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ScienceDirect
Metabolism Clinical and Experimental 57 (Suppl 2) (2008) S11 – S15
Metabolism
Clinical and Experimental
www.metabolismjournal.com

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

Bruce S. McEwen*

Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10065, USA

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

STATEMENT OF CONFLICT OF INTEREST: The author is a member of the Scientific Committee of the Collège International de Recherche Servier (CIRS).

* Tel.: +1 212 327 8624; fax: +1 212 327 8634.
E-mail address: mcewen@rockefeller.edu.

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doi:10.1016/j.metabol.2008.07.006

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

an elevation in body mass, as well as poor dental health [30]. Social isolation in childhood increases the risk of cardiovascular disease later in life [31], and childhood abuse is linked to an increased proinflammatory tone, as measured by elevated C-reactive protein levels decades later [32].

4. Importance of gene-environment interactions

In addition to the effects of experiences, genetic differences also play an important role as part of the nature-nurture interaction. This is a vast and growing topic, and only some examples will be noted here. For example, alleles of the glucocorticoid receptor gene found in the normal population confer a higher sensitivity to glucocorticoids for both negative feedback and insulin reponsiveness [33] or glucocorticoid resistance [34]; moreover, there is evidence of increased likelihood of depression in individuals with these alleles and increased response to antidepressants in at least one of them. Another example is the consequence of having the Val66Met allele of the BDNF gene on hippocampal volume, memory, and mood disorders [35-38,39]. A mouse model of this genotype has revealed reduced dendritic branching in hippocampus, impaired contextual fear conditioning, and increased anxiety that is less sensitive to antidepressant treatment [39]. In yet another example of nature-nurture interactions, the short form of the serotonin transporter is associated with a number of conditions such as alcoholism [40,41], and individuals who have this allele are more vulnerable to respond to stressful experiences by developing depressive illness [42].

Although it is likely that early life experiences will interact with these alleles to produce differential outcomes of vulnerabililty or resilience to a variety of disorders, there are several studies that clearly point to the nature-nurture interaction and that, as a result, have become a paradigm for thinking about these issues. In childhood, individuals with an allele of the monoamine oxidase A gene are more vulnerable to abuse in childhood and more likely to themselves become abusers and to show antisocial behaviors compared to individuals with another commonly occurring allele [43]. A related study of the serotonin transporter alleles has shown that the quality and amount of social support moderated the risk for depression resulting from childhood abuse [44]. Moreover, children with the long-form of the serotonin transporter were also less likely to develop depression from maltreatment than those with the short-form allele, whereas the children with the short form of the serotonin transporter, and who also lacked social supports, had depression scores that were twice those of children with the same genotype who had no abuse. Furthermore, positive social support reduced the frequency of depression in children with the short-form allele to levels that were similar to nonabused children with the same allele [44].

5. Epigenetic regulation

As evidence accumulates for the complex interactions between genes and environment, there is a new chapter opening up dealing with the molecular basis of gene regulation. This is catalyzed by recasting of an older term with new molecular meaning. “Epigenetics,” meaning “above the genome,” was originally defined to mean the gene-environment interactions that bring about the phenotype of an individual. Now, “epigenetics” means something more specific in molecular terms, namely, the methylation of cytosine bases in DNA along with modifications of histones that modify unfolding of chromatin to expose DNA sequences that can be read and transcribed [45].

The pioneering work of Vincent Allfrey, Alfred Mirsky, and colleagues in the 1960s and 1970s demonstrated the relationship of transcriptional activation of chromatin and the modification of histones by acetylation and phosphorylation [46,47]. They also presented a conceptual framework for understanding the role of histone modifications in the unfolding of DNA-protein complexes to allow transcription during states of gene activation [48]. Recent work has revealed that there is a complex “language” of epigenetic modifications that regulate transcription, both up and down [49,50].

Epigenetic modifications are of several types. There are genes with metastable epialleles, that is, modifications that affect gene expression are reversible. For example, the murine agouti gene is linked to altered coat color, diabetes, obesity, and tumorigenesis, and genetically identical mice can be induced to show these traits by suitable dietary manipulations [45]. There are also imprinted genes that transfer the epigenetic state through the germline, for example, the murine IGF2 gene that is passed on in a modified state in the paternal genome and the IGF2R gene that is transferred in a modified state in the maternal genome. In humans, the severe developmental disorders, Prader-Willi and Angelman syndromes, are cited as examples of epigenetic modifications that are transmitted in the germline.

Besides transmission by chemicals in the environment, such as endocrine disruptors, there is also behavioral transmission of traits, for example, via maternal care. The studies noted above by Michael Meaney and colleagues are the best examples to date, and the proposed mechanism involves the quality and intensity of maternal care determining the demethylation of promotor regions of genes that affect expression of the glucocorticoid receptor in the brain and thereby alter the stress responsiveness of the individual [13]. Cross-fostering of infant rats and mice from good to poor mothers and vice versa is able to alter the behavioral phenotype accordingly [10,51]. Although the human organism is more complex, it is conceivable that similar epigenetic, behaviorally transmitted influences may occur as a result of both pre- and postnatal influences. One possible example might be the recent report showing that transmission of obesity is reduced in severely obese women by bariatric surgery leading to major weight loss before conception [52].

6. Interventions

We have seen that experiences have profound and long-lasting influences on the body and brain both during adult life and during development, when the effects of stressful events may have even a more profound and lasting influence on what happens during the life course. The lasting effects manifest themselves in the wear and tear referred to as allostatic overload [53].

What is the best approach to reducing the burden of allostatic overload? Clearly, interventions early in life that promote healthy mental and physical development will reduce problems later in life, whereas treatment of problems that arise in part from bad experiences early in life are likely to require more effort and cost and will not be as effective. The example of social support in children with early life abuse, cited above, emphasizes that conditions such as depression and the related physiological burden can be ameliorated and even prevented by means that do not involve pharmaceutical treatment but rather use emotional support and information by key persons in the child's life [44]. Furthermore, the pioneering work of Olds and colleagues [54-56] have demonstrated the important role of enhancing the home environment through visits to the home of an expectant mother by a skilled social worker before and after the birth of the child. Home visits combined with school enrichment programs were both involved in the very successful Perry School Project that has been summarized in an informative web site (http://www.evidencebasedprograms.org/Default.aspx?tabid=32).

Finally, the National Forum on Early Childhood Program Evaluation and the National Scientific Council on the Developing Child have developed a summary and analysis of successful elements of child intervention programs (www.developingchild.harvard.edu). This analysis will be useful in designed the most cost-effective interventions.

7. Conclusions

Early life experiences are particularly important in determining how the individual responds over the life course. Genetic variants of an increasing variety of genes are recognized as contributing to the vulnerability or resilience in the face of stressors. At the same time, the new science of "epigenetics" is revealing ways in which the genome is regulated and modified in either a metastable or transgenerational manner, which alters the expression of certain genes. Some of these modifiable genes are already recognized as being responsible for developmental disorders such as Prader-Willi and Angelman syndromes (at least in mice), and adult disorders, such as obesity and vulnerability to cancer [45].

The brain is itself malleable in response to stressors, and stress during early life alters how the brain responds to stressors later in life [57]. Stress in adolescence appears to have lasting effects on brain regions such as the hippocampus and alters mood- and anxiety-related behaviors in animal models, as well as cognitive function. Stressors in adult life alter neuronal morphology in brain regions such as the hippocampus, amygdala, and prefrontal cortex and influence learning, anxiety, executive function, and somatic-visceral functions. It remains to be shown how much early life experiences determine the degree and qualitative nature of the brain response to stressors later in life, as well as the time course and qualitative nature of the changes with aging. Moreover, translation to the human condition is becoming possible with the introduction of brain imaging techniques. At the same time, studies of vulnerable human populations are revealing the extent and nature of allostatic load later in life, but we also know that these conditions begin much earlier in life.

When it comes to interventions, although medicines are indispensable when a severe condition such as depression or cardiovascular disease has arisen, this is a last-ditch strategy. Rather, intervention programs designed to prevent these severe conditions are mandated. Such programs are complex and require up-front expenditures and commitment by government and the private sector, but in the long run they are the most cost-effective way of making a difference.

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