Models of Stress in Nonhuman Primates and Their Relevance for Human Psychopathology and Endocrine Dysfunction

Jerrold S. Meyer and Amanda F. Hamel

Abstract

Stressful life events have been linked to the onset of severe psychopathology and endocrine dysfunction in many patients. Moreover, vulnerability to the later development of such disorders can be increased by stress or adversity during development (e.g., childhood neglect, abuse, or trauma). This review discusses the methodological features and results of various models of stress in nonhuman primates in the context of their potential relevance for human psychopathology and endocrine dysfunction, particularly mood disorders and dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) system. Such models have typically examined the effects of stress on the animals’ behavior, endocrine function (primarily the HPA and hypothalamic-pituitary-gonadal systems), and, in some cases, immune status. Manipulations such as relocation and/or removal of an animal from its current social group or, alternatively, formation of a new social group can have adverse effects on all of these outcome measures that may be either transient or more persistent depending on the species, sex, and other experimental conditions. Social primates may also experience significant stress associated with their rank in the group’s dominance hierarchy. Finally, stress during prenatal development or during the early postnatal period may have long-lasting neurobiological and endocrine effects that manifest in an altered ability to cope behaviorally and physiologically with later challenges. Whereas early exposure to severe stress usually results in deficient coping abilities, certain kinds of milder stressors can promote subsequent resilience in the animal. We conclude that studies of stress in nonhuman primates can model many features of stress exposure in human populations and that such studies can play a valuable role in helping to elucidate the mechanisms underlying the role of stress in human psychopathology and endocrine dysfunction.

Key Words: behavior; cortisol; hypothalamic-pituitary-adrenocortical; primates; psychopathology; stress

Introduction

Stress is thought to be an important factor in the precipitation and maintenance of psychopathology and endocrine dysfunction in many patients who suffer from major depression, anxiety disorders, and even psychosis (Bosch et al. 2012; Holtzman et al. 2012; Pêgo et al. 2010). As seen in this special issue, many rodent models have been developed to study these disorders and, in some cases, the role of stress in eliciting abnormal behavior and physiology in the animals. Nevertheless, in accordance with other primate researchers contributing to this issue, we would argue that because of their phylogenetic relatedness to humans and the complexity of their cognitive abilities and social organizations, nonhuman primates deserve a special place in the search to determine the adverse consequences of stress (especially when chronic) and the relevance of such consequences for human psychopathology and pathophysiology.

Modern stress research arose from the seminal work of Hans Selye (1950). Although we all have a rough idea of the meaning of stress when the term is used in common parlance, this concept has been more difficult to define in the scientific realm. Two ideas that have received considerable attention are (1) that stress involves a threat to homeostasis (Chrousos and Gold 1992) and (2) that stressors (stimuli that evoke a stress response) are stimuli that are unpredictable and/or uncontrollable (Levine and Ursin 1991). Although these ideas have considerable utility in helping us conceptualize the concepts of stress, stressors, and stress responses, they also have limitations that have been addressed in more recent models. McEwen and Wingfield (2003) proposed that the effects of repeated or long-term stress in both biomedical and ecological contexts could be understood more adequately by applying Sterling and Eyer’s (1988) concept of allostatics. As stated by Sterling (2004), “Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a ‘setpoint’ and feeding back to correct the error. Allostasis describes mechanisms that change the controlled variable by predicting what level will be needed and overriding local feedback to meet anticipated...
demand.” (p. 2). For example, sustained activation of the hypothalamic-pituitary-adrenocortical (HPA) system by a chronic stressor might lead to changes in basal glucocorticoid levels and subsequent stress responses that are explained better by an allostasis model than by homeostasis. Even more recently, Romero and colleagues (2009) identified limitations of the allostasis model and suggested a new framework, termed the Reactive Scope Model, which incorporates elements of both homeostasis and allostasis.

With only a few exceptions (e.g., Howell and Sanchez 2011; Maestriperi and Hoffman 2011), most of the research on stress in nonhuman primates has not yet incorporated either the allostasis or reactive scope models. For this reason, this review will mainly use the classic terminology of stress, stressors, and stress responses. Single exposures to severe stressors can alter subsequent stress responses, as seen in both the experimental animal literature (Armario et al. 2004) and many cases of post-traumatic stress disorder (Yehuda 2006). However, most of the programmatic studies of long-term stress effects in primates have used models of repeated or persistent stressor exposure, and thus it is on this literature that we have focused for this review. The review begins with models of stress in adult animals, followed by stress occurring during earlier stages of development. In both cases, outcome measures typically include measures of behavior, HPA activity, and occasionally reproductive and/or immunologic function. Nevertheless, it is important to remember that chronic stress can lead to adverse health consequences encompassing many additional physiologic systems (McEwen and Gianaros 2010). We also note that most of the primate HPA studies to date have assessed adrenocortical activity by measuring plasma or fecal glucocorticoid levels. However, our group and others have shown that slow incorporation of cortisol into hair over time provides an index of long-term adrenocortical activity and, in some cases, a measure of the HPA response to major life or environmental stressors (Davenport et al. 2008; Dettmer et al. 2014; Meyer and Novak 2012; Sanchez et al. 2012). We anticipate that over time, this approach will become more widely used in nonhuman primate models of chronic stress.

**Stress in Adulthood**

Models of stress in adult nonhuman primates often involve psychosocial events in which animals are removed from an existing social environment, placed into a new social environment, or subjected to disruptive social interactions from group members of a higher or lower rank. The following discussion will review some of the major findings from this literature.

**Stress Related to Relocation and/or Social Separation**

Relocating captive nonhuman primates from a familiar home cage or colony room to a novel environment is a potent psychosocial stressor. The new and unfamiliar environment presents a sudden, uncontrollable, and unpredictable change. Carolyn Crockett and colleagues at the Washington National Primate Research Center have examined the physiologic and behavioral responses of macaques to different types of relocations, both to new colony rooms within the same facility and to unfamiliar cage environments. The researchers first moved individually housed longtailed macaques (Macaca fascicularis) into a new colony room for a period of 2 weeks and subsequently exposed them to five different cages of varying size for 2 weeks at a time (Crockett et al. 1990; Crockett et al. 1993; Crockett et al. 1995). Relocation to a novel colony room, but not transfer into a new cage, resulted in increased levels of urinary cortisol that remained elevated through the first night and day after placement in the new room (Crockett et al. 1993). Appetite was also suppressed during this period of time, as monkeys consumed significantly fewer biscuits during the first day after the move than during the baseline period (Crockett et al. 1990). Relocation to the new colony room, as well as subsequent moves into each of the new cages, continually resulted in disrupted sleep and suppressed activity patterns during the first night and day spent in the new environments. Specifically, monkeys spent more time in an inactive state, less time self-grooming, and less time sleeping during each first day and night after a move. These data demonstrate that relocation to a novel room is a stressful experience that initially results in activation of the HPA axis and suppressed patterns of activity. Transfer to new cages within the same colony room elicits similar behavioral responses. However, throughout the 2-week period that monkeys spent in the new colony room, the frequency of behavioral change was elevated (Crockett et al. 1995), meaning that monkeys were engaging in an increased number of behaviors. These data suggest that after an initial period of suppressed activity, the new environment may ultimately increase levels of arousal.

The same investigators also examined the responses of pigtailed macaques (Macaca nemestrina) to a similar relocation paradigm, exposing them to a new room environment for a 2-week period and subsequently rotating them through four different cages of varying size for 2 weeks each. The pigtailed macaques were less reactive than longtailed macaques to the relocations; unlike the longtailed macaques, the pigtailed macaques did not exhibit activation of the HPA axis in response to relocation and had slightly increased levels of biscuit consumption during the first 3 days spent in the new colony room (Crockett et al. 2000). However, in the next phase, the appetite of the pigtailed monkeys was markedly suppressed during the first day in the first of the four new cages. Overall, the investigator’s relocation paradigm demonstrated a significant species difference that may be related to other findings that suggest that longtailed macaques have a more cautious and fearful temperament than pigtailed macaques (Sussman et al. 2013). The response of captive primates to relocation has been demonstrated to last for a period much longer than the 2-week period examined by Crockett and colleagues. Work from our laboratory found that individually housed adult male rhesus macaques (Macaca mulatta) subjected to a mandated relocation to a new facility had elevated plasma cortisol levels
measured both 1 week and 1 year after relocation (Davenport et al. 2008). A subgroup of monkeys that engaged in occasional self-biting additionally showed a persistent increase in this behavior (see Novak et al. 2014). One interpretation of these data is that relocation is a potent stressor with chronic effects that can last many months; alternatively, the observed effects may reflect the monkeys’ response to a new environment that is more stressful than the previous one. In either case, it is clear that significant environmental change can elicit potent behavioral and endocrine responses with potentially adverse consequences.

A combination of relocation plus social separation stress occurs when primates that have been housed socially are transferred to individual caging. For example, female baboons (Papio sp.) moved from outdoor social cages to indoor individual cages exhibited increasing urinary cortisol levels for approximately 3 months after relocation before levels began to decline (O’Connor et al. 2011). In addition, the stressor was sufficient to disrupt the female baboons’ menstrual cycles. The length of the follicular phase was shortened after relocation, resulting in overall shorter cycle lengths. Normal cyclicity returned after approximately 4 or 5 months (four or five cycles) after relocation (O’Connor et al. 2011). Relocated female baboons required a number of months before habituating to a new environment.

In addition to activating an initial stress response, the experience of relocation and social separation can alter later reactivity of the HPA axis. Female rhesus macaques removed from their social group and placed in individual cage housing for 7 days were challenged with corticotropin-releasing factor (CRF; also called corticotropin-releasing hormone), a test that assesses overall system reactivity at the levels of the pituitary and adrenal glands. Control female macaques responded to CRF administration with significant increases in plasma adrenocorticotropic hormone (ACTH), whereas relocated female macaques demonstrated no significant change. Furthermore, the plasma cortisol response to the CRF challenge was greater in control macaques than in relocated female macaques (Gust et al. 2000). Thus, relocation and social separation resulted in blunted responsivity of the HPA axis, which was hypothesized to be related to changes in pituitary CRF receptor density that resulted from psychosocial stress.

Although relocation has been demonstrated to be a potent stressor, response to the stress may be attenuated by the presence of a social partner. Most nonhuman primate species are naturally social, organized in large social groups or smaller family units. Consequently, the animals often form positive relationships with cage mates or colony roommates in captivity. Several investigators have demonstrated that different species of marmosets relocated from their home cage to a new environment, in the absence of their familiar social partner, respond with elevated cortisol concentrations (Johnson et al. 1996; Norcross and Newman 1999; Smith et al. 1998). However, black tufted-ear marmosets (Callithrix kuhlii) that were relocated to the new environment in the presence of their pairmate exhibited no observed increase in urinary cortisol. In addition, behavioral increases in locomotion and vocalization observed in singly relocated marmosets were not observed in marmosets relocated with their pairmate (Smith et al. 1998). Common marmosets (Callithrix jacchus) removed from their home cage and placed, along with their partner, in a novel cage for 24 hours had blunted plasma cortisol levels compared with marmosets that were relocated in the absence of their pairmate (Norcross and Newman 1999). Similar effects were observed in titi monkeys (Callicebus moloch). That is, the plasma cortisol response of titi monkeys to relocation to a new room was lower when monkeys were relocated with their pairmate (Hennessy et al. 1995). For social species, therefore, separation from group members may be a contributing factor to the potent stress of relocation. Alternatively, the presence of a social partner may play a direct role in blunting the stress response. This social modulation of stress has been demonstrated in a variety of species, including humans, and supports the idea that positive social interactions can blunt activation of the stress response and protect against the deleterious effects of stress (DeVries et al. 2003; Eisenberger 2013; Hennessy et al. 2009; Hostinar and Gunnar 2013).

Primate models of relocation and social separation stress are relevant for a number of different human circumstances. For example, relocation of elderly people who move from their private residence to a community living setting (e.g., assisted-living or nursing home) can result in a so-called relocation stress syndrome, which is characterized by depressed mood, anxiety, social withdrawal, and somatic symptoms (Kao et al. 2004). Transient HPA activation may also occur (Hodgson et al. 2004; but see Lutgendorf et al. 2001). Social separation stress is particularly strong in individuals who have lost a loved family member. Such loss has been associated with an increased risk for psychiatric and somatic illness (Stroebe et al. 2007), as well as dysregulation of the HPA axis (Dietz et al. 2013; Holland et al. 2014; Pfeffer et al. 2009). As with the primate studies, social support can ameliorate the negative effects of stressors such as relocation or separation (Biondi and Picardi 1996, 1999).

Group Formation Stress

Relocation can be especially stressful when it involves the introduction of unfamiliar conspecifics. Male squirrel monkeys (Saimiri sciureus) placed into social housing with unfamiliar conspecifics exhibited elevated plasma cortisol concentrations for up to 4 weeks after group formation, at which point introduction of unfamiliar females to the social group caused further increases in cortisol concentrations (Mendoza et al. 1979). The formation of a new social group requires the establishment of a dominance hierarchy, during which increased levels of aggression and wounding are often observed. One study by Goo and Sassenrath (1980) demonstrated that relocation of unfamiliar female rhesus macaques, a highly aggressive species, into two harem groups resulted in such excessive aggression and wounding that the most dominant two female macaques were removed from the social groups. The harem
group female macaques showed an initial rise in plasma cortisol levels upon group formation. Cortisol levels were reduced upon removal of the dominant individuals and subsequently elevated upon their reentry into the group. Indeed, plasma cortisol concentrations did not return to baseline until 3 weeks after the initial formation of the social group (Goo and Sassenrath 1980). An ACTH challenge was also administered to the female macaques before and after harem group formation. Plasma cortisol response to the ACTH challenge was elevated in harem female macaques, compared with baseline levels, after group formation. Female macaques in one harem group continued to have an elevated response to the ACTH challenge even 13 weeks after group formation (Goo and Sassenrath 1980). For female rhesus macaques, therefore, sensitivity of the HPA axis was elevated for an extended period of time after the psychosocial stress of relocation and group formation.

Several studies have demonstrated that participation in aggressive alterations is associated with relocation-induced activation of the HPA axis. High levels of aggression and wounding were observed upon the transfer of unfamiliar male and female marmosets into social housing. Both female marmosets that had been wounded and female marmosets that had wounded another animal had elevated levels of cortisol up to 3 days after relocation (Saltzman et al. 1994). After the stress of relocation and group formation, stabilization of the dominance hierarchy is seemingly associated with decreased HPA axis activity. The relocation of marmoset male and female pairs into large social groups resulted initially in elevated plasma cortisol concentrations. However, when establishment of the ranking structure was observed to be stable by the absence of aggressive and submissive interactions, these concentrations had returned to near baseline levels (Johnson et al. 1996). Finally, the stress response of a new social group can be shortened or attenuated when dominance hierarchies are formed without direct physical aggression. For example, when Gust and colleagues (1991) relocated eight unfamiliar female rhesus macaques into a social group, they found elevated plasma cortisol levels and reduced numbers of circulating lymphocytes at 24 hours after relocation but not at later time points. Importantly, the researchers noted that group dynamics had stabilized within 48 hours without any serious aggressive interactions (Gust et al. 1991). In summary, the psychosocial stress of forming a social group with unfamiliar conspecifics can be exacerbated by realignment of a previous dominance hierarchy and the aggressive interactions that sometimes accompany social organization. HPA activity may normalize once the new social structure has stabilized.

Stress and Social Rank

In wild-living primates with social (dominance) hierarchies, the highest ranked animals have the greatest access to natural resources (e.g., food and resting or sleeping places) and mates (de Ruiter and van Hoof 1993; Dittus 1977), and they are able to displace lower ranked (subordinate) animals and win aggressive encounters against subordinates. This social structure raises the important question of whether social rank is associated with differential amounts of stress, and researchers have addressed this question by examining the relationship between rank and endocrine physiology or, alternatively, various health outcome measures. For captive primates, the best characterized model of dominance hierarchy and stress is Carol Shively’s work on group-housed female cynomolgus monkeys (Macaca fascicularis). The animals are maintained in groups of three to five, a condition under which they form stable linear hierarchies as shown by agonistic and other social interactions. A number of studies conducted by Shively and colleagues demonstrated that compared with dominant female monkeys, subordinates have higher baseline cortisol levels, increased response to an ACTH challenge, reduced sensitivity to cortisol suppression in the dexamethasone suppression test, and increased behavioral vigilance (Shively and Willard 2012). These findings suggest that the subordinate monkeys are more highly stressed than the dominant animals. Moreover, a certain percentage of subordinate monkeys develop behavioral and physiologic signs of depression (e.g., reduced activity, hunched posture, exacerbated coronary artery disease), which occurs much less frequently in the dominant animals (Willard and Shively 2012). In this animal model, therefore, the stress of social subordination seems to be a risk factor for the development of a depressive syndrome.

An extensively studied model of social rank and stress in wild primates comes from the research of Robert Sapolsky on free-ranging adult and subadult male olive baboons (Papio anubis) living in troops in the Masai Mara National Reserve in Kenya. Social status of the animals was ascertained by extensive behavioral observations, whereas HPA system function was assessed by measurement of plasma cortisol. Animals were anesthetized by an intramuscular phencyclidine injection delivered by a dart gun, and cortisol levels were measured at multiple time points after injection to determine stress responsivity as well as baseline (i.e., before the anesthesia-induced cortisol rise had begun). The first report of this work was based on data collected during a period of social stability within the troop (Sapolsky 1982). Interestingly, during this time, social rank was not associated with increased aggressiveness or amount of fighting, presumably because the higher ranking male baboons were not being challenged for their social status. Nevertheless, the low-ranked male baboons had higher baseline cortisol concentrations than the highest ranked animals and showed a smaller absolute cortisol rise to the stress of darting and anesthetization (Sapolsky 1982). Experimental manipulation of the HPA system suggested that the chronic hypercortisolism (i.e., elevated baseline cortisol levels) seen in low-ranking animals originates in enhanced CRF release by the hypothalamus and reduced sensitivity of the glucocorticoid negative feedback system that normally keeps adrenocortical secretion in check (Sapolsky 1989, 1990). Moreover, a number of additional studies found that high-ranking (dominant) male baboons show less stress-induced suppression of testosterone.
levels than lower ranking baboons, lower baseline blood pressure but a greater cardiovascular response to an activating stimulus, higher concentrations of the protective high-density lipoprotein cholesterol, and enhanced immune function as indicated by circulating lymphocyte numbers (Sapolsky 1995).

It should be noted that the relationship between social rank and HPA activity in baboons is modulated by several important factors (Sapolsky 1995). First, endocrine differences associated with social rank depend on the stability of the existing hierarchy. During a period of social instability characterized by shifts in rank and escalated aggression among high-ranking male baboons, the high-ranked animals did not differ from low-ranked animals in baseline cortisol levels, nor did they exhibit a differential stress response to darting and anesthetization (Sapolsky 1995; however, see Gesquiere et al. 2011 for different results with savannah baboons). Second, an individual animal’s specific experiences within the social hierarchy exert an important influence on that individual’s HPA system. An extreme example comes from the rare occurrence of an aggressive, fully mature male baboon (given the name Hobbes) transferring from one troop to another. In this instance, the ensuing increase in fighting due to Hobbes’s struggle for dominance caused a substantial elevation of baseline cortisol throughout all of the male baboons, with Hobbes showing the highest level (Sapolsky 1995). Blood lymphocyte counts were also suppressed in all the male baboons, with the lowest counts observed in Hobbes. Third, even during periods of relative troop stability, behavioral characteristics of the high-ranking male baboons are associated with differences in baseline cortisol. Specifically, high-ranking animals showed elevated cortisol levels if they were less “sophisticated” in their assessment of male competitors and their interactions with those competitors or if they had low rates of affiliative interactions with nonestrus female baboons and infants (Sapolsky 1995). Moreover, a recent study of male savannah baboons (Papio cynocephalus) in Kenya found that the very highest ranked (alpha) male in a given troop also had the highest fecal glucocorticoid levels, whereas other highly ranked males had lower levels than low-ranked animals (Gesquiere et al. 2011). It is possible that the challenges to alpha male status among the savannah baboon troops are more stressful than those encountered by the alpha male baboons in the previously studied olive baboon troops, thereby accounting for the elevated HPA activity (Sapolsky 2011). Together, these findings show that the relationship between social rank and stress is complex, depending not only on rank per se, but also on the current structure of the animals’ society as well as the individual’s characteristic behavior within that society.

Before concluding this section, we may ask how broadly applicable are these results obtained in male olive baboons. In particular, are similar rank-related differences in the HPA system found in female baboons, in male baboons residing in troops with low levels of aggression, and in other species of nonhuman primates? Robert Seyfarth, Dorothy Cheney, and their colleagues have investigated the social factors influencing fecal glucocorticoid levels in wild female chacma baboons (Papio hamadryas ursinus) living in the Okavango Delta of Botswana. Unlike male baboons, which emigrate when they approach reproductive maturity, female baboons usually remain within their natal troop. The female baboons within a troop have their own maternal dominance hierarchy in which daughters attain a social rank similar to that of their mother. Studies of these female chacma baboons revealed that fecal glucocorticoid levels were not strongly related to social rank during a period of troop stability (Crockford et al. 2008). Rather, greater glucocorticoid excretion was observed in cycling and pregnant female baboons that received high levels of aggression from other animals, independent of rank. Low glucocorticoid excretion was found in baboons that received a high rate of “grunts,” a benign vocalization that signals lack of aggressive intent. When the male dominance hierarchy was in a period of instability and female baboons were at risk for death of their infants, fecal glucocorticoid levels rose dramatically during the next 1 to 2 weeks (Wittig et al. 2008). Interestingly, over succeeding weeks the high-ranked female baboons showed a more rapid decline toward baseline levels than the lower-ranked female baboons. Personality assessment of the female baboons in this troop additionally revealed that animals designated as “loners” (characterized by low sociality and high rates of grunting to high-ranking females) had high levels of glucocorticoid excretion (Seyfarth et al. 2012). Returning to male olive baboons, Sapolsky and Share (2004) reported on an unusual Kenya troop with relatively peaceful social relationships and enhanced affiliative behavior of male baboons toward the female baboons. In this instance, baseline cortisol levels were the same in low- and high-ranking male baboons. Finally, Abbott and colleagues (2003) performed a meta-analysis to ascertain the relationship between social rank and baseline cortisol levels in a variety of primate species (both Old and New World) under stable dominance hierarchy conditions. Three different patterns were observed: (1) equal cortisol levels between dominant and subordinate animals (e.g., captive male rhesus macaques living in large troops; captive female squirrel monkeys living in large single or mixed sex groups); (2) lower cortisol levels in subordinate animals (e.g., captive female common marmosets living in mixed sex groups); and (3) higher cortisol levels in subordinate animals (e.g., captive male squirrel monkeys living in large single- or mixed-sex groups; free-ranging male olive baboons described earlier). Based on the characteristics of the social structure of each primate society, the authors concluded that hypercortisolism among subordinates generally occurs when the animals are subjected to a high degree of social stress, have few kin within the group, and receive a low level of social support from other group members. In contrast, the low cortisol levels in subordinate female marmosets may be an adaptation to their hypoestrogenic state and suppressed breeding.

In summary, social disruption and overt challenges to dominance can be highly stressful to male primates living in groups where rank is established by physical aggression (e.g., typical free-ranging baboon troops). When dominance hierarchies are stable, physiologic stress responses as measured by plasma cortisol or fecal glucocorticoids may be greatest for...
either low- or high-ranking animals, depending on several different factors including species, sex, living conditions, and individual temperament. The potential applicability of primate models of rank-associated stress to humans can be illustrated with a few examples. As noted by Sapolsky (2005), the risk of developing stress-related somatic and/or psychiatric illness in Western societies is inversely related to socioeconomic status. Low socioeconomic status is hypothesized to promote the onset of stress-related disease through allostatic load ("wear-and-tear on the body and brain resulting from chronic dysregulation [i.e., over-activity or inactivity] of physiological systems that are normally involved in adaptation to environmental challenge"); McEwen and Gianaros 2010, p. 194). In addition to this general relationship between stress and socioeconomic status, there are specific examples of increased stress associated with low social rank and social rejection. Both acute and chronic social rejection by peers provoke subjective distress and increases in salivary cortisol (Blackhart et al. 2007; Peters et al. 2011; Stroud et al. 2002). Chronic peer rejection has been associated with additional HPA dysregulation shown by a flattening of the diurnal cortisol rhythm. A particularly severe form of social rejection is bullying behavior. Interestingly, recent studies have reported that victims of repeated bullying either at school or in the workplace show reduced baseline salivary cortisol levels and a blunted cortisol response to a psychosocial stressor (Hansen et al. 2006; Hansen et al. 2011; Hogh et al. 2012; Knack et al. 2011; Ouellet-Morin, Danese, et al. 2011; Ouellet-Morin, Ogders, et al. 2011). Such blunting is consistent with a downregulation of HPA system responsiveness due to chronic stress exposure. Taken together, the primate and human studies suggest that the relationship between social status and stress is highly complex and that no single primate model is capable of capturing this complexity. Nevertheless, the various primate models should ultimately prove valuable in elucidating the biological mechanisms that mediate the effects of stress on vulnerability for developing psychopathology and endocrine dysfunction.

**Stress in Development**

Early development is likely to be a time when the brain is particularly vulnerable to the deleterious effects of stress. Indeed, clinical research has increasingly demonstrated an important link between early stress and later psychopathology (Carr et al. 2013; Juster et al. 2011; Norman et al. 2012). We summarize current information on the effects of prenatal or early postnatal stress on primate behavior and physiology.

**Prenatal Stress**

One of the best-studied models of developmental stress in nonhuman primates is the prenatal stress work of Mary Schneider and colleagues (for review, see Schneider et al. 2001; Schneider et al. 2002). These investigators subjected pregnant rhesus macaques to a procedure involving removal from the home cage, placement in a small transport cage in a dark room, and administration of three noise bursts from an alarm horn within a 10-minute period. This noise stress was applied 5 days per week, usually during the period from day 90 through day 145 of pregnancy (i.e., mid-to-late gestation of a 165-day gestation period). Control macaques were undisturbed except for normal husbandry procedures. Infants born of stressed and control macaques were reared by their natural mothers in some studies or surrogate-peer reared in the nursery (see Rupenthal 1979) in other studies. Early studies from this group found that compared with control offspring, the offspring of stressed mothers displayed deficient motor development during the first 30 days postpartum as measured by a monkey neurobehavioral assessment scale (Schneider 1992b; Schneider et al. 1991; Schneider et al. 1999), delayed object permanence development (Schneider 1992a), more disturbance behavior and less exploratory behavior when tested at 6 months of age in a novel playroom setting (Schneider 1992c), abnormal social behaviors when tested at 18 months (Clarke and Schneider 1993), and elevated ACTH and cortisol concentrations in response to several different types of stressors (Clarke et al. 1994). Behavioral abnormalities associated with prenatal stress exposure were still evident when offspring were tested at 4 years of age (Clarke et al. 1996).

Subsequent studies investigated some of the potential mechanisms underlying the adverse effects of prenatal stress in rhesus macaques. One such study found that daily administration of ACTH to female macaques from day 120 to day 134 of pregnancy led to behavioral deficits in infants tested using the neurobehavioral assessment scale (Roughton et al. 1998). This finding indicated that at least some of the effects of prenatal stress may be mediated by activation of the mother’s HPA axis. Behavioral abnormalities in stressed offspring may also be related to the neurochemical alterations that persist beyond the early developmental period. This hypothesis is supported by studies demonstrating elevated cerebrospinal levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol and the dopamine metabolite dihydroxyphenylacetic acid in the infants at 8 and 18 months of age (Schneider et al. 1998). Neuroimaging of stressed offspring at 5 to 7 years of age additionally showed increased striatal dopamine D2 receptor binding availability (compared with control offspring) and an increase in the ratio of D2 binding to dopamine synthesis (Roberts et al. 2004). It is important to note that, although abnormal catecholamine functioning may play some mediating role in the effects of prenatal stress, numerous other neurochemical systems that have not yet been evaluated may be equally or more important in the development and persistence of such effects. Finally, Coe and colleagues (2003) exposed pregnant rhesus macaques to noise stress (5 days per week) either during early (day 50 to 92) or late (day 105 to 147) gestation. Offspring of stressed and control macaques were examined at 2.0 to 2.5 years of age. The two periods of prenatal stress exposure had nearly identical effects on the subjects—namely, significantly decreased exploratory behavior (and a tendency toward increased pacing) in the home-cage setting, elevated plasma cortisol levels both under basal conditions and after a dexamethasone suppression test, and reduced
hippocampal neurogenesis and hippocampal volume. These findings demonstrate that prenatal stress during two different periods of fetal development exerts long-lasting effects suggestive of increased emotionality and hyperactivity of the HPA axis, both of which may be related to hippocampal dysfunction.

In some nonhuman primate studies, the potent synthetic glucocorticoid dexamethasone was administered during pregnancy to ascertain the influence of stress-induced glucocorticoid elevations on offspring brain development and behavior. In studies by Uno and colleagues, prenatal dexamethasone exposure in rhesus macaques (a single treatment on day 132 or multiple treatments on days 132 to 133 of gestation) led to degeneration of hippocampal neurons when offspring were examined later in fetal development (Uno et al. 1990), as well as reduced hippocampal volume and elevated cortisol levels assessed during the juvenile period (Uno et al. 1994). Subsequent studies from the groups of Eberhard Fuchs and Joachim Gerber in Göttingen, Germany, and Joran Feldon and Christopher Pryce in Zurich, Switzerland, determined the effects of prenatal dexamethasone in marmoset monkeys. The drug was typically administered at an oral dose of 5 mg/kg daily from gestational day 42 to 48 (during organogenesis) or day 90 to 96 (later pregnancy) of a 144- to 145-day gestational period. Importantly, these dosing regimens were not grossly toxic to the developing fetus based on body weight at birth and over the next 48 weeks of life (Hauser et al. 2007; Hauser et al. 2008; Tauber et al. 2006). On the other hand, dexamethasone exposure during either period of development caused a significant decrease in cell proliferation in the hippocampal dentate gyrus of newborn marmosets (Tauber et al. 2006). Neither cell differentiation nor apoptotic cell death was altered in the drug-treated monkeys. Behaviorally, early dexamethasone exposure led to increases in mobility, time spent eating, amount of solitary play, and incidence of tail hair piloerection (Hauser et al. 2007). Deleterious effects were also observed on the development of social contact, initiation of play, and development of skilled motor reaching, with the precise effects dependent on the period of drug administration (Hauser et al. 2008). Interestingly, 2-year-old marmosets exposed to dexamethasone prenatally did not differ from control monkeys with respect to dentate gyrus volume, granule cell proliferation, or various neurochemical markers measured in corpus callosum white matter, supra-callosal gray matter, or thalamus (Michaelis et al. 2009; Tauber et al. 2008). Thus, at least some of the adverse effects of prenatal dexamethasone recover over time in this species.

Stress During the Neonatal Period

Mother–Infant Separation

Several models of early stress in primates involve manipulations carried out with neonates such as separation of infant monkeys from their mothers. The first such studies were conducted by Harlow and colleagues and showed that infant rhesus macaques physically separated from their mothers at approximately 6 to 7 months of age exhibited severe disturbance behavior characterized by crying vocalizations, depressed play behavior (both nonsocial play and social play with familiar age-mates), and heightened clinging behavior upon reunion with the mother (Seay and Harlow 1965; Seay et al. 1962). More crying was observed when the infant was permitted visual and auditory contact with its mother during the separation period. These findings were replicated and extended by Levine and colleagues, who demonstrated an inverse relationship between distress vocalization and plasma cortisol in the separated infants. Thus, totally isolated infants showed high cortisol levels but relatively few vocalizations, whereas the opposite pattern was found when the mother was present nearby but in a separate cage (Levine et al. 1984; Levine et al. 1985).

Separation studies have also been conducted on rhesus macaque infants reared with peers (peer-only reared; PR) instead of a mother (mother-reared; MR). In general, separated PR macaques exhibited higher levels of distress vocalizations and self-directed behaviors, as well as more time spent in passive behavior, than separated MR macaques (Suomi 1991). Moreover, recent studies have shown that both behavioral and endocrine responses to separation stress are modulated by an interaction between rearing condition and a length polymorphism in the promoter region of the rhesus macaque serotonin transporter gene (rh5-HTTLPR) (the short [s] allele of this polymorphism is associated with reduced serotonin uptake as well as other perturbations of the serotonergic system; Singh et al. 2012). Specifically, gene × environment interactions have been reported in which 6-month-old PR infants with the l/s genotype (the s allele is relatively infrequent, and thus it is often difficult to find sufficient homozygous s/s subjects to study) exhibited greater levels of behavioral pathology (i.e., stereotyped behaviors) and higher plasma ACTH concentrations than l/l PR macaques or MR macaques of either genotype (Barr et al. 2004; Spinelli et al. 2007). l/s PR macaques also showed a greater degree of separation-induced behavioral despair (vocalizations, self-directed behaviors, and passivity) than the other three groups. Thus, both the behavioral and endocrine responses to separation stress in infant rhesus macaques depend on a complex interaction between the rearing experience of the animals and genetically mediated serotonergic function. Such findings represent an important model for the proposed gene × environment interactions in determining vulnerability to psychopathology in humans exposed to traumatic events early in life (Uher and McGuffin 2008).

Stress Related to Variable Foraging Demand

Another important model of developmental stress in nonhuman primates originated in the work of Leonard Rosenblum and colleagues. These investigators imposed a variable foraging demand (VFD) on bonnet macaque (Macaca radiata) mothers whereby the macaques were subjected to alternating...
VFD animals additionally found reductions in corpus callosum area, hippocampal and temporal gyrus volumes, and levels of the putative neuronal marker N-acetylaspartate in the anterior cingulate cortex and medial temporal lobe (including hippocampus) (Coplan et al. 2010; Jackowski et al. 2011; Mathew et al. 2003). These findings suggest that early life stress produces long-lasting neuronal deficits in several regions of the cerebral cortex and hippocampus.

Adverse early experiences can exert transgenerational effects that are mediated by epigenetic mechanisms (Champagne 2013). In this regard, it is interesting that VFD rearing was recently shown to produce blunted behavioral responses to stress in adolescent offspring of VFD-reared mothers (i.e., monkey mothers that experienced VFD conditions during their infancy) but not in the mothers themselves (Kinnally et al. 2013). It remains to be determined whether this important result, which adds to the growing literature on transgenerational effects of early experience, is due to epigenetic changes passed on from mothers to their offspring.

**Maternal Abuse**

The social problem of abused or neglected children has received growing attention due to evidence for long-lasting neurobehavioral problems observed in such children (Lindert et al. 2014). Spontaneously occurring infant abuse in macaque monkeys is a potentially valuable model for the stress produced by child abuse in humans. Maestripieri and colleagues have shown that a small percentage of rhesus macaque mothers exhibit abusive behaviors such as dragging, crushing, throwing, hitting, dropping, or stepping on the infant (Maestripieri 1998; Maestripieri and Carroll 1998). Moreover, maternal abuse can be transgenerational, in that female monkeys who were abused by their mothers during infancy are at increased risk of being abusive mothers themselves (Maestripieri 2005). Investigators have reported several other adverse consequences of being abused during infancy, including increased distress vocalizations and “tantrums,” delayed social development, and complex changes in central monoamine systems and in HPA activity (Maestripieri et al. 2006; McCormack et al. 2006; McCormack et al. 2009; Sanchez et al. 2010; Sanchez et al. 2012). With respect to the HPA axis, for example, abused infants carrying the s allele of the serotonin transporter had elevated resting cortisol levels at 1 month of age, when the frequency of abusive behaviors by the mother is greatest (McCormack et al. 2009). Moreover, hair cortisol levels measured at 6 months of age were substantially increased in abused compared with control infants (Sanchez et al. 2012). Particularly relevant to stress responsiveness is the finding of elevated cortisol responses to a CRF challenge from 6 months to 3 years of age in the abused group, the latest time point at which the animals were tested (Sanchez et al. 2010). Further studies are needed to determine whether these animals are more sensitive to social or environmental stressors and whether such an effect persists into adulthood.
Early Experience and Stress Resilience

The previously described nonhuman primate models of severe neonatal stress all lead to adverse physiologic and behavioral outcomes in the stressed offspring. However, because not all children who are raised under high-risk conditions exhibit psychopathology later in life, researchers have been interested in determining the factors that underlie resilience to early life stressors (Masten 2001; Rutter 2006; Tronick 2006). A primate model, sometimes termed “stress inoculation,” has been developed by a group headed by David Lyons and Karen Parker for the purpose of studying the mechanisms of resilience (see reviews by Lyons and Parker 2007; Lyons et al. 2009; Lyons et al. 2010). In this model, infants of socially housed squirrel monkeys are subjected to weekly 1-hour separations from the mother and the rest of the social group beginning at 17 weeks of age and continuing for a period of 10 weeks. Separated animals are then compared with nonseparated controls on a variety of behavioral, endocrine, and neurobiological outcome measures at later time points. Behaviorally, the separated animals showed less anxiety-like behavior (based on a reduction in maternal clinging and an increase in exploratory behavior) in a novel environment at 9 months of age, enhanced performance in a test of inhibitory control at 1.5 years of age, and increased exploration and curiosity in a low-stress test situation at 2.5 years of age (Lyons and Parker 2007; Lyons et al. 2010). The separation manipulation additionally led to reduced baseline cortisol levels and

Figure 1 Model of the factors that contribute to the effects of early stress exposure on developmental outcome. Reprinted from Parker KJ, Maestripieri D. 2011. Identifying key features of early stressful experiences that produce stress vulnerability and resilience in primates. Neurosci Biobehav Rev 35:1466–1483, with permission from Elsevier.
diminished HPA stress responses when examined at the 9-month time point. Finally, neuroimaging studies conducted at 3.3 years of age revealed increased surface area, volume, and myelination of the ventromedial prefrontal cortex, a brain area implicated in decision-making and emotion regulation (Blair 2008). Interestingly, stress inoculation of infant squirrel monkeys does not seem to involve increased maternal care, which is unlike findings in rodents that have given rise to a “maternal mediation” hypothesis of resilience in some rodent neonatal stress studies (Macri and Würbel 2006). Overall, the stress inoculation model shows that certain kinds of stress relatively early in development may program both the nervous and endocrine systems to cope better with later stressors by enhancing inhibitory control over behavioral and HPA axis responses.

As with humans, adverse early experiences in primates can lead to several different developmental trajectories depending on the nature of the experience, the animal’s social (rearing) environment, and genetic/epigenetic factors. The interaction among these variables is shown in a model of early life stress exposure proposed by Parker and Maestripieri (2011), which posits that certain kinds of moderate stress exposure may decrease rather than increase vulnerability to stressors later in life (see Figure 1). A major challenge for future research will be to identify the relevant genetic and epigenetic factors and to characterize the “neurobiological programming” believed to mediate the influence of early stress exposure on later stress vulnerability.

Conclusions

Adult primates living in a social setting can experience significant stress when removed from the social group or when the social hierarchy of the group is unstable. The first kind of situation would seem to model the adverse effects of relocation or social isolation in humans and the potential contribution of such events to the development of psychopathology. On the other hand, social group instability may be relevant for modeling the stress of social conflicts whether within an individual’s family or within his/her social network of friends, colleagues, classmates, and so on. In primate societies where low-ranking animals appear to be the most highly stressed, parallels may be drawn to groups in human societies that are disadvantaged with respect to income, education, occupation, and general social status. As mentioned earlier, the negative health consequences (both psychological and somatic) of such psychosocial stress can be explained by the concept of allostatic load. One of the challenges for future primate stress research will be to design studies with the allostatic load concept in mind to forge a closer link with contemporary human psychosocial stress research.

Stress during development can evoke particularly long-lasting changes in offspring. In some instances, the pregnant female experiences stress that may impact the developing fetus. The precise consequences of and mechanisms underlying prenatal stress in humans are not well understood; yet, there is ample epidemiologic evidence for developmental programming of many illnesses, including some that involve significant psychopathology (Harris and Seckl 2011; Piper et al. 2012; Warner and Ozanne 2010). Future primate studies could prove instrumental, not only in characterizing more fully the neurobehavioral effects of prenatal stress exposure but also in helping to determine the mechanisms underlying such effects. More extensively studied in both humans and nonhuman primates is the impact of early postnatal stress/adversity. Childhood adversity has been linked to later psychopathology (Carr et al. 2013; Norman et al. 2012), and researchers are beginning to elucidate the neurobiological and neuroendocrine mechanisms underlying this linkage (Ehlert 2013; Heim and Binder 2012; McGowan and Szyf 2010; Tyrka et al. 2013). Primate models of early stress and adversity have already led to important findings regarding altered vulnerability to later behavioral and physiologic abnormalities (i.e., either increased vulnerability or resilience) (Gilmer and McKinney 2003; Parker and Maestripieri 2011; Sanchez 2006). Continued research in this area is expected to have substantial translational relevance for understanding the consequences of childhood abuse, neglect, or trauma, as well as the means to promote favorable outcomes after such adverse experiences.

Acknowledgments

Preparation of this review was supported by National Institutes of Health grant 7R24OD011180.

References


Sanchez M, Shi Y, Meyer JS, Zhang X, Stynner M, Howell BR. 2012. Early life stress leads to increased fear and aggressive responses to threat in infant rhesus monkeys: Associations with increased cortisol and amygdala volume. Society for Neuroscience Meeting, New Orleans, LA. Available online (http://www.abstractsonline.com/Plan/ViewAbstract.aspx?miD=2946a&key=472a87ad-f4c1-4530-8c99-a8f959cebf6e&cKey= d9d0dfb4-7019-44d0-ab99-34ae0kmKey=70007181-01e9-4de9-a92e-e6f14cd9f1), accessed on December 8, 2013.


