. In nonhuman primates, these studies generally have found inverse associations between maternal circulating or

excreted postpartum cortisol levels and the quality or intensity of maternal care. In captive Western lowland gorillas, for example, mothers' postpartum urinary cortisol concentrations, divided by their prepartum urinary cortisol levels ("postpartum stress index"), correlated negatively with the proportion of time that mothers spent in ventro-ventral-supported contact with their infants, especially during locomotion (Bahr et al., 1988). Similarly, among captive baboons, mothers with higher urinary cortisol concentrations postpartum spent less time maintaining contact with their infants than those with lower urinary cortisol levels (Bardi et al., 2004). Among captive Japanese macaques, mothers' fecal cortisol levels postpartum were not significantly associated with time spent in contact with the infant, but were positively correlated with the frequency of maternal rejection of infants (Bardi et al., 2003a). Similarly, in free-ranging, provisioned, multiparous rhesus macaques, mothers' plasma cortisol concentrations following capture and overnight cage-housing were significantly and positively correlated with measures of maternal rejection during the preceding weeks or months, but were not associated with measures of maternal protectiveness or maternal warmth (Maestripieri et al., 2009).

In contrast to these findings of negative associations between maternal behavior and mothers' postpartum cortisol levels, two studies have found small but significant positive correlations between postpartum maternal behavior and *prepartum* cortisol levels in baboon mothers (but see Bardi et al., 2003a, for negative results). In free-ranging yellow baboons (*Papio cynocephalus*), females with high fecal glucocorticoid levels during the last two weeks of pregnancy were subsequently more responsive to their infants' distress cries, during the first eight weeks postpartum, than those with lower fecal glucocorticoid levels (Nguyen et al., 2008), whereas in captive savannah baboon mothers, urinary cortisol concentrations during the last six weeks of pregnancy were positively correlated with measures of maternal affiliation during the first four weeks postpartum (Bardi et al., 2004).

Importantly, in each of the studies investigating correlations between pre- or postpartum cortisol levels and maternal behavior in nonhuman primates, all or most of the focal mothers were experienced (multiparous) breeders. It is conceivable that a different pattern of results would be found with inexperienced mothers, similar to findings in rats. For example, a positive correlation between circulating plasma cortisol levels and interest in infants was found in juvenile female rhesus macaques, in which interest in infants was measured by the rate of handling of other females' infants (Maestripieri, 2005a). Finally, in humans, Fleming and her collaborators (Fleming et al., 1987, 1997b; Krpan et al., 2005) found maternal cortisol levels to be positively correlated with several measures of attraction to infants and maternal responsiveness to infant signals in young and inexperienced mothers, although some aspects of maternal behavior showed a negative rather than a positive association with cortisol (see also Feldman et al., 2007).

In the only experimental study reported to date investigating effects of cortisol on maternal behavior in primates, Saltzman and Abbott (2009) gave daily injections of hydrocortisone or vehicle to multiparous, lactating female common marmosets for 8 days and characterized maternal behavior under both undisturbed conditions in the home cage and stressful conditions (exposure to an unpredictable, loud noise) in a test cage. Females with chronically elevated cortisol levels showed no differences in maternal behavior during stress tests, as compared to vehicle-injected controls, but spent significantly less time carrying their infants during home-cage observations. Importantly, cortisol treatment, which elevated circulating cortisol levels into or above the stress range, did not increase mothers' aggressive behavior toward their infants. These results support the findings from correlational studies, described above, that elevated cortisol levels are associated with diminished maternal behavior in experienced primate mothers, especially in nonhuman

species, but do not provide any evidence that high maternal cortisol levels promote infant abuse.

Although reports of positive and negative correlations between cortisol and maternal behavior may be interpreted as contradictory and inconclusive evidence, we believe that a consistent pattern emerges from most nonhuman primate and human studies. Taken together, these studies suggest that circulating cortisol levels have a positive relationship with maternal responsiveness to infant stimuli, possibly through arousal-dependent mechanisms, especially in young females (see also Fleming et al., 1987; Maestripieri, 2010). At the same time, cortisol has a negative relationship with maternal caregiving behavior because high cortisol levels associated with stress or depression can suppress maternal motivation and enhance maternal rejection, through arousal-independent mechanisms, especially in older and more experienced mothers (see also Krpan et al., 2005).

Might other hormones of the HPA axis contribute to stress-induced disruptions of maternal behavior or increases in abusive behavior? As described above, CRH plays a critical role in mediating behavioral responses to stressors, largely through trans-synaptic actions within the brain mediated by type-1 CRH receptors (Takahashi, 2001; Holmes et al., 2003; Rotzinger et al., 2010). In rodents and primates, intracerebroventricular (ICV) CRH treatment elicits many behavioral responses that are similar or identical to those associated with stress and/or anxiety (Dunn and Berridge, 1990; Broadbear, 2006). Conversely, specific CRH type-1 receptor antagonists elicit effects opposite to those of ICV CRH treatment, generally exerting anxiolytic-like and antidepressant-like effects (Takahashi, 2001; Holmes et al., 2003; Rotzinger et al., 2010).

In rodents, ICV infusion of CRH has been found to inhibit several components of maternal behavior, including the onset and subsequent re-emergence of pup-induced maternal behavior in nulliparous female rats (Pedersen et al., 1991), nursing behavior in lactating rats (Almeida et al., 1994), and maternal aggression toward male intruders in lactating mice (Gammie et al., 2004). ICV CRH treatment also increased rates of pup-killing in nulliparous rats that had no previous experience with pups (Pedersen et al., 1991). In contrast, ICV CRH treatment increased acceptance and decreased rejection of lambs in ovariectomized, estrogen-treated ewes (Keverne and Kendrick, 1991).

Indirect evidence for an inhibitory effect of CRH on primate maternal behavior comes from studies of early childhood trauma. In humans and nonhuman primates, traumatic events early in life, such as maternal deprivation or abuse, lead to chronic dysregulation of the CRH systems and HPA axis in adulthood (e.g., Claes, 2004; Sanchez et al., 2010). Individuals who experience trauma early in life also frequently exhibit impaired parental behavior as adults, which may be associated with depressive symptoms or anxiety (Fleming et al., 2002; Claes, 2004; Maestripieri, 2005b). In rhesus macaques, abusive mothers that were themselves abused as infants had higher CSF CRH concentrations than nonabusive mothers that were not abused as infants (Maestripieri et al., 2005). In sum, these findings suggest that persistent hyperactivity of the central CRH systems as a result of early-life trauma may directly disrupt maternal behavior and promote infant abuse, and thus may mediate the intergenerational transfer of deficient maternal behavior (Champagne and Meaney, 2001; Maestripieri et al., 2005; Sanchez et al., 2010).

Only a single study has experimentally tested the effects of CRH on maternal behavior in primates. Primiparous common marmosets received ICV infusions of CRH or vehicle during the early- to mid-lactational period and were tested with one of their infants during the subsequent hour (Saltzman W. and Abbott D.H., unpublished data). When tested in their familiar home cage, mothers spent significantly less time carrying their infants following infusion of a high dose of CRH than following infusion of vehicle, although no other significant behavioral differences were detected. Mothers subsequently underwent a "confined-infant test", in which they were placed in a novel cage in an unfamiliar room, and could approach their confined (but

visible and audible) infant only by descending to the cage floor (which appears to be anxiogenic in marmosets: Hannaford, 1996; Buchanan-Smith et al., 2002) and crossing through a hole in a partition. CRH significantly reduced the mothers' time spent on the cage floor, and therefore prevented them from approaching or attempting to retrieve their infants. As ICV CRH treatment also significantly elevated circulating cortisol concentrations, however, it could not be determined whether inhibitory effects of CRH on maternal motivation were mediated directly by intracerebral CRH or indirectly through activation of the HPA axis.

In summary, a growing body of research suggests that hormones of the HPA axis can modulate maternal behavior in primate mothers. Correlational studies in monkeys, apes, and humans suggest that HPA activity can enhance arousability in response to infant stimuli, particularly in young and inexperienced females. Insofar as the motivation to engage in infant-caregiving activities is dependent on arousal in young females, maternal behavior too can be enhanced by HPA axis activation. Maternal behavior in older and multiparous mothers, however, may depend less on arousal in response to infant stimuli and more on experience and other internal and environmental factors that affect motivation. Consistent with the notion that stress and depression can interfere with maternal behavior in humans, experimental studies of monkeys have demonstrated that both acute elevations of CRH within the brain (and corresponding acute elevations of cortisol in the circulation) and chronic elevations of circulating cortisol levels can inhibit specific aspects of maternal behavior, especially infant-carrying.

8. Endogenous opioids

The endogenous opioid peptides, including the endorphins, enkephalins, dynorphins, and endomorphins, are released both peripherally from the pituitary and centrally within a number of brain regions (Van Ree et al., 2000; Numan and Insel, 2003). Reproduction-related changes in opioids and their receptors have not been well characterized in primates, but plasma β-endorphin concentrations in women have been reported to be low during pregnancy and high during labor and the early postpartum period, as compared to nonpregnant, nonlactating women (Hoffman et al., 1984). Release of β-endorphin into the peripheral circulation is stimulated by suckling in women and possibly in nonhuman primates (Franceschini et al., 1989; Gordon et al., 1992).

The endogenous opioids are well known to influence social bonding and affiliative behavior. Based on similarities between opiate addiction and social attachment, Panksepp and colleagues (Panksepp et al., 1980; Nelson and Panksepp, 1998) have hypothesized that endogenous opioids mediate the rewarding properties of social affiliation. Specifically, they proposed that opioids are released during social contact, and that this release is rewarding. Consequently, high endogenous opioid levels, or treatment with opiate receptor agonists, should blunt the response to social separation and reduce motivation to seek social contact, whereas low basal levels of endogenous opioids, or treatment with opiate receptor antagonists, should increase contact-seeking behavior. This "brain opioid theory of social attachment" has been supported by numerous findings in a variety of mammalian and avian species, including studies of mother–infant interactions (reviewed by Panksepp et al., 1980, 1994; Maestripieri, 2010).

A large body of literature has demonstrated that opioids influence maternal behavior in rodents and sheep (reviewed by Numan and Insel, 2003). In rats, the specific effects of opioid peptides and receptor antagonists are highly variable, depending on the particular brain regions, opiate receptors, and components of maternal behavior involved. For example, activation of mu-opiate receptors in the medial preoptic area appears to inhibit the initiation and, to a lesser extent, maintenance of maternal behavior, whereas opioids may act in the ventral tegmental area to facilitate the onset of pup-induced maternal

behavior (i.e., sensitization) in virgin females. In ewes, endogenous opioids have more consistent positive effects, potentiating the effects of vaginocervical stimulation on the onset of maternal behavior as well as on release of oxytocin within the brain (reviewed by Keverne and Kendrick, 1994; Numan and Insel, 2003; Dwyer, 2008).

Several experimental studies have also implicated the endogenous opioids in modulating primate maternal behavior. As predicted by the brain opioid theory of social attachment, treatment of rhesus macaque mothers with naltrexone, a relatively non-selective opiate receptor antagonist, at the end of a 20-minute separation from their infants, significantly increased the amount of time that mothers and infants spent clinging to one another upon reunion, whereas treatment with morphine, a mu-opiate receptor agonist, produced the opposite effect (Kalin et al., 1995). Similarly, long-tailed macaque (Macaca fascicularis) mothers that were treated with heroin, a mu-receptor agonist, immediately before brief separation from their infants subsequently engaged in lower levels of maternal behavior upon reunion with their infants than mothers treated with saline (Misiti et al., 1991). In contrast, naloxone, a mu-opioid receptor antagonist, significantly reduced the time that rhesus macaque mothers spent grooming their infants and their frequency of restraining their infants (i.e., protectiveness toward the infant). Other aspects of maternal behavior were not affected (Martel et al., 1993). Finally, repeated treatment with naltrexone during the first four weeks postpartum did not alter maternal behavior or infant abuse in rhesus macaque mothers with a history of abusing their infants (Graves et al., 2002). The causes of these differences in findings among studies are unclear but might include such factors as the specific agonist or antagonist used, dose, and testing conditions (Maestripieri, 2010). Nonetheless, taken together, these findings generally support the hypothesis that the endogenous opioids influence maternal behavior in primates. The exact nature of these effects remains to be clarified.

9. Serotonin

Serotonin is a monoamine neurotransmitter released by neurons that originate in the brainstem raphe nuclei and project to numerous brain regions (Lechin et al., 2006). The brain serotonergic system plays an important role in impulse control and in reducing the probability that risky, dangerous, or aggressive behaviors will be expressed in response to internal or external stimuli (e.g. Higley, 2003; Maestripieri, 2008a). Although serotonin is an obvious candidate neurotransmitter for the regulation of maternal care, surprisingly few studies have addressed its relationship to maternal behavior in rodents or other mammals (Numan and Insel, 2003). A study of rats found that lesions of the median raphe serotonergic neurons disrupted maternal behavior on day 1 of lactation (Barofsky et al., 1983), but the results of this study have been questioned and the effects on maternal behavior have been ascribed to the surgical procedure rather than to the specific loss of a serotonergic pathway (Numan and Insel, 2003). Other studies of rats involving pharmacological manipulations of the brain serotonergic system reported some effects on maternal aggression but few or no effects on pup retrieval or other aspects of maternal care (reviewed by Numan and Insel, 2003; but see Johns et al., 2005). Studies of knockout mice carrying a null mutation for the serotonin 1A or 1B receptor gene reported higher fearfulness, impulsivity, and hyperactivity in these individuals, as well as impaired maternal behavior (Brunner et al., 1999; Gingrich and Hen, 2001; Weller et al., 2003; Jacobs and Emeson, 2006).

The relative paucity of studies of serotonin and maternal behavior in rodents may reflect the belief that the motivational bases of maternal behaviors such as nest-building, crouching over the pups, licking/grooming, and pup retrieval depend on the direct actions of hormones and neuropeptides such as prolactin and oxytocin in specific regions of the brain (e.g. the medial preoptic area of the hypothalamus; Numan and Insel, 2003). Although serotonin may

affect maternal motivation through its actions on oxytocin or prolactin release, serotonin and other monoamines are viewed as having nonspecific effects on emotionality, motivation, or memory rather than specific effects on parentally motivated behaviors (Insel and Winslow, 1998; Numan and Insel, 2003). Research with rodents has established a strong link between anxiety/impulsivity and maternal aggression (e.g., Lonstein and Gammie, 2002), but the emotional substrate of other aspects of rodent maternal behavior is not well established (but see Weller et al., 2003; Johns et al., 2005). Emotions do, however, play a fundamental role in the regulation of maternal behavior in nonhuman primates and humans (Dix, 1991; Pryce, 1992; Maestripieri, 1999, 2010).

Performing studies involving brain lesions or genetic manipulations in primates is problematic; therefore, researchers who have investigated the relationship between serotonin and primate behavior have relied on measures of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the CSF. Consistent with a large body of human research (e.g. Linnoila and Virkkunen, 1992), studies of rhesus macaques and vervet monkeys (*Chlorocebus aethiops*) have shown that, in adult males, low levels of CSF 5-HIAA are associated with high impulsivity, risk-taking behavior, and propensity to engage in severe forms of aggression (reviewed by Higley, 2003). Similarly, adult female monkeys with low CSF 5-HIAA have been reported to be more likely to be wounded, to engage in violent aggression, and to be lower-ranking than females with high CSF 5-HIAA (reviewed by Higley, 2003; but see Cleveland et al., 2004). Adult females with low CSF 5-HIAA also appear to be less socially oriented, spending more time alone, grooming less, and having fewer conspecifics in close proximity (Cleveland et al., 2004).

Early studies of serotonin and maternal behavior in monkeys reported that mothers with low CSF 5-HIAA were more protective and restrictive, and that their infants spent more time in contact with them, than mothers with high CSF 5-HIAA (Lindell et al., 1997; Fairbanks et al., 1998). Cleveland et al. (2004) found no relationship between CSF 5-HIAA and maternal behavior in rhesus macaque mothers in the first few days postpartum, but on postpartum days 15 and 20, mothers with low CSF 5-HIAA broke contact and left their infants less frequently than females with high CSF 5-HIAA. A preliminary study reported a positive correlation between CSF 5-HIAA concentrations measured during pregnancy and maternal rejection behaviors in the first month postpartum in multiparous female rhesus macaques (Maestripieri et al., 2005). More recent work involving multiple measurements of CSF 5-HIAA during development, however, reported a negative correlation between CSF 5-HIAA and maternal rejection among first-time rhesus macaque mothers (Maestripieri et al., 2007). Taken together, these studies support the notion that variation in serotonergic function can contribute to the expression of differences in maternal behavior, although the relationship between serotonin and primate maternal behavior is not yet fully understood.

Motherhood can be psychologically stressful for human and nonhuman primates. In rhesus macaques, the first few months of an infant's life result in a number of anxiety-eliciting situations for the mother (Maestripieri, 1993a). Rhesus macaque mothers exhibit marked individual differences in anxiety, and such differences translate into differences in maternal style (Maestripieri, 1993b). Maternal anxiety has also been implicated in the etiology of infant abuse (Troisi and D'Amato, 1984, 1991, 1994). Although the role of emotionality, and particularly of impulsivity, in primate maternal behavior is still poorly understood, it is possible that impulsivity affects how primate mothers interact with their infants, and that high impulsivity is expressed as high rejection rates and, as other studies suggest, greater maternal protectiveness. Recent findings suggest that variation in impulsivity and maternal rejection originates, at least in part, from early experience, such that receiving high rates of maternal rejection results in low serotonergic function, which in turn results in high rates of maternal rejection later in life (Maestripieri et al., 2007).

In a longitudinal developmental study of rhesus macaques, Maestripieri et al. (2006a,b) reported that individuals exposed to high rates of maternal rejection in infancy had significantly lower CSF concentrations of 5-HIAA across their first 3 years of life than those exposed to low rates of maternal rejection. When data were analyzed separately for crossfostered and non-crossfostered individuals, a similar relationship between maternal rejection and CSF 5-HIAA was found in both groups, suggesting that this association was not due to genetic similarities between mothers and offspring. In contrast, there were no differences in CSF 5-HIAA between offspring reared by high- and low-protectiveness mothers. When females reached 3–4 years of age and gave birth for the first time, the maternal rejection rates of daughters closely resembled those of the biological or foster mother by which they had been raised (there were no similarities in maternal protectiveness; Maestripieri et al., 2007). The resemblance was particularly strong for the crossfostered females and their foster mothers. This finding is consistent with a previously reported intergenerational correlation of maternal rejection rates in another population of rhesus macaques (Berman, 1990) and suggests that this correlation is the result of early experience and not of genetic similarities between mothers and daughters. Furthermore, Maestripieri et al. (2007) found that the crossfostered females' CSF 5-HIAA concentrations were negatively correlated with the rates of maternal rejection that they performed, such that individuals with lower CSF 5-HIAA exhibited higher rates of rejection toward their infants. Therefore, exposure to variable rates of maternal rejection in infancy may affect the development of the brain serotonergic system, and variation in serotonergic function, in turn, may contribute to the expression of maternal rejection toward one's own offspring later in life.

Maternal rejection has a complex relationship with maternal abuse, perhaps not dissimilar from the relationship between child neglect and abuse in humans. Abusive parenting in rhesus macaques co-occurs with high rates of maternal rejection. Abusive mothers begin rejecting their infants shortly after birth (whereas rejection by nonabusive mothers begins much later, after 3–4 weeks) and continue to do so at much higher rates than nonabusive mothers (Maestripieri, 1998; McCormack et al., 2006). Although there were no direct effects of infant abuse on the offspring's CSF 5-HIAA levels, the observed significant effects of maternal rejection on CSF 5-HIAA were likely driven by abused infants, who were exposed to much higher levels of rejection than nonabused infants. In addition to the intergenerational transmission of maternal rejection rates, there is also evidence for the intergenerational transmission of infant abuse. Specifically, about half of the females who were abused by their mothers early in life, whether crossfostered or non-crossfostered (all crossfostered females reared by abusive mothers were also abused by them), exhibited abusive parenting toward their first-born offspring, whereas none of the females reared by nonabusive mothers did (including those born to abusive mothers; Maestripieri, 2005b). Moreover, the abused females, both crossfostered and non-crossfostered, who became abusive mothers had lower CSF 5-HIAA concentrations than the abused females who did not become abusive mothers (Maestripieri et al., 2006a). This finding suggests that experience-induced, long-term alterations in serotonergic function in females reared by abusive mothers may contribute to the manifestation of abusive parenting in adulthood (Maestripieri, 2008b).

It is possible that experience-induced reduction in serotonergic function results in elevated anxiety and impaired impulse control, and that high anxiety and impulsivity increase the probability of abusive parenting (e.g. Troisi and D'Amato, 1984, 1991), perhaps in conjunction with social learning resulting from direct experience of abuse early in life or observation of abusive parenting displayed by one's own mother with siblings. The intergenerational transmission of infant abuse, however, is likely to be a complex process with multiple determinants and influences. The finding that abusive mothers were more likely to carry the short allele of the serotonin transporter gene

(McCormack et al., 2009) suggests that genetically based variation in brain serotonergic function may also play a role in the manifestation of abusive parenting and its transmission across generations.

10. Summary and conclusions

The last two decades have witnessed an enormous increase in the number of studies investigating the endocrinology and neurobiology of maternal behavior in human and nonhuman primates. All but a handful of these studies have been correlational, however, and effects of specific hormones, neuropeptides, and neurotransmitters on the expression of primate maternal behavior have rarely been investigated systematically across doses, contexts, or reproductive conditions. Thus, very few firm conclusions can yet be drawn about the roles of the endocrine and neuroendocrine systems in primate maternal behavior.

Like other aspects of social behavior, maternal behavior in the anthropoid primates appears to be largely emancipated from hormonal influences (Nelson, 2005): interest in infants and infant-caregiving behavior can be expressed spontaneously by females – and, in some species, males – of all ages and reproductive conditions. Nonetheless, the studies reviewed above indicate that aspects of maternal responsiveness and maternal behavior often correlate with, and can be modulated by, specific hormones and neuropeptides. As in other mammals, neuroendocrine changes occurring during pregnancy, parturition, and lactation appear to facilitate the onset of maternal behavior in primates. Elevated estrogen concentrations during pregnancy promote responsiveness to infant stimuli, while intracerebral oxytocin may increase interest in and affiliation towards infants. Prolactin and placental lactogen also seem likely to influence the expression of primate maternal behavior, as they do in nonprimate mammals; however, very few studies, and no experimental studies to date, have addressed this possibility in primate mothers.

In addition to these reproductive hormones, several stress-related hormones and neuropeptides may influence primate maternal behavior. Elevations in circulating cortisol concentrations appear to increase arousal and responsiveness to infant stimuli in young, relatively inexperienced females, but may disrupt the expression of maternal behavior in older and more experienced mothers. High CRH levels, associated with stress, anxiety, or psychopathology, may also interfere with maternal behavior in primate mothers, possibly through intracerebral actions. Endogenous opioids appear to affect maternal attachment to infants, but the precise nature of this effect is not yet clear. Finally, serotonin acts within the brain to reduce anxiety and impulsivity, which in turn may affect maternal behaviors such as infant retrieval or rejection of infants' attempts to make contact with the mother. Both serotonin and CRH have been implicated in mediating intergenerational transmission of maternal behavior and of infant abuse.

Clearly, our understanding of the neuroendocrinology of primate maternal behavior is still in its infancy. Much more experimental work is needed to establish the roles of particular hormones, neuropeptides, and neurotransmitters in activating, modulating, or inhibiting specific aspects of maternal behavior, as well as to identify the organismal and environmental conditions under which such effects are expressed. Furthermore, essentially nothing is known of the mechanisms by which hormones and neuropeptides influence primate maternal behavior. Thus, future work should identify the neural sites at which hormones and neuropeptides act to modulate maternal reponsiveness and maternal behavior, as well as the mechanisms – e.g., the molecular, sensory, perceptual, cognitive, affective, or motor processes – by which such effects are mediated. By necessity, such work is likely to focus on a small number of primate species that have been studied extensively under laboratory conditions. At the same time, however, expanding the study of the neuroendocrinology of maternal behavior to a broader range of primate taxa – especially the prosimians, tarsiers, colobine monkeys, and Asian apes – would provide valuable comparative perspectives. Together, the dual approaches of incisive, experimental laboratory studies on a small number of species and focused, correlational studies on a broad range of primate taxa, studied under natural conditions, will yield complementary, novel insights into the biology of primate parenting and its neuroendocrine control.

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