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Understanding the potency of stressful early life experiences on brain and body function

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Abstract

Early life experiences have powerful effects on the brain and body lasting throughout the entire life span and influencing brain function, behavior, and the risk for a number of systemic and mental disorders. Animal models of early life adversity are providing mechanistic insights, including glimpses into the fascinating world that is now called "epigenetics" as well as the role of naturally occurring alleles of a number of genes. These studies also provide insights into the adaptive value as well as the negative consequences, of early life stress, exposure to novelty, and poor-quality vs good-quality maternal care. Animal models begin to provide a mechanistic basis for understanding how brain development and physiological functioning is affected in children exposed to early life abuse and neglect, where there is a burgeoning literature on the consequences for physical health and emotional and cognitive development. An important goal is to identify interventions that are likely to be most effective in early life and some guidelines are provided.

1. Introduction

Early life adversity has widespread effects on both brain and body. For example, early life physical and sexual abuse carry with it a life-long burden of behavioral and pathophysiologic problems [1,2]. Moreover, cold and uncaring families, as well as chaos in the home environment, produce long-lasting emotional problems in children [3,4]. Some of these effects are seen on brain structure and function and in the risk for later depression and posttraumatic stress disorder [5-7]. Other manifestations include increased risk for obesity and cardiovascular disease [8,9].

Recent progress in neuroscience and biomedicine is providing a better understanding of mechanisms and pathways for these effects. This article will provide an overview by discussing 3 aspects. The first concerns animal models of early life adversity that provide mechanistic insights, including glimpses into the fascinating world that is now called "epigenetics." Second, the translation of animal studies to understand and investigate the impact of early life adversity in humans will be discussed. Finally, the types of interventions that are likely to be most effective in early life will be considered. They will also be compared with the relative merits of pharmaceutical, medical, and psychosocial interventions to deal with the effects of early life adversity.

2. The long-lasting influence of early life experiences: contributions of animal models

The aging process begins at conception, and experiences early in life have a profound influence on the quality and length of life. Animal models have provided important insights. In rodents, early life maternal care is a powerful determinant of life-long emotional reactivity and stress hormone reactivity, and increases in both are associated with earlier cognitive decline and a shorter life span [10,11]. Strong maternal behavior, involving licking and grooming of the offspring, produces a "neophilic" animal that is more exploratory of novel environments and less emotionally reactive. This also produces a lower and more contained glucocorticoid stress response in novel situations; poor maternal care leads to a "neophobic" phenotype with increased emotional and hypothalamic-pituitary-adrenal (HPA) reactivity and less exploration of a novel situation [12]. Effects of early maternal care are transmitted across generations by the subsequent behavior of the female offspring as they become mothers, and methylation of

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DNA on key genes appears to play a role in this epigenetic transmission [10,13], as will be described below.

The effects of maternal care explain at least part of the effects of "neonatal handling" that involved the short-term separation of pups from their mothers [14]. The neonatal handling procedure overcomes the deleterious effects of prenatal stress to increase emotionality of offspring [15]. Interestingly, more prolonged separation of pups from mothers increases emotionality and stress reactivity, in part by decreasing maternal care when pups are returned to their mothers [16]. An enriched environment during the peripubertal period ameliorates these deficits [17].

Abuse of the young, that is, rough handling by the rodent mother, is associated with an attachment to, rather than an avoidance of, the abusive mother, an effect that increases the chances that the infant can continue to obtain food and other support until weaning [18]. One way to demonstrate the positive, rather than avoidance, effects of aversive stimuli in neonates is via shock-odor conditioning. In this paradigm, neonates become attracted to the odor, at least until they are almost 2 weeks of age, when the presence of the mother during conditioning leads to an attraction to the odor paired with shock. As for mechanism, the presence of the mother is able to suppress the pup's corticosterone production, which otherwise would increase an aversive reaction. This has been demonstrated by overriding the maternal suppression of HPA activity in rat pups by implanting corticosterone in the amygdala; this manipulation instates fear and fear conditioning and produces an aversive reaction [19].

Increased emotional reactivity and fear of novelty in young rats, whatever its cause, has consequences for longevity and for cognitive function. Male rats were screened at 43 days old for anxiety and divided into "high" and "low" anxiety groups and then subjected to 21 days of daily restraint stress when they were 72 days old; compared to the "low" anxiety" group given chronic stress and also compared to unstressed controls, the "high" anxiety rats showed impaired spatial memory in a subsequent test using the Y maze [20]. In another study, the profiling of anxiety in even younger rats also has predictive power: male rats that were "neophobic" as pups continued this pattern into adult life and showed a significantly shorter life span by around 200 days compared to young rats that were "neophilic," that is, showed lower cortisol and emotional reactivity to novelty [11]. However, the cause of death for the neophobic male rats was unclear. A subsequent study of female rats focused on tumors as the likely cause of death of neophobic females, which died 6 months sooner than neophilic females. In contrast to the story for males, neophobic females had lower corticosterone levels than their neophilic counterparts, and they showed abnormal patterns of prolactin and estrogen secretion, pointing away from glucocorticoid dysregulation as the sole cause of pathophysiology [21].

Yet, not all consequences of the neophilic state are necessarily beneficial. For example, in mice, neonatal handling, the procedure that induces the neophilic state, increases the damage associated with elevated corticosterone during ischemia, at least in part by increasing poststroke proinflammatory cytokine expression [22]. The underlying mechanisms are as yet unexplored.

It is important to note that other conditions that affect the rearing process can also affect emotionality in offspring. For example, uncertainty in the food supply for rhesus monkey mothers leads to increased emotionality in offspring and possibly an earlier onset of obesity and diabetes [23]. On a more positive side, the experience of novelty has beneficial effects for cognitive function and social interactions that go beyond the maternal influence [24]. Exposure of pups to novelty away from the home environment has been carried out in a carefully controlled paradigm that dissociates maternal individual differences from a direct stimulation effect on the offspring. Such exposure resulted in enhancement of spatial working memory, social competition, and corticosterone response to an unexpected stressor during adulthood in comparison to their home-staying siblings. These functional enhancements in novelty-exposed rats occurred despite evidence that maternal care was preferentially directed toward home-staying instead of novelty-exposed pups, indicating that a greater maternal care is neither necessary nor sufficient for these early stimulation-induced functional enhancements [24].

3. Translation to understanding early life influences on human physiology and behavior

The animal models are very useful in helping to understand how early life experiences affect human physiology and behavior. Early life physical and sexual abuse carry with it a life-long burden of behavioral and pathophysiologic problems [1,2], including an increased proinflammatory tone 20 years later [25]. Moreover, cold and uncaring families produce long-lasting emotional problems in children [3]. Some of these effects are seen on brain structure and function and in the risk for later depression and posttraumatic stress disorder [5-7].

Prenatal stress is believed to be a factor in causing preterm birth, as well as full-term birth with low birth weight [26,27]. Low birth weight is a risk factor for cardiovascular disease and high body mass [26,28]. Childhood experiences in emotionally cold families increase likelihood of poor mental and physical health later in life [3], and abuse in childhood is a well-known risk factor for depression, posttraumatic stress disorder, idiopathic chronic pain disorders, substance abuse, antisocial behavior, as well as obesity, diabetes, and cardiovascular disease [1,2,9].

Chaos in the home environment is a key determinant of poor self-regulatory behaviors, a sense of helplessness and psychological distress [4], as well as increased body mass and elevated blood pressure [29]. One of the lasting consequences of low socioeconomic status in childhood is