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Maternal programming of defensive responses through sustained effects on gene expression

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Abstract

There are profound maternal effects on individual differences in defensive responses and reproductive strategies in species ranging literally from plants to insects to birds. Maternal effects commonly reflect the quality of the environment and are most likely mediated by the quality of the maternal provision (egg, propagule, etc.), which in turn determines growth rates and adult phenotype. In this paper we review data from the rat that suggest comparable forms of maternal effects on defensive responses stress, which are mediated by the effects of variations in maternal behavior on gene expression. Under conditions of environmental adversity maternal effects enhance the capacity for defensive responses in the offspring. In mammals, these effects appear to 'program' emotional, cognitive and endocrine systems towards increased sensitivity to adversity. In environments with an increased level of adversity, such effects can be considered adaptive, enhancing the probability of offspring survival to sexual maturity; the cost is that of an increased risk for multiple forms of pathology in later life.

Keywords: Maternal programming; Gene expression; Emotional learning

There is renewed interest among neuroscientists in the effects of early environment on neural development and emotional/cognitive function. This enthusiasm derives, in part at least, from epidemiological studies revealing the importance of family function and early life events as predictors of mental health in adulthood (Repetti et al., 2002). Such studies show that the quality of family life influences the development of individual differences in vulnerability to illness throughout life. Importantly, such effects include vulnerability for obesity, metabolic disorders and heart disease as well as affective disorders and drug abuse (e.g., Lissau and Sorensen, 1994; McCauley et al., 1997; Felitti et al., 1998). Recent findings from epidemiological studies (e.g., Caspi et al., 2003) as well as from primate models (e.g., Bennett et al., 2002) further suggest that developmentally determined vulnerability can emerge from the interaction between genotype and early environmental events, including early life adversity. The critical questions concern the identity of the relevant genomic targets, the nature of the gene–environment interactions and their relation to phenotype.

'Stress diathesis' models have emerged as explanations for the effects of early life on health in adulthood and suggest that adversity in early life alters the development of neural systems in a manner that predisposes individuals to disease in adulthood. These models place considerable emphasis on the influence of early experience on the development of defensive responses and the relevance of these effects for vulnerability over the lifespan. Chronic illness is thought to emerge as a function of the altered responses to environmental demand (stressors) in conjunction with an increased level of prevailing adversity. There are two critical assumptions here: first, that prolonged activation of neural and hormonal responses to stressors can promote illness and second that early environmental events influence the development of stress responses.

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There is strong evidence in favor of both ideas. In humans, physical and/or sexual abuse in early life, poor parental bonding and family dysfunction increase endocrine and autonomic responses to stress in adulthood (De Bellis et al., 1994; Heim et al., 2000, 2002; Essex et al., 2002; Pruessner et al., 2004; Luecken and Lemery, 2004) as well as cognitive processing of potentially threatening stimuli (Pollack). There is evidence for comparable developmental effects in primates (Higley et al., 1991; Suomi, 1997; Bennett et al., 2002) and rodents (e.g., Plotsky and Meaney, 1993; Newport et al., 2002; Plotsky et al., 2005), albeit with models that rely on prolonged periods of separation of parent and offspring. Moreover, sustained exposure to elevated levels of stress hormones, including corticotrophin-releasing factor (CRF), catecholamines, most notably norepinepherine and glucocorticoids can actively promote the development of a diverse range of high risk conditions, such as visceral obesity, hypertension and insulin intolerance, or overt pathology, including diabetes, depression, anxiety disorders, drug addiction and multiple forms of coronary heart disease (Chrousos and Gold, 1992; Schulkin et al., 1994; Dallman et al., 2001, 2004; McEwen, 1998; Arborelius et al., 1999).

The relation between the quality of the early environment and health in adulthood appears to be mediated by parental influences on the development of neural systems that underlie the expression of behavioral and endocrine responses to stress (Meaney, 2001). There is strong evidence for such parental mediation in developmental psychology. As one example, the effects of poverty on emotional and cognitive development are mediated by variations in parent–offspring interactions: if parental care factors are statistically controlled, there no longer remains any discernible effect of poverty of child development (e.g., Conger et al., 1994; McLloyd, 1998). Such findings are not surprising. Poverty imposes considerable stress on the family unit and stressors seriously compromise the quality of parental care (Repetti et al., 2002; Hart and Risley, 1995). In humans, high levels of maternal stress during the transition to parenthood are associated with depressed/anxious mood states and less sensitive parent–child interactions that, in turn, influence the quality of parent–child attachment (Fleming and Corter, 1988; Fleming, 1999; Goldstein et al., 1996). Unstable/stressful environments, such as those prevailing under conditions of poverty, are associated with greater variability in the quality of infant–mother attachments (Vaughn et al., 1979). Parents that experience poverty or other environmental stressors, more frequently experience negative emotions such as irritability, depressed and anxious moods, which can then lead to more punitive forms parenting (Conger et al., 1984; Grolnick et al., 2002; Belsky, 1997). Reduced education of parents, low income, multiple children, the absence of social support, and single parenthood predict forms of parenting (verbal threats, pushing or grabbing the child, emotional neglect, overt physical abuse and more controlling attitudes toward child) that compromise cognitive development and result in more anxious and behaviorally inhibited children. In this review we consider environmental effects occurring during the early postnatal period. There is, of course, considerable evidence for the effects of adversity on the mother and offspring during the prenatal period (e.g., McCormick et al., 1995; Weinstock, 1997; Seckl, 2001; Glover and O'Connor, 2002; Matthews and Meaney, in press) and thus the influence of adversity is best seen as being continuous, with effects through development at multiple genomic targets and influences on a wide range of functional outcomes. Importantly, prenatal adversity is also associated with increased HPA and autonomic responses to stressors (Wadhwa et al., 2001; Weinstock, 2001; Chapillon et al., 2002; Maccari et al., 2003; Amiel-Tison et al., 2004).

Support for the basic elements of stress diathesis models appears compelling. Adversity during perinatal life alters development in a manner that seems likely to promote vulnerability, especially for stress-related diseases. Diathesis describes the interaction between development, including the potential influence of genomic variations, and the prevailing level of stress in predicting health outcomes. Such models could identify both the origins and the nature of vulnerability. Nevertheless, there is a troubling aspect to the discussion surrounding these developmental models. Within the health sciences such models seem to imply an ideal form of phenotypic development and, by implication, ideal forms of early environment, including parenting. For example, dampened stress reactivity and enhanced capacity for declarative memory are often considered as indicators of "positive" development. By such criteria postnatal handling or environmental enrichment commonly used in rodent studies are thought to be beneficial for development. Indeed, both manipulations result in increased hippocampal synaptic development. Stressors, such as neglect or prolonged separation of mother and offspring, in early life are thought to compromise development and lead to negative outcomes, such as increased stress reactivity (e.g., Plotsky and Meaney, 1993; Biagini et al., 1998; Vazquez, 1998) and decreased hippocampal synaptic development (Huot et al., 2002) as well as decreased capacity for hippocampal neurogenesis in adulthood (Mirescu et al., 2004). But positive or negative in relation to what? In an evolutionary sense, health outcomes are a relevant consideration only if they influence reproduction. Fitness is defined by success in the arena of reproductive competition; health in the post-reproductive phase of the life cycle is of importance only to the extent that it bears on the survival and reproduction of the progeny.

We certainly do not dispute the idea that there are predictable relationships between certain forms of early experience and specific health outcomes (see above). The ability to identify risk factors for illness is critical and provides an empirical basis for prevention. Nevertheless, the idea that any form of phenotypic variation is in and of itself positive or negative is an anathema to biology. The merit of any variation in phenotype is understandable only in terms of the degree to which it serves to enhance adaptation to environmental demands with respect to reproductive outcomes. Traits that enhance survival (prior to and through periods of active reproduction) and reproduction within any specific environmental context are favored. The value of any trait is contextually determined. This proposal may