Maternal Care and Individual Differences in Defensive Responses

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ABSTRACT—*Familial transmission of mental illness is common. Recent studies in behavioral neuroscience and biological psychiatry reveal the importance of epigenetic mechanisms of transmission that center on the developmental consequences of variations in parental care. Studies with rats suggest that environmental adversity results in patterns of parent–offspring interactions that increase stress reactivity through sustained effects on gene expression in brain regions known to regulate behavioral, endocrine, and autonomic responses to stress. While such effects might be adaptive, the associated cost involves an increased risk for stress-related illness.*

KEYWORDS—*maternal care; stress responses; epigenesis; stress hormones; individual differences*

To explain the relation between family function and health in adulthood, researchers have proposed *stress-diathesis* models (Repetti, Taylor, & Seeman, 2002). These models suggest that a decreased quality of parental care alters the development of neural and endocrine systems, increasing the magnitude of emotional, autonomic, and endocrine responses to stress (collectively referred to here as defensive responses) and thus predisposing individuals to illness. The term diathesis refers to the interaction between development—including the potential influence of genetic variations—and the prevailing level of stress experienced by an individual in predicting health outcomes. Such models have considerable appeal, and could identify both the origins of illness and the nature of underlying vulnerabilities.

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A critical assumption of stress-diathesis models is that the increased expression of defensive responses endangers health. In response to neural signals associated with the perception of a stressor, there is an increased release into the bloodstream of stress hormones, including glucocorticoids from the adrenal gland and catecholamines, particularly norepinephrine, from the sympathetic nervous system. These hormones increase the availability of energy (such as derived from fat and glucose metabolism) to maintain the normal cellular output and organ efficiency and protect against catastrophies such as hypotensive shock (a crash in blood pressure). These stress hormones, along with the release of catecholamines in the brain, increase vigilance and fear and enhance adaptive processes such as avoidance learning and fear conditioning. However, there are costs associated with chronic activation of stress hormones: chronically enhanced emotional arousal, persistent increases in blood sugars and fats, and disruption of sleep and normal cognitive and emotional function. For this reason, chronic activation of defensive responses can predispose individuals to illnesses such as diabetes, heart disease, and mood disorders, and individuals with enhanced stress reactivity are at greater risk for chronic illness. However, insufficient activation of defensive responses under appropriate conditions also compromises health and is associated with chronic fatigue, chronic pain, and hyperinflammation. People walk a fine line.

THE ORIGINS OF INDIVIDUAL DIFFERENCES IN DEFENSIVE RESPONSES

In the late 1950s and early 1960s, psychologists Seymore Levine and Victor Denenberg reported that postnatal handling of infant rats or mice by researchers decreased the magnitude of both behavioral and hypothalamic-pituitary-adrenal (HPA) responses to stress in adulthood (see Fig. 1). These findings demonstrated

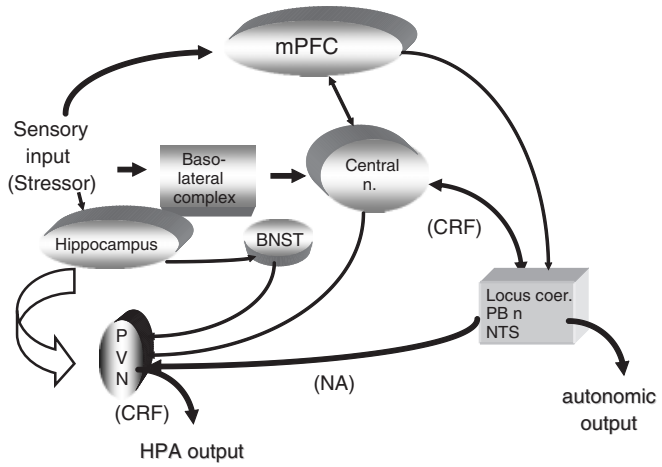

Fig. 1. Systems involving the peptide hormone corticotropin-releasing factor (CRF) that mediate defensive responses to stress in mammals. CRF is released from neurons in the paraventricular hypothalamus (PVN) into the blood supply of the pituitary, activating a hypothalamic–pituitary–adrenal (HPA) response that includes the release of pituitary adrenocorticotropin and glucocorticoids from the adrenal gland. CRF production and release is subsequently inhibited through a negative-feedback system involving the action of glucocorticoids in a number of brain regions including the hippocampus. CRF is also produced in the neurons of the central nucleus of the amygdala and the bed nucleus of the stria terminalis (BNST) that project directly to the locus coeruleus and nucleus tractus solitarius (NTS)/parabrachial nucleus (PBn), stimulating the increased release of noradrenaline (NA) throughout the forebrain, including the medial prefrontal cortex (mPFC) and the PVN.

the influence of the early environment on the development of rudimentary defensive responses to threat. Levine and others suggested that the effects of handling are actually mediated by changes in maternal care. Indeed handling by the researcher increases the licking and grooming of pups by the mother (e.g., Liu et al., 1997), a major source of tactile stimulation for newborn rats. Subsequent studies examining the consequences of naturally occurring variations in pup licking and grooming among lactating rats support the maternal-mediation hypothesis. Thus, the adult offspring of mothers that naturally exhibit increased levels of pup licking and grooming (high-LG mothers) resemble postnatally handled animals on measures of behavioral and endocrine responses to stress, while those of low-LG mothers are comparable to animals that weren't handled (Liu et al., 1997; Caldji et al., 1998). Specifically, the offspring of high-LG mothers show reduced fearfulness and more modest HPA responses to stress. Cross-fostering studies, in which pups born to high-LG mothers are raised by low-LG mothers (and vice versa), suggest a direct relationship between maternal care and the postnatal development of individual differences in behavioral and HPA responses to stress (Francis, Diorio, Liu, & Meaney, 1999).

It is important to note that, in these rodent studies, the experimental design is one that maximizes the chances of detecting maternal effects. Following weaning, animals are housed under very stable laboratory conditions. Although the maternal effects are certainly reliable, the environmental complexity of a real natural setting that would normally be experienced in the post-weaning period might obscure such effects. Nevertheless, these studies also suggest that rather subtle variations within a normal range of parental care can dramatically alter development. In large measure, 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 following independence from the parent (Hinde 1986).

The effects of maternal care on the development of defensive responses to stress in rats involve alterations in the production and activity of a hormone called corticotropin-releasing factor (CRF; Fig. 1) in brain regions that activate behavioral, emotional, autonomic, and endocrine responses to stressors. As adults, the offspring of high-LG mothers showed decreased CRF production in the hypothalamus, as well as reduced plasma adrenocorticotropin (ACTH) and glucocorticoid responses to acute stress, as compared with the adult offspring of low-LG mothers (Liu et al., 1997). The offspring of the high- and low-LG mothers also differed in behavioral responses to novelty (Caldji et al., 1998; Francis et al., 1999). As adults, the offspring of high-LG mothers showed decreased startle responses, substantially less fear in novel environments, and decreased defensive burying of an electrified probe placed into the home cage.

Increased pup licking and grooming is associated with enhanced sensitivity in systems that inhibit CRF expression, including the hippocampal glucocorticoid receptor and the receptor for the neurotransmitter $GABA_A$ in the amygdala. Both effects involve sustained alterations in gene expression (or activity) as a function of maternal care. The complexity of such maternal effects on gene expression is apparent in the alterations in $GABA_A$ receptor function. The adult offspring of high-LG mothers show significantly increased expression of specific proteins within this receptor that increase its function of inhibiting CRF expression; this effect is unique to the amygdala and is reversed with cross-fostering. Thus, for both the glucocorticoid-receptor feedback system and the $GABA_A$ receptor there is an increased capacity for the inhibition of stress responses as a function of maternal licking and grooming. These findings suggest that maternal care can "program" responses to stress in the offspring through effects on the expression of genes in brain regions that mediate responses to stress. These findings provide a potential mechanism for the influence of parental care on vulnerability or resistance to stress-induced illness over the lifespan.

TRANSGENERATIONAL EFFECTS

Maternal effects might serve as a possible nongenomic, or *epigenetic*, mechanism by which selected traits are transmitted across generations. Indeed, low-LG mothers are more fearful than high-LG mothers are: Fearful mothers beget more stress-

reactive offspring. The question concerns the mode of inheritance. The results of cross-fostering studies cited above indicate that individual differences in stress reactivity or in the expression of relevant genes can be directly altered by maternal behavior. A critical finding of the cross-fostering studies is that individual differences in maternal behavior are also transmitted from mothers to female offspring. Hence, the female offspring of more fearful, low-LG mothers are, as adults, more fearful, low-LG mothers. The mechanism for the intergenerational transmission of such individual differences is the difference in pup licking and grooming.

Variations in pup licking and grooming involve individual differences in estrogen-receptor-gene expression in the medial preoptic area (MPOA) of the hypothalamus, a region that is critical for maternal behavior in the rat. Estrogen increases oxytocin-receptor levels in this region; oxytocin appears to act there to facilitate the release of dopamine from neurons in another region called the ventral tegmental nucleus. The increased dopamine release activates maternal licking and grooming (Champagne, Stevenson, Gratton, & Meaney, 2004). Infusing an oxytocin-receptor antagonist directly into the brain completely eliminates the differences in maternal behavior between high- and low-LG mothers. And again, differences in estrogen-receptor expression or in oxytocin-receptor levels are reversed with cross-fostering, suggesting that maternal care regulates the activity of the estrogen receptor, forming the basis for subsequent "inherited" differences in maternal behavior (Champagne, Weaver, Diorio, Sharma, & Meaney, 2003).

ADAPTIVE VALUE OF ENHANCED STRESS REACTIVITY IN MAMMALS

The interesting question is, why bother? Why would nature configure such a process? Why transmit individual differences in stress reactivity across generations?

Environmental adversity influences emotional well-being in parents, and these effects are reflected in alterations in parental care. In humans, parental depression and anxiety are associated with harsh, inconsistent discipline, neglect, and abuse, which can enhance stress reactivity of the offspring. In other words, the anxiety of parents is transmitted to their offspring. Since offspring usually inhabit an environment that is similar to their parents, the transmission of individual differences in traits from parent to offspring could be adaptive with respect to survival. Adversity over the adult life of the parent is likely to predict more of the same for the offspring. Under conditions of increased environmental demand, it is commonly in the animal's interest to enhance its behavioral (e.g., vigilance, fearfulness) and endocrine (HPA and metabolic/cardiovascular) responses to stress. These responses promote detection of potential threats, fear conditioning to stimuli associated with threats, and avoidance learning. Moreover, stress hormones mobilize energy reserves, essential for animals exposed to famine. Impoverished environments are also commonly associated with multiple sources of infection, and adrenal glucocorticoids are a potent defense against increased immunological activity that can lead to septic shock (organ failure). Rats with increased HPA responses to bacteria are at reduced risk for septic shock. These findings underscore the potentially adaptive value of increased HPA responses to threat.

THE EFFECTS OF STRESS ON MATERNAL BEHAVIOR IN MAMMALS

If parent–offspring interactions are to serve as a forecast for the young, then there must be a predictable relation between the quality of the environment and parental care. Perhaps the most compelling evidence for such a relation emerges from the studies of Rosenblum, Coplan, and colleagues with nonhuman primates (Coplan et al., 1996). In Bonnet macaque mother–infant pairs kept in conditions requiring extensive maternal effort to obtain food, there were severe disruptions in the quality of mother–infant interactions. Infants of mothers housed under these conditions were more timid and fearful and, even while in contact with their mothers, actually showed signs of depression commonly observed in infants who have been separated from their mothers. As adolescents, the infants reared in the more demanding conditions were more fearful and submissive and showed less social-play behavior. As expected, these conditions affected the development of neural systems that mediate behavioral and endocrine response to stress, increasing their CRF levels and their noradrenergic responses to stress. It will be fascinating to see if these traits are then transmitted to the next generation.

The critical issue is the effect of environmental adversity on maternal behavior. High-LG rat mothers exposed daily to stress during pregnancy showed a decrease in their licking and grooming to levels comparable to those of low-LG mothers. And the effects on maternal behavior were apparent in the offspring. As adults, the offspring of high-LG mothers who had been gestationally stressed were comparable to those of low-LG mothers on measures of behavioral responses to stress. These effects were due to a "prenatal stress" effect, as the decreased maternal licking and grooming and the same developmental scenario were apparent in a subsequent litter, even in the absence of any further experimental manipulation. The effects of gestational stress were also apparent in the maternal behavior of the female offspring. The female offspring of high-LG mothers exposed to gestational stress, even in a previous pregnancy, behaved toward their pups in a manner consistent with the behavior of their mothers; as adults, these females were low-LG mothers with reduced levels of oxytocin-receptor binding in the MPOA. Hence the effects of environmental adversity are transmitted from parent to offspring.

IMPLICATIONS

The question of vulnerability lies very much at the heart of research on anxiety disorders such as posttraumatic stress disorder (PTSD). Surprisingly, only a minority (roughly 20–30%) of people subjected to profound trauma develop PTSD, and early family life serves as a highly significant predictor of vulnerability to PTSD following trauma. These findings suggest that early-life events might alter the development of neural systems in brain regions that mediate emotional and cognitive responses to adversity and thus contribute to individual differences in vulnerability to anxiety disorders. Childhood abuse significantly alters autonomic and HPA responses to stress (Heim et al., 2000); and there is evidence for more subtle effects that do not involve stressors as extreme as persistent neglect or abuse. For example, Maternal Care scores on the Parental Bonding Index predict trait anxiety, HPA responses to stress, and stress-induced activation of the brain catecholamine system (Pruessner, Champagne, Meaney & Dagher, 2004).

There is also evidence that vulnerability to anxiety disorders may be transmitted from generation to generation. Yehuda et al. (2000) found that the adult offspring of Holocaust survivors exhibited altered HPA function and were at increased risk for PTSD. More recent studies suggest that the intergenerational transmission of the risk for PTSD in this population is mediated by alterations in parental care. This finding is consistent with earlier studies revealing that anxiety is a strong, negative predictor of maternal responsiveness in humans.

Recent studies reflect the potential for the epigenetic transmission of individual differences in behavior and gene expression from parent to offspring. Studies with humans and nonhuman primates show that variants of the serotonin-transporter gene (which metabolizes serotonin) are associated with forms of temperament that predispose individuals to depression and alcoholism (Bennett et al., 2002; Caspi et al., 2003). However, this effect is modified by environmental conditions, especially the availability of parent–offspring interactions, prevailing during early development. In macaques, normal mother–infant relations reduced the risk for impaired serotonin metabolism and impulse control that is otherwise associated with the serotonin-transporter variant. These findings remind us that measures of heritability, by definition, reflect both variation in the genome and interactions between genes and the environment.

Traits that render individuals vulnerable for psychopathology emerge as a function of the constant interaction of genes and environment over the course of development. Indeed, there is currently considerable confusion in distinguishing the characteristics of pathology from those of developmentally determined vulnerabilities. In a study involving Vietnam veterans and their twins, Gilbertson et al. (2002) found that individuals who experienced combat service in Vietnam and developed PTSD showed reduced hippocampal volume by comparison to those with a similar military history but no PTSD; importantly, the twins who never served in Vietnam or showed PTSD showed the same difference, suggesting that the reduced hippocampal volume is a trait that preceded the PTSD. These and other studies focus researchers on the developmental origins of psychopathology and on critical questions, such as how reduced hippocampal volume or other neurobiological aspects of phenotypes might render individuals vulnerable to psychopathology.

Nowhere is the interplay between genes and environment more evident than in the relationships that exist between family environment and vulnerability or resistance to chronic illness. Vulnerability for mental illness is increased by a wide range of risk factors that are common in families living in conditions of adversity, such as low socioeconomic status. These risk factors include genetic variations, complications of pregnancy and birth, familial dysfunction, child abuse and neglect, and maternal depression. Such factors define "risky" families (Repetti, Taylor, & Seeman, 2002). All forms of mental disorders are "familial"—they run in families—and the mechanisms by which vulnerability is transmitted from parent to offspring involve both genomic and epigenetic processes of transmission. The challenge is to clearly define the mechanisms of transmission; the reward would be the ability to identify remarkably effective targets for prevention. Of particular interest are the parent–child relations that define family life and the mechanisms by which the effects of family life become "biologically embedded," thereby influencing vulnerability and resistance. We (Weaver et al., 2004) recently described the effect of maternal care on the structure (not sequence) of the DNA that regulates the activity of the gene encoding for the glucocorticoid receptor in the hippocampus. These epigenetic modifications of the DNA regulate glucocorticoid-receptor expression and thus HPA responses to stress. Such findings might illustrate the processes by which a dynamic environment interacts with a fixed genome to produce a phenotype. Understanding such processes requires not only the relevant biological tools but a clear understanding of the relevant environmental signals. Obviously, such studies will require a commitment to research at the biological, psychological, and social levels of analysis.

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