Maternal care and the development of stress responses

Darlene D Francis* and Michael J Meaney†

Studies dating from the 1950s have documented the impact of early life events on the development of behavioral and endocrine responses to stress. Recent findings suggest that these effects are mediated through changes in mother–offspring interactions and have identified central corticotropin-releasing factor systems as a critical target for the effects of variations in maternal care.

Addresses
Developmental Neuroendocrinology Laboratory, Douglas Hospital Research Center, Departments of Psychiatry and Neurology & Neurosurgery, 6875 Boul LaSalle, McGill University, Montréal, Canada H4H 1R3
*e-mail: cyd6@musica.mcgill.ca
†e-mail: mdmm@musica.mcgill.ca

Current Opinion in Neurobiology 1999, **9**:128–134

http://biomednet.com/elecref/0959438800900128

 ISSN 0959-4388

Abbreviations

ACTH	adrenocorticotropin hormone
CBZ	central benzodiazepine
CnAmy	central nucleus of the amygdala
CRF	corticotropin-releasing factor
GABA	γ-aminobutyric acid
GR	glucocorticoid receptor
HPA	hypothalamic–pituitary–adrenal axis
LC	locus coeruleus
LG-ABN	licking/grooming and arched-back nursing
MR	mineral corticoid receptor
PVNh	paraventricular nucleus of the hypothalamus
SHR	spontaneously hypertensive rat
VFD	variable foraging demand
WKY	Wistar–Kyoto

Introduction

Stress is a risk factor for a variety of illnesses, ranging from auto-immune disorders to mental illness. The pathways through which stressful events can promote the development of such divergent forms of illness involve the same hormones that ensure survival during a period of stress [1••]. Stress-induced increases in adrenal release of catecholamines (adrenaline and noradrenaline) and glucocorticoids orchestrate an increase in catabolism, involving lipolysis and the mobilization of glucose reserves (see Table 1; [2,3•]). These actions serve to increase the availability and distribution of energy substrates. There are also emotional and cognitive responses to stressors [4•]. During periods of stress, feelings of apprehension and fear predominate, and individuals become hypervigilant. The level of attention directed to the surrounding environment is increased at the expense of our ability to concentrate on tasks not related to the stressor. Glucocorticoids act on brain structures such as the hippocampus and amygdala, to disrupt episodic memory [5•]. At the same time, glucocorticoids and catecholamines act on areas of the brain, such as the amygdala, to enhance learning and memory for emotional stimuli (see [6–8]). Even though these responses are highly adaptive, chronic activation of these systems can promote the development of hyperlipidemia, hypertension, chronic immunosuppression and decreased viral resistance, states of anxiety and dysphoria, and sleep disorders [1••,2,9].

We will discuss the implications of altered maternal behavior early in an organism's life on its subsequent vulnerability to stress later in adulthood.

Corticotropin-releasing hormone

Behavioral and endocrine responses to stress are largely governed by two central corticotropin-releasing factor (CRF) neuronal populations (see [10–12]). One population of CRF neurons is in the parvocellular region of the paraventricular nucleus of the hypothalamus (PVNh), which project to the hypophysial-portal system of the anterior pituitary [10]. In responses to stressors, CRF, as well as co-secretagogues such as arginine vasopressin, are released from PVNh neurons into the portal blood supply of the anterior pituitary, where it provokes the synthesis and release of adrenocorticotropin hormone (ACTH; see [10]). Pituitary ACTH, in turn, causes the release of glucocorticoids from the adrenal gland. CRF neurons in the PVNh also activate adrenomedullary catecholamine release [10]. The second population of CRF neurons is in the central nucleus of the amygdala (CnAmy) and projects to the locus coeruleus (LC). They increase the firing rate of LC neurons, resulting in increased noradrenaline release in the vast terminal fields of this ascending noradrenergic system (see [13,14]).

The CRF neurons of the PVNh are an important noradrenergic target. Noradrenaline is the primary stimulus of CRF release from PVNh neurons during stress [10]. The amygdaloid CRF projection to the LC [13,14] is also critical for the expression of behavioral responses to stress (see [8,14,15]). Hence, the CRF neurons in the PVNh and the CnAmy serve as important mediators of both behavioral and endocrine responses to stress.

These findings have provided a basis for understanding how stress can influence health. Yet, the influence of stress on health can only be fully appreciated when the individual's response to stress is taken into consideration. One hypothesis that guides research on the development of psychopathology focuses on the role of early life events in determining individual differences in vulnerability to stress [16–18]. This hypothesis is derived from the finding that chronic activation of central and endocrine stress responses can promote illness (see references cited above). Thus, early life events that increase stress reactivity result in a greater exposure to 'stress hormones' and thus greater vulnerability for stress-induced illness over the lifespan. Support for this hypothesis has emerged from studies

examining the influence of early life events on the development of neural systems that regulate the expression stress responses.

Environmental regulation of the hypothalamic–pituitary–adrenal axis and behavioral responses to stress

One of the strongest models for environmental regulation of the development of responses to stress is the postnatal handling research with rodents. Handling involves a brief (i.e. 3–15 min) daily period of separation of the pup from the mother. In the rat and mouse, postnatal handling decreases the magnitude of behavioral and endocrine responses to stress in adulthood (see [19] for a review). In contrast, longer periods (i.e. 3–6 h) of daily separation from the mother increase behavioral and endocrine responses to stress [20•,21]. These effects persist throughout the life of the animal (see e.g. [22]) and are associated with differences in health outcomes under conditions of stress [22–24].

The central CRF systems are critical targets for these environmental effects (see Table 2). Postnatal handling decreases, and maternal separation increases, CRF gene expression in the PVNh and the CnAmy. Moreover, there are potent effects on systems known to regulate CRF gene expression in the PVNh and the CnAmy. Glucocorticoid receptor systems are modulated, which then serve to inhibit CRF synthesis and release in PVNh neurons [2,3•]. GABAergic/central benzodiazepine (CBZ) systems, which regulate both amygdaloid CRF activity and noradrenergic neurons of the LC [12], are also affected. Predictably, stress-induced activation of ascending noradrenergic systems in adult animals is increased by maternal separation and decreased by handling in early life [25]. Thus, environmental manipulations can alter the expression of behavioral and endocrine responses to stress by altering the development of central CRF systems, as well as systems that regulate CRF activity.

In addition, maternal separation in early life alters the development of ascending serotonergic systems in both monkeys (see [26]) and rats [27]. Repeated periods of maternal separation in early life increase cerebrospinal fluid measures of central noradrenaline and serotonin responses to stress in the rhesus monkey [28]. Considering the importance of the ascending noradrenergic and serotonergic systems in depression, these findings suggest a mechanism whereby early life events might predispose an individual to depression in later life (see [17]).

Thus, long periods of maternal separation during infancy may have long-term effects on stress-mediating pathways. It is not clear, however, whether maternal care actively contributes to the normal development of the neural systems that mediate stress responses or whether it is simply the absence of the mother that is so disruptive to the development of these systems. If maternal care is important, then what are the relevant features of mother–infant interactions and how do they influence neural development?

Table 1

Summary of major metabolic/cardiovascular effects of stress-induced increases in catecholamines and glucocorticoids*.

Target organ/tissue	Effect	Function
Liver	Increase gluconeogenesis	Maintain stable blood sugar level
Selected macromolecular storage sites	Increase glycogenolysis and lipolysis	Increase available energy substrates
Heart, circulatory system	Increase heart rate and blood pressure	Increase blood flow
GH target tissue	Decrease sensitivity to GH	Dampen anabolic processes

*Generated from [1••,2,9]. GH, growth hormone.

What are the critical features of environmental manipulations?

Handling, although a brief interlude in the routine of mother–pup interactions, does alter the behavior of the mother towards its offspring [29]. Mothers of handled pups spend the same amount of time with their litters as mothers of nonhandled pups; however, mothers of handled litters spend significantly more time licking/grooming their pups [30•]. The question, then, is whether this altered pattern of maternal behavior serves as a critical stimulus for the environmental effects on the development of endocrine and behavioral responses to stress.

Interestingly, there are substantial, naturally occurring variations in maternal licking/grooming in rat dams. Maternal licking/grooming of pups occurs most frequently while the mother nurses in the arched-back position; the frequency of the two behaviors are closely correlated ($r = +0.91$) across mothers [30•]. In a series of studies, mothers were divided into two groups: those that spent a large amount of time licking/grooming and arched-back nursing (LG-ABN) and those that spent little time performing these behaviors. Note, there were no differences between these groups in relation to the overall amount of time the mother was in contact with her pups [31•]. If handling-induced differences in licking/grooming or arched-back nursing are relevant for effects on HPA development, then the offspring of high LG-ABN mothers should resemble the handled animals. This is exactly what was found [30•]. As adults, the offspring of high LG-ABN mothers showed reduced plasma ACTH and corticosterone responses to restraint stress. In the adult rat, glucocorticoids act at specific receptor sites within selected brain regions, such as the hippocampus, to decrease CRF synthesis in PVNh neurons (see [3•]). The high LG-ABN animals also showed significantly increased hippocampal glucocorticoid receptor mRNA expression,

Table 2

A summary of the effects of postnatal handling or maternal separation on neural mediators of behavioral and HPA responses to stress in the rat*.

Target	Postnatal handling	Maternal separation
CRF mRNA (PVNh)	↓	↑
CRF mRNA (CnAmy)	↓	↑
CRFir (locus coeruleus)	↓	↑
CRF receptor binding (locus coeruleus, raphé)	↓	↑
GR mRNA (hippocampus)	↑	↓
GR mRNA (PVNh)	No effect	↓
GC feedback inhibition of CRF	↑	↓
$GABA_A$ receptor	↑	↓
CBZ receptor/γ2 mRNA† (amygdala, locus coeruleus, nucleus tractus solitarius)	↑	↓

*Generated from [16,19,21,27]. †The γ2 subunit of the $GABA_A$ receptor complex is thought to encode for the CBZ receptor site. CRFir, immunoreactive CRF; GC, glucocorticoid.

enhanced glucocorticoid negative feedback sensitivity and decreased hypothalamic CRF mRNA levels. Moreover, the magnitude of the corticosterone response to acute stress was significantly correlated with the frequency of both maternal licking/grooming ($r = -0.61$) and arched-back nursing ($r = -0.64$) during the first 10 days of life, as were the levels of hippocampal glucocorticoid receptor mRNA and hypothalamic CRF mRNA expression (all correlation values > 0.70) [30•]. These studies suggest that the critical feature for the handling effect on HPA development involves an increase in maternal licking/grooming.

The offspring of the high and low LG-ABN mothers also differed in their behavioral responses to novelty [31•]. As adults, the offspring of the low LG-ABN mothers showed increased startle responses, decreased open-field exploration, and longer latencies to eat food provided in a novel environment, reflecting a greater fear of novelty. These animals also showed increased CRF receptor levels in the locus coeruleus and decreased CBZ receptor levels in the basolateral and central nucleus of the amygdala, as well as in the LC, and increased CRF mRNA expression in the CnAmy (DD Francis, J Diorio, MJ Meaney, unpublished data). These differences map perfectly onto the differences between handled and nonhandled animals, and provide support for the idea that the effects of handling are mediated by changes in maternal behavior.

It may be surprising that rather subtle variations in maternal behavior have such a profound impact on development. However, for a rat pup, the first weeks of life do not hold a great deal of stimulus diversity. Stability is the theme of the burrow, and the social environment in the first days of life is defined by the mother and littermates. The mother serves as a primary link between the environment and the developing animal. It seems reasonable that variations in the mother–pup interaction would serve to carry so much importance for development.

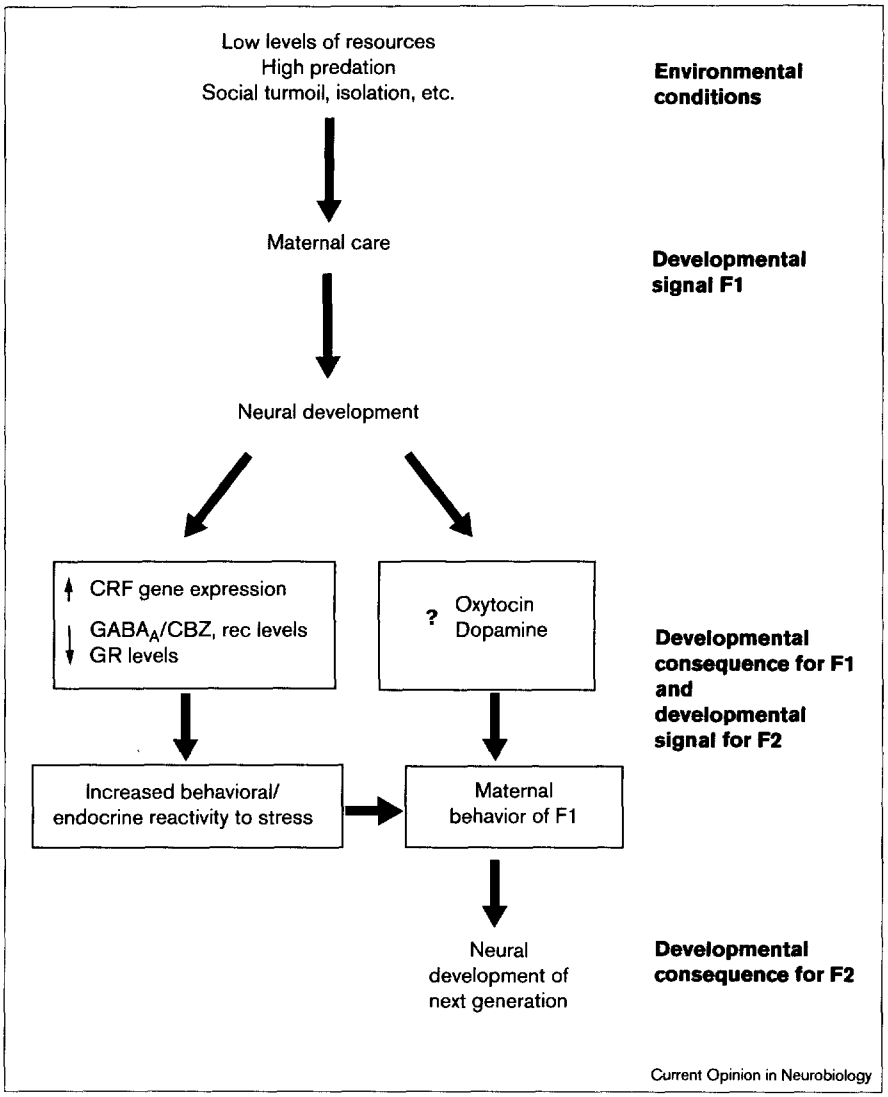
These findings are consistent with the results of studies using the cross-fostering technique as a test for the maternal-mediation hypotheses. For example, the spontaneously hypertensive rat (SHR) is a strain bred for hypertension. Even though the selective breeding suggests a genetic background, the expression of hypertension is also influenced by epigenetic factors (see [32]). SHR pups reared by wild-type (Wistar–Kyoto [WKY]) mothers do not exhibit hypertension to the extent of kin reared by SHR dams. When borderline hypertensive rats (BHRs), a hybrid formed by SHR–WKY matings, are reared by WKY mothers, they do not express the hypertensive phenotype.

The influence of maternal behavior on the development of behavioral and endocrine responses to stress is also apparent in studies with BALBc mice, a strain that normally is very fearful and shows elevated HPA responses to stress. BALBc mice cross-fostered to C57 mothers are significantly less fearful and have reduced HPA responses to stress [33]. Importantly, C57 mothers normally lick and groom their pups about twice as frequently as BALBc mothers. C57 pups cross-fostered to BALBc mothers are more fearful, but not to the same level as non cross-fostered BALBc mice. Comparable findings have emerged from studies of rat strains: for example, Fischer 344 rats, by comparison to Long-Evans rats, are more responsive to novelty and have increased HPA responses to acute stress. Interestingly, Long-Evans dams lick/groom their offspring significantly more often than do Fischer 344 mothers [34].

Under normal circumstances, of course, BALBc mice are reared by BALBc mothers. The genetic and environmental factors conspire to produce an excessively fearful animal. This is the essence of nature and nurture: genetic and environmental factors work in concert, and are often correlated (see [35]). Because parents provide both genes and environment for their biological offspring, the offspring's environment is correlated with their genes. The environment the parent provides commonly serves to enhance the genetic differences — they are redundant mechanisms. The knowledge of an animal's BALBc pedigree is sufficient to predict a high level of timidity in adulthood. Additional information on maternal care would statistically add little to the predictability — the two factors work in the same direction. But this is clearly different from concluding that maternal care is not relevant, and the results of cross-fostering studies attest to the importance of such epigenetic influences. The value of this process is that it can provide for variation. If

Figure 1

A schematic representing the potential outcomes of the proposed relationship between environmental adversity and infant care. The key feature of this formulation is the hypothesized relationship between fearfulness (i.e. reactivity to stress) and maternal behavior (see [43] for a review). Thus, variations in maternal care affect the development of neural systems that mediate stress reactivity (see [16,19,21,27,30•,31•]), which may then influence maternal behavior. These effects then serve to influence the development of the subsequent generation and thus provide a basis for the transmission of individual differences in stress reactivity from one generation to the next. F1, first generation; F2, second generation; rec, receptor.



a genetically determined trajectory is not adaptive for the animal, then development that can move in the direction of the current environmental signal would be of adaptive value. Hence, environmental events may alter the path of developmental trajectories in favor of more adaptive outcomes.

The transmission of individual differences in maternal care to the offspring

Individual differences in behavioral and neuroendocrine responses to stress are, in part, derived from variations in maternal care. Such effects might serve as a mechanism by which selected traits could be transmitted from one generation to the next. This includes individual differences in maternal behavior. Adult, female offspring of high LG-ABN mothers show significantly more LG-ABN than female offspring of low LG-ABN mothers (DD Francis *et al.*, *Soc Neurosci Abstr* 1998, 24:452). Moreover, handling of female pups in early life causes them to become high LG-ABN mothers, regardless of parentage, which suggests that the mode of transmission is indeed behavioral.

The intergenerational transmission of parental behavior has also been reported in primates. In rhesus monkeys, for example, there is evidence for family lineages expressing abuse of infants [36]. Fairbanks [37] found that daughters reared by mothers who consistently spent a large amount of time in physical contact with their offspring became mothers who were similarly more attentive to their offspring. Also, in rhesus monkeys, Berman [38] found that the rejection of infants by their mothers is correlated to whether their mothers were rejected as infants. In all cases, these findings were independent of the social rank of the mother. In humans, measures of parental bonding between a mother and daughter were highly correlated with the same measures of bonding between the daughter and her child [39].

These findings suggest a common process of intergenerational transmission of maternal behavior.

Environmental regulation of maternal behavior

In humans, social, emotional and socio-economic context are overriding determinants of the quality of the relationship between a parent and child [40]. Parental care is disturbed under conditions of chronic stress. Conditions that most commonly characterize abusive and neglectful homes involve economic hardship, martial strife and a lack of social and emotional support (see [40]). Such homes, in turn, breed neglectful and even abusive parents. More subtle variations in parental care also show continuity across generations. Scores on the parental bonding index, a measure of parent–child attachment, are highly correlated across generations of mothers and daughters (DD Francis *et al.*, *Soc Neurosci Abstr* 1998, 24:452). So what are the mechanisms that underlie this apparent transmission of parental behavior from one generation to the next?

Individual differences in behavioral and endocrine responses to stress in the rat are associated with variations in maternal care during infancy [31•,32]. Predictably, the stress responsivity of the offspring mirrors that of their mothers. Low LG-ABN mothers are more fearful than are high LG-ABN dams, and likewise, their offspring are more fearful and timid than are those of high LG-ABN mothers. This is a crucial point in understanding the basis for the transmission of individual differences in parental behavior.

In the rat, maternal behavior emerges as a resolution of an interesting conflict [41]. Females rats, unless they are in late pregnancy or lactating, generally show an aversion towards pups. The novelty of the pups is a source of aversion for females, which is typical of the generally neophobic adult rat. Amygdaloid lesions or specific hormonal regimens that dampen fearful reactions to novelty also increase maternal responsivity in nulliparous females [42,43]. Importantly, intracerebroventricular infusion of CRF reduces maternal responsivity [44]. In humans, the mother's attitude towards her newborn is highly correlated with her level of anxiety [43]. Mothers who feel depressed and anxious are, unsurprisingly, less positive towards their baby (see also [45]). That is to say, more fearful, anxious mothers, such as low LG-ABN rat dams, appear to be less maternally responsive towards their offspring. Uvnas-Moberg [46] has proposed a neural basis for these effects that is based on the functionally antagonist effects of oxytocin and CRF. She suggests that oxytocin has anxiolytic effects and promotes parental care, whereas CRF is anxiogenic and apparently disruptive of maternal behavior.

Under natural conditions, and the sanctity of the burrow, rat pups have little direct experience with the environment. Instead, it is their mother — and thus maternal care — that is affected by conditions such as the scarcity of food, social instability and low dominance status. The effects of these environmental challenges on the development of the pups may then be mediated by alterations in maternal care (see Figure 1). Variations in maternal care could, in turn, serve to transduce an environmental signal to the pups and thus influence the development of neural systems that mediate behavioral and HPA responses to stress. Unfavorable environmental conditions produce animals that are more neophobic (see [19]) and lower in maternal responsivity to pups (i.e. low LG-ABN mothers). This pattern of maternal care could then result in offspring that are more fearful and, ultimately, become low LG-ABN mothers. Hence, these individual differences in the quality of maternal care may serve as the basis for comparable patterns of maternal behavior in the offspring (F1) and for the transmission of these traits to subsequent generations (see Figure 1). A key question here concerns the effects of early life events on the development of neural systems that mediate maternal behavior (see Figure 1 and [46]).

Perhaps the most compelling evidence demonstating perturbations in the nature of maternal care emerges from the studies of Rosenblum and colleagues (see [47]). Bonnet macaque mother–infant dyads were maintained under one of three foraging conditions: low foraging demand (LFD), where food was readily available; high foraging demand (HFD), where ample food was available, but required long periods of searching; and variable foraging demand (VFD), a mixture of the two conditions on a schedule that did not allow for predictability. Exposure to these conditions over a period of months had a significant influence on mother–infant interactions. The VFD condition was clearly the most disruptive. Mother–infant conflict increased in the VFD condition. Infants of mothers housed under these conditions were significantly more timid and fearful. These infants also showed signs of depression commonly observed in maternally separated macaque infants. As adolescents, the infants reared in the VFD conditions were more fearful, submissive and showed less social play behavior.

More recent studies have demonstrated the effects of these conditions on the development of neurobiological systems that mediate the organism's behavioral and endocrine/metabolic response to stress [48,49••] As adults, monkeys reared under VFD conditions showed increased cerebrospinal fluid levels of CRF. Increased central CRF drive would suggest altered noradrenergic and serotonergic responses to stress, and this is exactly what was seen in adolescent VFD-reared animals. These findings provide a mechanism for the increased fearfulness observed in the VFD-reared animals. We would predict that if the environmental conditions remained stable, these differences would, in turn, be transmitted to the offspring (see Figure 1).

Conclusions

The studies reviewed here underscore two critically important points. First, variations in maternal care that fall within the normal range of the species can still have a profound influence on development. One does not need to appeal to the more extreme conditions of abuse and

neglect to see evidence for the importance of parental care. Second, environmental demands can alter parental care and thus infant development. Indeed, we hypothesize that environmentally induced alterations in maternal care mediate the effect of variations in the early postnatal environment on the development of specific neural systems that mediate the expression of fearfulness. Such individual differences in fearfulness, in turn, influence the parental care of the offspring, providing a neurobiological basis for the intergenerational transmission of specific behavioral traits. The key issue, and one with broad social implications, is understanding the neural mechanisms that underlie the relationship between environmental stressors and maternal care.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. McEwen BS: **Protective and damaging effects of stress mediators.**
•• *N Engl J Med* 1998, **338**:171-179.

This review outlines the importance of catecholamine and glucocorticoid action during a period of stress and the physiological costs associated with chronic activation of stress hormone release. The author summarizes our current understanding of the pathways through which elevated levels of corticosteroids and noradrenaline can promote various disease states. The article provides a physiological link between stress and illness.

2. Dallman MF, Akana SF, Strack AM, Hanson ES, Sebastian RJ: **The neural network that regulates energy balance is responsive to glucocorticoids and insulin and also regulates HPA axis responsivity at a site proximal to CRF neurons.** *Ann NY Acad Sci* 1995, **771**:730-742.

3. De Kloet ER, Vregdenhil E, Oitzl MS, Joels M: **Brain corticosteroid**
• **receptor balance in health and disease.** *Endocr Rev* 1998, **19**:269-301.

This very timely review outlines the common actions of glucocorticoid and mineralocorticoid receptor activation on neurons, with a focus on the hippocampus, where GR and MR are co-expressed. The focus is on the role of these receptors in mediating negative feedback inhibition over HPA function. MR activation appears to mediate tonic inhibition over basal HPA activity, whereas GR activation regulates dynamic inhibition over stress-induced HPA activity. In addition, these steroid receptors regulate neuronal function in neocortical, limbic and midbrain regions. These actions appear to mediate the pronounced effects of corticosteroids on cognitive function.

4. Arnsten AF: **The biology of being frazzled.** *Science* 1998,
• **280**:1711-1712.

A very readable summary of the cognitive changes that occur during periods of acute stress with references to recent key studies.

5. Lupien S, Sharma S, Nair NPV, Hauger R, McEwen BS, de Leon M,
• Meaney MJ: **Glucocorticoids and human brain aging.** *Nat Neurosci* 1998, **1**:69-73.

This paper describes the relationship between individual differences in basal cortisol levels, hippocampal volume and episodic memory. Amongst elderly human subjects, cortisol levels were inversely correlated to hippocampal volume. In turn, hippocampal volume was correlated with episodic memory. These findings underscore the importance of individual differences in HPA activity for health over the lifespan.

6. Pitkanen A, Savander V, LeDoux JE: **Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala.** *Trends Neurosci* 1998, **20**:517-523.

7. Davis M, Walker DL, Lee Y: **Amygdala and bed nucleus of the stria terminalis: different roles in fear and anxiety measured with the acoustic startle reflex.** *Philos Trans R Soc Lond [Biol]* 1997, **352**:1675-1687.

8. Quirarte GL, Roozendaal B, McGaugh JL: **Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala.** *Proc Natl Acad Sci USA*

9. Rosmond R, Dallman MF, Bjorntorp P: **Stress-related cortisol secretion in men: relationship with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities.** *J Clin Endocrinol Metabol* 1998, **83**:1853-1859.

10. Plotsky PM: **Pathways to the secretion of adrenocorticotropin: a view from the portal.** *J Neuroendocrinol* 1991, **3**:1-9.

11. Koob GF, Heinrichs SC, Menzaghi F, Pich EM, Britton KT: **Corticotropin releasing factor, stress and behavior.** *Semin Neurosci* 1994, **6**:221-229.

12. Owens MJ, Nemeroff CB: **Physiology and pharmacology of corticotropin-releasing factor.** *Pharmacol Rev* 1991, **43**:425-473.

13. Gray TS, Bingaman EW: **The amygdala: corticotropin-releasing factor, steroids, and stress.** *Crit Rev Neurobiol* 1996, **10**:155-168.

14. Valentino RJ, Curtis AL, Page ME, Pavcovich LA, Florin-Lechner SM: **Activation of the locus coeruleus brain noradrenergic system during stress: circuitry, consequences, and regulation.** *Adv Pharmacol* 1998, **42**:781-784.

15. Rosen JB, Schulkin J: **From normal fear to pathological anxiety.** *Psychol Rev* 1998, **105**:325-350.

16. Caldji C, Francis D, Liu D, Plotsky PM, Meaney MJ: **The role of early experience in the development of individual differences in behavioral and endocrine responses to stress.** In *Handbook of Physiology: Coping with the Environment.* Edited by McEwen BS, Steller E. Oxford: Oxford University Press; in press.

17. Heim C, Owens MJ, Plotsky PM, Nemeroff CB: **Persistent changes in corticotropin-releasing factor systems due to early life stress: relationship to the pathophysiology of major depression and post-traumatic stress disorder.** *Psychopharmacol Bull* 1997, **33**:185-192.

18. Seckl JR, Meaney MJ: **Early life events and later development of ischaemic heart disease.** *Lancet* 1994, **342**:1236.

19. Meaney MJ, Diorio J, Widdowson J, LaPlante P, Caldji C, Seckl JR, Plotsky PM: **Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress.** *Dev Neurosci* 1996, **18**:49-72.

20. van Oers HJ, de Kloet ER, Levine S: **The ontogeny of glucocorticoid**
• **negative feedback: influence of maternal deprivation.** *Endocrinology* 1998, **139**:2838-2846.

Maternal deprivation has immediate effects on neonatal physiology. Interestingly, these effects have revealed the importance of the mother in regulating the endocrine and metabolic responses to stress in the neonate. This paper is one of a series in which Levine and colleagues have described the role of the mother in maintaining a stable HPA environment during critical periods of neural development. In the absence of the mother, glucocorticoid feedback inhibition of HPA activity is reduced, permitting a greater HPA response to stress and exposure to elevated glucocorticoid levels. The importance of this research can be appreciated in terms of the well-established inhibitory effects of glucocorticoids on synaptic plasticity.

21. Plotsky PM, Meaney MJ: **Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats.** *Mol Brain Res* 1993, **18**:195-200.

22. Meaney MJ, Aitken DH, Bhatnagar S, Van Berkel CH, Sapolsky RM: **Postnatal handling attenuates neuroendocrine, anatomical, and cognitive impairments related to the aged hippocampus.** *Science* 1988, **238**:766-768.

23. Bhatnagar S, Shanks N, Meaney MJ: **Plaque-forming cell responses and antibody titers following injection of sheep-red blood cells in nonstressed, acute and/or chronically stressed handled and nonhandled animals.** *Dev Psychobiol* 1996, **29**:171-181.

24. Laban O, Markovic BM, Dimitrijevic M, Jankovic BD: **Maternal deprivation and early weaning modulate experimental allergic encephalomyelitis in the rat.** *Brain Behav Immunol* 1995, **9**:9-19.

25. Liu D, Caldji C, Sharma S, Plotsky PM, Meaney MJ: **The effects of early life events on *in vivo* release of norepinepherine in the paraventricular nucleus of the hypothalamus and hypothalamic-pituitary-adrenal responses during stress.** *J Neuroendocrinol* 1999, in press.

26. Higley JD, Haser MF, Suomi SJ, Linnoila M: **Nonhuman primate model of alcohol abuse: effects of early experience, personality and stress on alcohol consumption.** *Proc Natl Acad Sci USA* 1991,

27. Ladd CO, Owens MJ, Nemeroff CB: **Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation.** *Endocrinology* 1996, **137**:1212-1218.

28. Kraemer GW, Ebert MH, Schmidt DE, McKinney WT: **A longitudinal study of the effect of different social rearing conditions on cerebrospinal fluid norepinephrine and biogenic amine metabolites in rhesus monkeys.** *Neuropsychopharmacology* 1989, **2**:175-189.

29. Smotherman WP, Bell RW: **Maternal mediation of early experience.** In *Maternal Influences and Early Behavior.* Edited by Bell RW, Smotherman WP. New York: Spectrum Publications; 1980:282-296.

30. Liu D, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S,
• Pearson D, Plotsky PM, Meaney MJ: **Maternal care, hippocampal glucocorticoid receptor gene expression and hypothalamic-pituitary-adrenal responses to stress.** *Science* 1997, **277**:1659-1662.

This report describes the differences in hypothalamic–pituitary–adrenal responses to stress in adults whose mothers showed naturally occurring variations in maternal behavior. The offspring of mothers who showed increased levels of pup licking/grooming and arched-back nursing during the first 10 days of postnatal life showed significantly reduced plasma adrenocorticotropin and corticosterone responses to stress. These effects appear to be mediated, in part, by changes in hippocampal glucocorticoid receptor gene expression.

31. Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM,
• Meaney MJ: **Maternal care during infancy regulates the development of neural systems mediating the expression of behavioral fearfulness in adulthood in the rat.** *Proc Natl Acad Sci USA* 1998, **95**:5335-5340.

This is a follow-up to a previous study [30•], and it describes differences in the adult offspring of high or low LG-ABN mothers in behavioral responses to novelty as well as in potential neural mediators, including CRF, $\alpha 2$ adrenoreceptor, and central benzodiazepine/$GABA_A$ receptor binding in locus coeruleus and amygdala.

32. McCarty R, Cierpial MA, Murphy CA, Lee JH: **Maternal involvement in the development of cardiovascular phenotype.** *Experientia* 1992, **48**:315-322.

33. Anisman H, Zaharia MD, Meaney MJ, Merali Z: **Do early life events permanently alter behavioral and hormonal responses to stressors?** *Int J Dev Neurosci* 1998, **16**:149-164.

34. Moore CL, Lux BA: **Effects of lactation on sodium intake in Fischer-344 and Long-Evans rats** *Dev Psychobiol* 1998, **32**:51-56.

35. Scarr S, McCartney K: **How people make their own environments: a theory of genotype-environment effects.** *Child Dev* 1983, **54**:424-435.

36. Maestripieri D, Wallen K, Carroll KA: **Genealogical and demographic influences on infant abuse and neglect in group-lining sooty mangabeys (Cerocebus atys).** *Dev Psychobiol* 1997, **31**:175-180.

37. Fairbanks LM: **Individual differences in maternal style.** *Adv Study Behav* 1996, **25**:579-611.

38. Berman CM: **Intergenerational transmission of maternal rejection rates among free-ranging rhesus monkeys on Cayo Santiago.** *Anim Behav* 1990, **44**:247-258.

39. Miller L, Kramer R, Warner V, Wickramaratne P, Weissman M: **Intergenerational transmission of parental bonding among women.** *J Am Acad Child Adolesc Psychiatry* 1997, **36**:1134-1139.

40. Eisenberg L: **The biosocial context of parenting in human families.** In *Mammalian Parenting Biochemical, Neurobiological, and Behavioral Determinants.* Edited by Krasnegor NA, Bridges RS. New York: Oxford University Press; 1990:9-24.

41. Rosenblatt JS: **Psychobiology of maternal behavior: contribution to the clinical understanding of maternal behavior among humans.** *Acta Paediatr* 1994, **397(suppl)**:3-8.

42. Bridges RS: **The role of lactogenic hormones in maternal behavior in female rats.** *Acta Paediatr* 1994, **397(suppl)**:33-39.

43. Fleming AS: **Factors influencing maternal responsiveness in humans: usefulness of an animal model.** *Psychoneuroendocrinology* 1988, **13**:189-212.

44. Pedersen CA, Caldwell JD, McGuire M, Evans DL: **Corticotropin-releasing hormone inhibits maternal behavior and induces pup-killing.** *Life Sci* 1991, **48**:1537-1546.

45. Field T: **Maternal depression effects on infants and early interventions.** *Prev Med* 1998, **27**:200-203.

46. Uvnas-Moberg K: **The physiological and endocrine effects of social contact.** *Ann NY Acad Sci* 1997, **807**:146-163.

47. Rosenblum LA, Andrews MW: **Influences of environmental demand on maternal behavior and infant development.** *Acta Paediatr* 1994, **397(suppl)**:57-63.

48. Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, Nemeroff CB: **Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult non-human primates exposed to early-life stressors: implications for psychopathology of mood and anxiety disorders.** *Proc Natl Acad Sci USA* 1996, **93**:1619-1623.

49. Coplan JD, Trost RC, Owens MJ, Cooper TB, Gorman JM,
•• Nemeroff CB, Rosenblum LA: **Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions.** *Arch Gen Psychiatry* 1998, **55**:473-477.

This paper represents a follow-up of an earlier study [48] documenting increased cerebrospinal levels of CRF in monkeys reared under conditions of variable (i.e. unpredictable) food (VF) resource availability. The VF rearing condition was associated with increased cerebrospinal levels of dopamine and serotonin metabolites, which, in turn, were correlated with CRF levels. The findings reflect the potential importance of the relationship between environmental stressors and mother–infant interactions for neural development and vulnerability to stress-induced pathology in later life.