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Review

Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat

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Abstract

Increased levels of pup licking/grooming and arched-back nursing by rat mothers over the first week of life alter the epigenome at a glucocorticoid receptor gene promoter in the hippocampus of the offspring. Differences in the DNA methylation pattern between the offspring of High and Low licking/grooming—arched-back mothers emerge over the first week of life, are reversed with cross-fostering, persist into adulthood and are associated with altered histone acetylation and transcription factor (NGFI-A) binding to the glucocorticoid receptor promoter. Central infusion of the adult offspring with the histone deacetylase inhibitor trichostatin A removes the previously defined epigenomic group differences in histone acetylation, DNA methylation, NGFI-A binding, glucocorticoid receptor expression, and hypothalamic-pituitary-adrenal responses to stress, thus suggesting a causal relation between the epigenomic state, glucocorticoid receptor expression and the effects of maternal care on stress responses in the offspring. These findings demonstrate that an epigenomic state of a gene can be established through a behavioral mode of programming and that in spite of the inherent stability of this epigenomic mark, it is dynamic and potentially reversible.

Keywords: Maternal behavior; Glucocorticoid receptor; Stress responses; DNA methylation; Gene expression; Histone acetylation; NGFI-A; Estrogen receptor

1. Introduction

The quality of early family life influences the risk for multiple forms of chronic illness over the lifespan [173]. While these effects are clearly apparent in the risk for mental illness [9,16,22,24,69,84,85,87,142,153,209,215,223], such factors also predict visceral obesity, type II diabetes, coronary heart disease as well as gastroenterological and obstetric outcomes [39,48,54,68,102,108,117,163,164,181,215]. 'Stress diathesis' models (Fig. 1) have emerged as explanations for the relation between the quality of early life and health in adulthood. These models suggest that adversity in early life alters the development of neural and endocrine responses to stress and thus predisposes individuals to disease in adulthood (e.g. [75,76,82,126,129,163,187,198]). 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 [59,75,76,140,187,198]. Indeed, in human and nonhuman primates adversity or decreased quality of parental investment increases the magnitude of emotional, autonomic, central catecholamine and hypothalamic-pituitary-adrenal (HPA) responses to stress in adulthood [7,75,76,82,112,166,175,203]. In nonhuman primate and rodent models, repeated and prolonged periods of maternal separation over the first weeks postpartum result in enhanced behavioral and HPA responses to stress [7,60,13,20,43,82,109,129,160,162].

The logic for stress diathesis models is buttressed by the strong evidence for the endangering effects of prolonged

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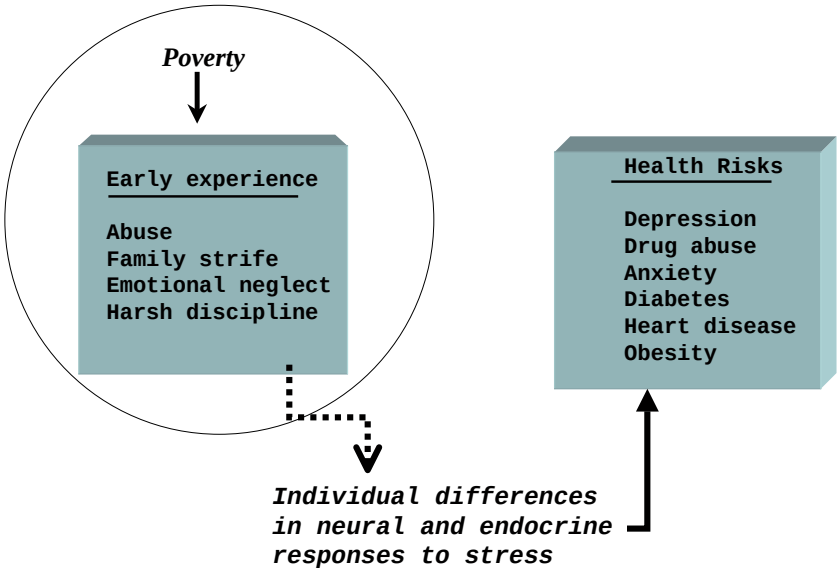

Fig. 1. A schema outlining the pathways implied in stress diathesis models. Familial adversity, such as poverty, influences the nature of parent–child interactions, which in turn influence the development of individual differences in neural and endocrine responses to stress. Resulting variations in exposure to stress mediators, such as corticotropin-releasing hormone (CRF), catecholamines and glucocorticoids, can then serve as the basis for individual differences in the risk for multiple forms of chromic-illness. According to such models the critical conditions are the presence in early life of forms of parent–offspring interactions that promote increased stress responses and chronic stress in adulthood. The focus of this chapter is the proposed link between variations in parent–offspring interactions and the development of individual differences in stress responses.

exposure to 'stress hormones' that provides further support for stress diathesis models. Thus, chronic exposure to elevated levels of stress hormones, including corticotrophin-releasing factor (CRF), catecholamines, most notably norepinepherine, and glucocorticoids 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, drug addiction and multiple forms of coronary heart disease [34,37,38,119,157,177,184,212]. Clinical-case studies show that increased cortisol levels are associated with visceral obesity, cardiovascular disease, type II diabetes and depression (for a review see [174]). Moreover, in prospective epidemiological studies, measures of peripheral catecholamines and glucocorticoids predict an increased risk for cardiovascular disease and overall mortality [189,190]. Moreover, polymorphisms of the glucocorticoid receptor are associated with chronic cardiovascular and metabolic illness [214]. The clinical risks associated with prolonged activation of the HPA and autonomic systems are a logical consequence of the otherwise adaptive and highly catabolic stress response. The increased release of glucocorticoids from the adrenal gland and catecholamines, particularly norepinepherine from the sympathetic system, increases the availability of energy substrates, such as those derived from lipids and glucose metabolism, in order to maintain the normal cellular output and organ efficiency. These actions protect against catastrophes such as hypotensive shock. These hormones, along with the central CRF, act on multiple brain regions to increase vigilance and fear, and enhance avoidance learning and fear conditioning, which reduces the chances of further encounters with the offending conditions. Prolonged exposure to CRF, glucocorticoids and catecholamines drives hyperlipidemia, increased cardiovascular tone, insulin resistance, and alterations of mood.

Support for the basic elements 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 genetic factors, and the prevailing level of stress in predicting health outcomes. Such models have considerable appeal, and could potentially identify both the origins and the nature of vulnerability derived from either epigenetic influences, such as early family life, or genomic variations. The question of interest to our labs is that of how environmental events in early life, particularly those involving parent–offspring interaction, might regulate the development of individual differences in stress responses. Of particular interest is the question of how early experience produces sustained effects on phenotype.

2. The development of individual differences in stress responses

The studies of Levine, Denenberg and others reveal that in rodents, postnatal handling (aka, infantile stimulation) alters the development of responses to adverse stimuli, or stressors [44,103,104]. The handling paradigm involves a brief, daily (i.e., ~15 min) separation of the pups from the dam. This period falls well within the range normal mother–pup separations that lie between nursing bouts and does not seem to constitute any major deprivation of