Epigenetic Programming of Stress Responses through Variations in Maternal Care

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ABSTRACT: Early life experiences shape an individual's physical and mental health across the lifespan. Not surprisingly, an upbringing that is associated with adversity can produce detrimental effects on health. A central theme that arises from studies in human and nonhuman species is that the effects of adversity are mediated by the interactions between a mother and her young. In this review we describe some of the long-term effects of maternal care on the offspring and we focus on the impact of naturally occurring variations in the behavior of female rats. Of particular interest are mothers that engage in high or low amounts of licking/grooming (LG) and arched-back nursing (ABN) of their pups, but do so within the normal range for this species. Such variations in LG-ABN can alter the function of the hypothalamic-pituitary-adrenal (HPA) axis, and cognitive and emotional development by directly affecting the underlying neural mechanisms. At the heart of these mechanisms is gene expression. By studying the hippocampal glucocorticoid receptor gene, we have identified that maternal care regulates its expression by changing two processes: the acetylation of histones H3-K9, and the methylation of the NGFI-A consensus sequence on the exon 1_7 promoter. Sustained "maternal effects" appear elsewhere in biology, including plants, insects, and lizards, and may have evolved to program advantages in the environments that the offspring will likely face as adults. Given the importance of early life and parent–child interactions to later behavior, prevention and intervention programs should target this critical phase of development.

KEYWORDS: parenting; HPA; GABA; glutamate; learning; anxiety; DNA; methylation

Studies of the effects of adversity on family function and child development reveal a consistent theme: Adversity alters parent–child interactions, and thus developmental outcomes. Family dysfunction and low income are associated with significantly increased risks of psychopathology, and cognitive development is inversely related to familial adversity.[1] Interestingly, the effects of poverty on intellectual and emotional development are mediated by variations in parental care. When the parental

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Ann. N.Y. Acad. Sci. 1036: 167–180 (2004).
doi: 10.1196/annals.1330.011

care factors are statistically controlled, there is no relationship between socioeconomic stress (SES) and child development.[2–4] Moreover, there is considerable evidence for the effect of adversity on human parenting and parent–child attachment. Environmental adversity can compromise the emotional well-being of the parent and thus influence the quality of parent–child relationships. While many factors contribute to the quality of the mother's attitude towards her newborn, none are correlated more highly than the woman's level of anxiety.[5] Mothers who feel depressed and anxious are, not surprisingly, less positive towards their babies. High levels of maternal stress are associated with less-sensitive childcare.[6,7] The children of highly stressed primary caregivers tend to develop more insecure parental attachment,[7,8] which predicts behavioral inhibition in childhood and an increased risk for depression. Vaughn *et al*.[8] found that unstable/stressful environments were associated with greater variability in the quality of infant–mother attachments. When parents suffer from poverty or other environmental stressors, they experience more negative emotions, irritability, and depressed, and anxious moods, which lead to more-punitive parenting.[9–11] The greater the number of environmental stressors, the less supportive the mothers are of their children, and the more severe and physical is the discipline. Low SES serves as a potent source of adversity, and Lupien *et al*.[12] found that children from low SES homes in comparison to middle-class peers exhibited significantly higher levels of basal salivary cortisol. The effect of SES on basal cortisol levels was entirely accounted for by the level of maternal depression. For humans, poverty and violence are tragically common conditions: One in five teenage females and one in six adult women experience abuse during pregnancy.[13,14]

MATERNAL CARE AND NEURODEVELOPMENT IN THE OFFSPRING

Understandably, the major weakness of human studies lies in the inherently correlational design. While intervention studies provide the opportunity for the definition of causal relations, the more common approach lies in studies of nonhuman species. We examine the relation between maternal care and the development of cognitive, behavioral, and endocrine responses to stress using a rather simple model of naturally occurring variations in maternal behavior over the first 8 days after birth.[15] We characterize individual differences in maternal behavior through direct observation of mother–pup interactions in normally reared animals. These observations reveal considerable variation in two forms of maternal behavior: licking/grooming (LG) of pups and arched-back nursing.[16] Licking/grooming includes both body as well as anogenital licking. Arched-back nursing, also referred to as "crouching," is characterized by a dam nursing her pups with her back conspicuously arched and legs splayed outward. While common, it is not the only posture from which dams nurse. A blanket posture represents a more relaxed version of the arched-back position, where the mother is almost lying on the suckling pups. As you can imagine, it provides substantially less opportunity for movement by the pups such as nipple-switching. Dams also nurse from their sides and often will move from one posture to another over the course of a nursing bout. Interestingly, the frequency of LG and arched-back nursing (ABN) is correlated across animals, and thus we are able to define mothers according to both behaviors as high or low LG-ABN mothers. For the sake of most of the studies described here, high and low LG-ABN mothers are fe-

males whose scores on both measures were ± 1 SD above (high) or below (low) the mean for their cohort. Importantly, high and low LG-ABN mothers do not differ in the amount of contact time with pups; differences in the frequency of LG or ABN do not occur simply as a function of time in contact with pups. High and low LG-ABN mothers raise a comparable number of pups to weaning and there are no differences in the weaning weights of the pups, suggesting an adequate level of maternal care across the groups. These findings also suggest that we are examining the consequences of variations in maternal care that occur within a normal range. Indeed, the frequency of both pup LG and ABN are normally distributed across large populations of lactating female rats.[15] What is important here is that differences in the expression of these maternal behaviors provide for varying levels of sensory stimulation for the offspring, especially tactile stimulation, over a critical period of neurodevelopment. The question then concerns the potential developmental consequences.

MATERNAL EFFECTS ON COGNITIVE DEVELOPMENT

Tactile stimulation from the mother stimulates the release of growth hormone as well as adrenal glucocorticoids in the offspring.[17,18] Pups exposed to prolonged periods of maternal separation show increased levels of glucocorticoids, and decreased levels of growth hormone. These effects can be reversed with "stroking" with a brush, a manipulation that mimics the tactile stimulation derived from maternal licking/grooming. Maternal deprivation also decreases the expression of brain-derived neurotrophic factor (BDNF) expression.[19] The results of these studies suggest that maternal licking/grooming can serve to promote an endocrine or paracrine state that fosters growth and development. cDNA array analyses[20] revealed major classes of maternal care effects on hippocampal gene expression in postnatal day 6 offspring, including (1) genes related to cellular metabolic activity (glucose transporter, cFOS, cytochrome oxydase, LDL receptor, etc.); (2) genes related to glutamate receptor function, including effects on the glycine receptor as well as those mentioned for the NMDA receptor subunits; and (3) genes encoding for growth factors, including brain-derived neurotrophic function (BDNF), bFGF and β-NGF. In each case expression was more than three-fold higher in hippocampal samples from offspring of high LG-ABN mothers.

Variations in maternal care also appear to be related to individual differences in the synaptic development of selected neural systems that mediate cognitive development. As adults, the offspring of high LG-ABN mothers show enhanced spatial learning/memory in the Morris water maze[21] as well as in object recognition.[22,23] The performance in both tasks is dependent upon hippocampal function[24,25] and maternal care altered hippocampal synaptogenesis. At either day 18 or day 90 there were significantly increased levels of N-CAM or synaptophysin-like immunoreactivity on Western blots in hippocampal samples from the high LG-ABN offspring, suggesting increased synapse formation/survival. More recent studies reveal significant effects of maternal care on neuron survival in the hippocampus.[23] There was increased evidence for long-term neuron survival of cells generated during the first week of postnatal life in the offspring of high compared with low LG-ABN mothers.

The influence of the hippocampus in spatial learning is thought to involve, in part at least, cholinergic innervation emerging from the medial septum.[26] We found increased hippocampal choline acetyltransferase (ChAT) activity and acetylcholinesterase staining as well as increased hippocampal basal and K^+-stimulated acetylcholine release in microdialysis studies in the adult offspring of the high LG-ABN mothers.[21] These findings suggest increased cholinergic synaptic number in the hippocampus of the high LG-ABN offspring. There was also increased hippocampal levels of brain-derived neurotrophic factor mRNA in the high LG-ABN offspring on day 8 of life.[27] BDNF is associated with the survival of cholinergic synapses in the rat forebrain.[28–30]

The expression of BDNF is regulated by NMDA receptor activation, and tactile stimulation has previously been shown to increase NMDA receptor expression in the barrel cells of mice.[31] There is increased mRNA expression of both the NR2A and NR2B subunits of the NMDA receptor in the offspring of high compared with low LG-ABN mothers at day 8 of age.[21] These effects are associated with increased NMDA receptor binding.

Naturally occurring variations in maternal licking/grooming and arched-back nursing were associated with the development of cholinergic innervation to the hippocampus, as well as differences in the expression of NMDA receptor subunit mRNAs. In adults, there was increased hippocampal NR1 mRNA expression. These findings provide a mechanism for the differences observed in spatial learning and memory in adult animals. In the adult rat, spatial learning and memory are dependent upon hippocampal integrity; lesions of the hippocampus result in profound spatial learning impairments. Moreover, spatial learning is regulated by both cholinergic or NMDA receptor activation or NR1 subunit knockout.[32,33] These finding suggest that maternal care increases hippocampal NMDA receptor levels, resulting in elevated BDNF expression and increased hippocampal synaptogenesis, and thus enhanced spatial learning in adulthood. These results are also consistent with the idea that maternal behavior actively stimulates hippocampal synaptogenesis in the offspring through systems known to mediate experience-dependent neural development.[34,35]

MATERNAL EFFECTS ON BEHAVIORAL AND ENDOCRINE STRESS RESPONSES

The question here concerns the potentially direct consequences of differences in maternal behavior for the development of behavioral and neuroendocrine responses to stress in the offspring.[36,37] The results of studies over the past years reveal persistent effects of naturally occurring variations in maternal care on the expression of specific genomic targets in brain regions that govern behavioral and hypothalamic-pituitary-adrenal (HPA) responses to stress (FIGS. 1 and 2). Two features of these finding are critical. First, the effects of maternal care on both gene expression and phenotype are stable and extend into adulthood. Second, there is the remarkable tissue specificity apparent in these effects. For example, effects of maternal care on the $\gamma 2$ subunit of the $GABA_A$ receptor are observed in the basolateral and central nuclei of the amygdala and the locus coeruleus, but no where else in the corticolimbic system, despite the fact that this is widely expressed throughout the forebrain.

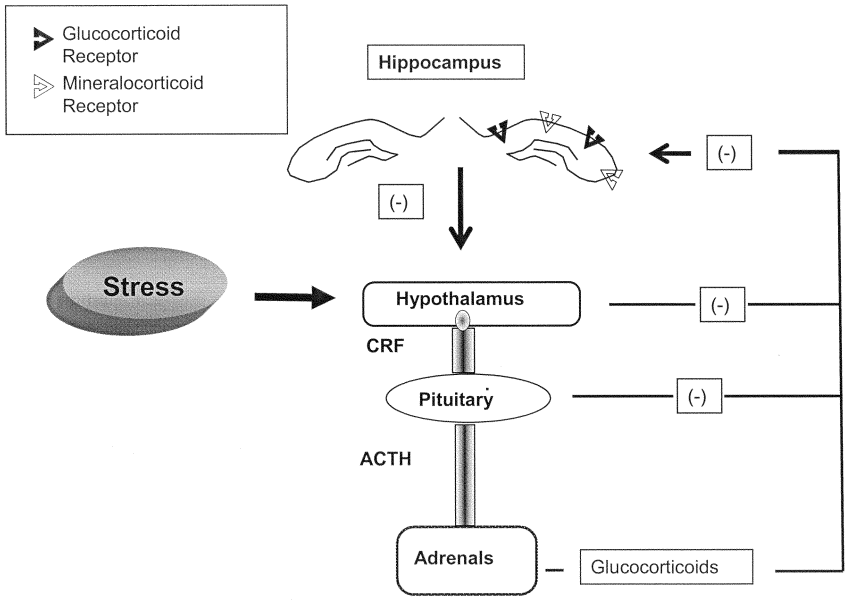

FIGURE 1. Central corticotropin-releasing factor (CRF) systems furnish the critical signal for the activation of behavioral, emotional, autonomic and endocrine responses to stressors. First, a CRF pathway from the parvocellular regions of the paraventricular nucleus of the hypothalamus (PVNh) to the hypophysial–portal system of the anterior pituitary, which serves as the principal mechanism for the transduction of a neural signal into a pituitary-adrenal response. 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 stimulates the synthesis and release of adrenocorticotropin hormone (ACTH). Pituitary ACTH, in turn, causes the release of glucocorticoids from the adrenal gland. CRF synthesis and release are subsequently inhibited through a glucocorticoid negative-feedback system mediated by both mineralocorticoid and glucocorticoid receptors in a number of brain regions including and perhaps especially in the hippocampus.

Maternal Effect on HPA Response to Stress

As adults, the offspring of high LG-ABN mothers show reduced plasma ACTH and corticosterone responses to acute stress by comparison to the adult offspring of low LG-ABN mothers. Circulating glucocorticoids act at glucocorticoid and mineralocorticoid receptor sites in corticolimbic structures, such as the hippocampus, to regulate HPA activity. Such feedback effects commonly target CRF synthesis and release at the level of the PVNh. The high LG-ABN offspring showed significantly increased hippocampal glucocorticoid receptor mRNA expression, enhanced glucocorticoid negative feedback sensitivity, and decreased hypothalamic CRH mRNA levels. Moreover, Liu *et al.*[36] found that the magnitude of the corticosterone response to acute stress was significantly correlated with the frequency of both maternal LG (r=−.61) and ABN (r=−0.64) during the first week of life, as was the level of hippocampal glucocorticoid receptor mRNA and hypothalamic CRH mRNA expression (all rs > 0.70).

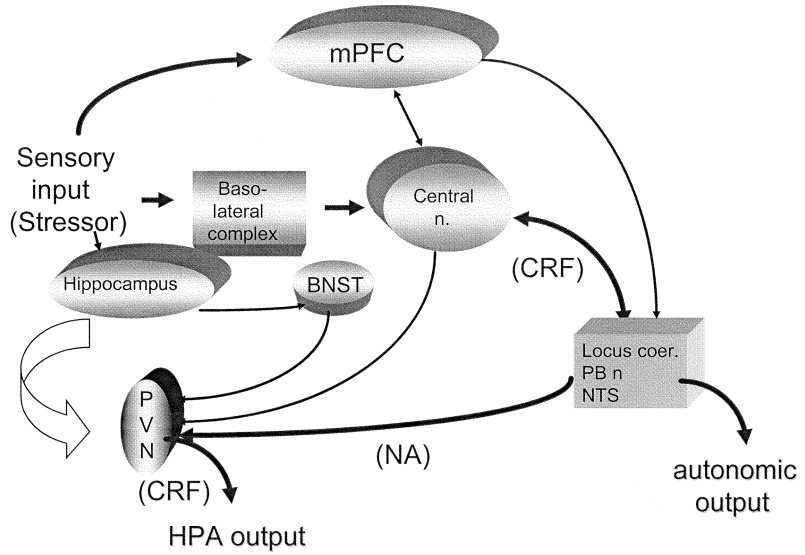

FIGURE 2. CRF neurons in the central nucleus of the amygdala project directly to the locus coeruleus and increase the firing rate of locus coeruleus neurons, resulting in increased noradrenaline release and the activation of behavioral and autonomic responses to stress. CRF plays a critical role in activating the release of noradrenaline from the noradrenergic cell body regions in the locus coeruleus, parabrachial nucleus (PB n), and the nucleus of the solitary tract (NTS). Noradrenaline is released into virtually all areas of the corticolimbic regions, including the hippocampus and medial prefrontal cortex (mPFC). At the level of the paraventricular hypothalamus (PVN) noradrenaline stimulates the release of CRF from the PVN, activating the HPA responses to stress. BNST = bed nucleus of the stria terminalis.

Behavioral Responses to Stress

The offspring of the high and low LG-ABN mothers also differed in behavioral responses to novelty.[38–41] As adults, the offspring of the high LG-ABN showed decreased startle responses, increased open-field exploration, and shorter latencies to eat food provided in a novel environment. The offspring of low LG-ABN mothers also show greater burying in the defensive-burying paradigm,[72] which involves an *active* response to a threat. The offspring of the high LG-ABN mothers also showed decreased CRF receptor levels in the locus coeruleus and increased $GABA_A$/benzodiazepine (BZ) receptor levels in the basolateral and central nucleus of the amygdala, as well as in the locus coeruleus,[41,42] and decreased CRF mRNA expression in the CnAmy (Francis, Diorio, and Meaney, unpublished material). Note that BZ agonists suppress CRF expression in the amygdala.[43] Predictably, stress-induced increases in PVNh levels of noradrenaline that are normally stimulated by CRF were significantly higher in the offspring of the low LG-ABN mothers.[44]

Maternal care during the first week of life is associated with stable individual differences in $GABA_A$ receptor subunit expression in brain regions that regulate stress reactivity. These findings provide a mechanism for increased GABAergic inhibition

of amygdala–locus coeruleus activity. The functional $GABA_A$ receptor complex, which often includes a BZ binding site, comprises at least 5 subunits that are derived from at least 19 possible subunits, providing for remarkable variation in receptor composition. Importantly, the subunit composition determines $GABA_A$ receptor function. A series of *in situ* hybridization experiments[42] illustrates the molecular mechanism for these differences in receptor binding and suggests that variations in maternal care might actually permanently alter the subunit composition of the $GABA_A$ receptor complex in the offspring. The offspring of the high LG-ABN mothers show increased levels of the mRNAs for the γ1 and γ2 subunits, which contribute to the formation of a functional BZ binding site. Such differences are not unique to the γ subunits. Levels of mRNA for the α1 subunit of the $GABA_A$/BZ receptor complex are significantly higher in the amygdala and locus coeruleus of high compared with low LG-ABN offspring. The α1 subunit appears to confer higher affinity for GABA, providing the most efficient form of the $GABA_A$ receptor complex, through increased receptor affinity for GABA. The adult offspring of the low LG-ABN mothers actually show increased expression of the mRNAs for the α3 and α4 subunits in the amygdala and the locus coeruleus. Interestingly, $GABA_A$/BZ receptor composed of the α3 and α4 subunits show a reduced affinity for GABA, by comparison to the α1 subunit. Moreover, the α4 subunit does not contribute to the formation of a BZ receptor site. These differences in subunit expression are tissue-specific; no such differences are apparent in the hippocampus, hypothalamus, or cortex. Thus, differences in $GABA_A$/BZ receptor binding are not simply due to a deficit in subunit expression in the offspring of the low LG-ABN mothers, but of an apparently "active" attempt to maintain a specific $GABA_A$/BZ receptor profile in selected brain regions.

The results of these studies suggest that the behavior of the mother towards her offspring can "program" behavioral and neuroendocrine responses to stress in adulthood. These effects are associated with sustained changes in the expression of genes in brain regions that mediate responses to stress and form the basis for stable individual differences in stress reactivity.

Individual differences in behavioral and neuroendocrine responses to stress in the rat are correlated with naturally occurring variations in maternal care. Such effects might serve as a possible mechanism by which selected traits might be transmitted from one generation to another. Indeed, low LG-ABN mothers are more fearful and show increased HPA responses to stress by comparison to high LG-ABN dams.[45] Individual differences in stress reactivity are apparently transmitted across generations: Fearful mothers beget more stress-reactive offspring. The obvious question is whether the transmission of these traits occurs only as a function of genomic-based inheritance. If this is the case, then the differences in maternal behavior may simply be epiphenomena and not causally related to the development of individual differences in stress responses. The issue is not one of inheritance, but the mode of inheritance.

The results of recent studies provide evidence for a non-genomic transmission of individual differences in stress reactivity and maternal behavior.[38–40] One study involved a reciprocal cross-fostering of the offspring of low and high LG-ABN mothers. The primary concern here was that the wholesale fostering of litters between mothers is known to affect maternal behavior.[46] To avert this problem and maintain the original character of the host litter, no more than 2 of 12 pups were fostered into

or from any one litter.[47] The critical groups of interest are the biological offspring of low LG-ABN mothers fostered onto high LG-ABN dams, and vice versa. The limited cross-fostering design did not result in any effect on group differences in maternal behavior. Hence, the frequency of pup licking/grooming and arched-back nursing across all groups of high LG-ABN mothers was significantly higher than that for any of the low LG-ABN dams regardless of litter composition.

The results of the behavioral studies are consistent with the idea that variations in maternal care are causally related to individual differences in the behavior of the offspring. The biological offspring of low LG-ABN dams reared by high LG-ABN mothers were significantly less fearful under conditions of novelty than were the offspring reared by low LG-ABN mothers, including the biological offspring of high LG-ABN mothers.[38–40] Subsequent studies have revealed similar findings for hippocampal glucocorticoid receptor expression[48] and for the differences in both the $\alpha 1$ and $\gamma 2$ $GABA_A$ receptor subunit expression in the amygdala.[42] These findings suggest that individual differences in patterns of gene expression and behavior can be directly linked to maternal care over the first week of life.

MECHANISM FOR THE MATERNAL EFFECT ON GENE EXPRESSION

A critical question concerns the mechanism whereby maternal care over the first week of life might alter gene expression and phenotype over the lifespan, obviously well beyond the period of mother–infant contact. This topic has been the subject of recent papers,[37,48,49,50] and we will therefore only summarize major findings. These studies focus on the effect of maternal care on the expression of the glucocorticoid receptor gene in the hippocampus.

Most DNA is tightly packaged into nucleosomes that involve a close relationship between DNA wrapped around and bound to histone proteins. This configuration regulates gene expression. The close relationship between DNA and histone is maintained by the electrostatic bonds between positively charged histones and negatively charged DNA. This DNA structure precludes transcription factor binding to DNA and underscores the importance of enzymes that modify histone–DNA interactions. One class of such proteins, histone acetyltransferase (HAT), serves to acetylate selected amino acids on the protruding histone tails, most commonly histone 3 (H3) or H4. For example, acetylation of a lysine (K) residue on H3 serves to neutralize the positively charged histone, relaxing the histone–DNA relationship, and permitting transcription factor binding to DNA. Thus, H3-K9 acetylation serves as a marker of active gene transcription. Many known transcriptional co-factors (e.g., creb-binding protein [CBP]) are HATs. Histone acetylation is dynamic and is also regulated by histone deacetylation (HDAC), which serves to block histone acetylation and suppress gene expression.

The binding of histone modifiers such as HATs or HDACs is influenced by the methylation state of the DNA. DNA methylation is known to be responsible for the silencing of expression of imprinted genes or those on the X chromosome. In part, such effects are mediated by the differential affinity of methylated DNA binding proteins for methylated DNA and the subsequent attraction of HDACs to the region of the DNA. Maternal care alters the methylation status of the consensus sequence for the transcription factor NGFI-A, which activates glucocorticoid receptor gene ex-

pression in the hippocampus through an interaction with a glucocorticoid receptor gene promoter (exon 1_7 promoter).[37,50] The adult offspring of high LG-ABN mothers show hypomethylation of the NGFI-A consensus sequence on the exon 1_7 promoter, increased H3-K9 acetylation and NGFI-A binding, and enhanced glucocorticoid receptor expression. These effects are reversed with cross-fostering, reflecting the direct effect of maternal care on DNA methylation. Moreover, the effect of maternal care on H3 acetylation and NGFI-A binding to the exon 1_7 promoter is completely eliminated with the infusion of an HDAC inhibitor. Predictably, this treatment also eliminates the maternal effect on hippocampal glucocorticoid receptor expression and HPA responses to stress. These findings provide an epigenetic mechanism for the sustained effects of parental care on gene expression and phenotype.

PARENTAL EFFECTS ON DEFENSIVE RESPONSES IN AN EVOLUTIONARY CONTEXT

What is perhaps surprising here is that developmental effects of such magnitude derive from variations in parental care that appear to lie within a normal range for the species. As Hinde[51] suggested, this is likely due to the fact that natural selection has shaped offspring to respond to subtle variations in parental behaviors as a forecast of the environmental conditions they will ultimately face after independence from the parent. The critical question of why such developmental effects might exist is best considered within an evolutionary context. Studies on the long-term effects of maternal care on defensive responses to threat in the rat are examples of what evolutionary biologists refer to as "maternal effects."[52,53] Within evolutionary biology, maternal or parental effects are defined as sustained influences on any component of the phenotype of the offspring that is derived from either the mother or the father, apart from nuclear genes. Such parental effects have been studied across a variety of different species and the results clearly indicate that environmentally induced modifications of the parental phenotype can be transmitted to offspring.

The fundamental theme is that of maternal influences over the development of defensive responses to stress. This is a stunningly common theme in biology. Not only are maternal effects on defensive responses not unique to mammals, they are not even unique to animals. Plants also show maternal effects, with basically the same characteristics as those reported in mammals (although, we assume, through very different mechanisms of transmission). In a remarkable paper, Agrawal *et al.*[54] provided evidence for transgenerational maternal effects in two models. The first of these models described maternal effects on the development of defensive responses in the offspring—in the radish. Herbivory commonly results in the expression of "inducible" defenses in plants. In the case of the radish, damage from a caterpillar, *Pieris rapae*, induces an increase in the production of mustard oil glycosides and higher densities of setose trichomes on newly formed leaves. The defense is termed "inducible" since its expression occurs only in response to a specific form of threat.[55] In contrast, a constitutive defense is constantly and invariably operative. Inducible defenses triggered by herbivory protect against subsequent predator attack. Under conditions where there is a prevailing threat of herbivory, plants expressing inducible defenses show a significantly greater lifetime seed production than do controls.[54,56]

To examine the consequences of herbivory of the maternal plant for the next generation, Agrawal and colleagues examined seeds from control and caterpillar-damaged plants. The seedlings from the damaged radishes showed significant changes in glucosinolate profiles. Herbivory of the maternal plant also altered trichome expression: The number of trichomes per leaf was increased in seedlings as a function of maternal herbivory. Such changes were adaptive. Caterpillars gained significantly less weight, presumably from reduced consumption, when exposed to seedlings from damaged versus undamaged mothers.

Maternal effects have been reported with inducible defenses in many invertebrate species.[53] Inducible defenses, as opposed to constitutive defenses, emerge or develop to full strength in response to signals from environmental threats, such as those associated with predators. For example, in response to chemosignals, or kairomones, from aquatic predators, water fleas (*Daphnia*) form impressive, helmet-like growths on their necks and spines along their tails.[57] These morphologic changes render the animals less likely to be captured and successfully ingested.[55,58] This is an inducible, morphologic defense. And there is evidence for transgenerational effects, comparable to those reported in the behavioral and endocrine responses to stress in the rat. In the rat, low LG-ABN mothers are more fearful, and beget more fearful, stress-reactive offspring. The mechanism for this transgenerational effect involves variations in maternal behavior. In *Daphnia*, the mechanism is unknown, but the evidence for intergenerational transmission is no less compelling. The F1 and F2 generations of mothers exposed to kairomones up until pregnancy, and clean water thereafter, exhibited significantly larger helmets than those of mothers consistently maintained in clean-water environments.[54] Exposure of the mother to kairomones was sufficient to alter the morphology of the completely kairomone-naïve offspring.

Larger scincid lizards with longer tails are preyed upon less successfully by snakes. Again, there is evidence for plasticity in morphologic defenses, and for the transmission across generations. Female scincid lizards (*Pseudomoia pagenstecheri*) exposed to the scent of lizard-eating snakes during gestation, but not thereafter, gave birth to offspring that were heavier, had unusually long tails, and were significantly more sensitive to the odor of the predator.[59] Thus the anti-predator responses to the offspring were modified by the experience of the mother. Functionally such effects reflect an influence of the mother over the vulnerability of the offspring to predatory snakes—presumably an adaptive modification of the offspring's phenotype.

These examples yield a common theme: spite the mother, fight the offspring. In each case exposure of the mother to conditions that threaten survival result in variations in offspring phenotype that serve to increase the capacity of the offspring to resist attack by predators: evidence for maternal effects on phenotypic plasticity. We argue that the effects of maternal behavior on the development of individual differences in defensive responses in the rat represent similar examples of maternal effects, in this case mediated by variations in maternal behavior. It is not surprising that among mammals, with extended periods of postnatal care, parental behavior should emerge as a critical mechanism for such effects. If this is indeed the case then environmental adversity should have a significant effect on maternal behavior. This idea is certainly consistent with the literature on human parenting (see above). Such studies are, of course, correlational. Perhaps the most compelling evidence for a direct effect of environmental adversity on parent–infant interactions emerges from the studies of Rosenblum, Coplan and colleagues with nonhuman primates.[60,61]

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. At the time that these conditions were imposed, there were no differences in the nature of mother–infant interactions. However, after a number of months of these conditions, there were highly significant differences in 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 showed signs of depression commonly observed in maternally separated macaque infants, remarkably, even while the infants were in contact with their mothers. As adolescents, the infants reared in the VFD conditions were more fearful, submissive, and showed less social play behavior.

More recent studies demonstrate the effects of these conditions on the development of neural systems that mediate behavioral and endocrine responses to stress. As adults, monkeys reared under VFD conditions showed increased CSF levels of CRF.[61,62] 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. It will be fascinating to see whether these traits are then transmitted to the next generation.

In summary, evidence from studies with human and nonhuman species reveals the effects of environmental adversity on parental care and neurodevelopment in the offspring. Studies with rodents suggest that these effects are stable and involve alterations in gene expression associated with DNA methylation and chromatin structure. Perhaps the critical point here is the impressive support for the idea that parental care mediates the effects of environmental conditions on the development of the offspring. Such findings suggest that parental care is indeed a highly valuable target for prevention studies, a theme that is raised in a number of the papers in this volume.

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