

Impact of early life experience on adult health.

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Abstract

Early life stress (ELS) causes multiple epigenetic modifications (e.g. methylation of genes and histones) in a developing child's genome. Early life stress comes in various forms: Serious physical and mental abuse for example by parents, relatives, or caregivers; a poor social environment involving drug addicts and gang warfare; or loss of all parents and close relatives. This brief review is an attempt to update the information in the above-mentioned opus with a focus on in part on events in the brain and emphasizes that dissociable domains compose executive function.

Keywords: Early life stress, Epigenetics, Glucocorticoids.

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Introduction

Details how ELS may have long-term effects on the individual, in part mediated by methylation of the exon 1F variant (site of binding of the transcription factor NGF1-A) of the glucocorticoid receptor Nr3c1, in the hippocampus, at least in some individuals who later committed suicide are reviewed by Turecki and Meaney [1,2]. In a complex way ELS impacts on a set of higher order cognitive processes that enable individuals to orient towards the future, demonstrate self-control, and complete goal-directed behavior encompassed under the term executive function [3]. This includes impulse control, response inhibition, attention, working memory, cognitive flexibility, planning, judgement and decision making. Cowan et al. and colleagues have reviewed possible mechanisms regarding how early-life adversity could impact descendants. Exploratory behavior, curiosity, and an urge for adventure (to explore) may also be related traits, but are poorly understood [4].

Recent Research

Jawahar et al. has provided a detailed analysis of the current situation, which is complicated by the variety of protocols used (in rodents) to induce ELS [5]. Many genes within the HPA (hypothalamus, pituitary, adrenal) axis are activated and BDNF (bone-derived neurotrophic factor) is produced, which stimulates glucocorticoid production that in turn activates a plethora of downstream genes (the "fight or flight" response) The serotonin transporter, 5-HTT, the estrogen receptor α , glutamate decarboxylase 1, and Reelin (involved in neuron migration) are involved according to a variety of reports. A comparison of a group of children raised in an institution with a group raised by their parents revealed differences in whole genome methylation as assessed in peripheral lymphocytes, which are representative of many tissues in the body [6]. In this extensive study 815 CpG sites showed increased methylation and 99 showed decreased methylation. Rodgers et al. reported that sperm of chronically stressed male mice carry certain miRNAs that reduce HPA axis reactivity, "recapitulating" the effect of paternal stress [7].

Others have shown that epigenetic marks found in male mice exposed to malnutrition or drugs of abuse can be passed on to

offspring. Murphy et al. quantified differential methylation of regulatory regions of imprinted genes in human cord blood and other tissues; these included SGCE/PEG10 and H19, which are imprinted by only one of the parents [8]. PEG10 (paternally expressed gene 10) functions in trophoblast proliferation and promotes trophoblast invasion. H19 is a lncRNA (long non-coding RNA) that contains within it the sequence encoding the micro RNA miR-675, which together with H19 are important in controlling many physiological functions, including the epithelial/mesenchymal transitions in both directions.

Discussion

Poor quality maternal diet (in mice) and subsequent gestational growth disturbances contribute to the etiology of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia and abnormalities in executive function. These were linked in part to transcriptional changes in four epigenetic modulators: DNMT1 (DNA methyltransferase), COMT (catechol-O-methyltransferase), ORPD1 (δ -opioid receptor), and CNR1 (cannabinoid receptor 1) [9].

As detailed recently by Allan et al. considerable evidence suggests that executive function promotes a wide range of healthy behaviors, including increased physical, intellectual and social activity and a sensible low-fat diet with minimal smoking or drinking [10]. 5 hydroxy tryptophan-2a (5HT2a) is a serotonin receptor involved in executive function and is located in the prefrontal cortex just behind the forehead. It is essential in planning complex behavior, personality expression, decision making and moderating social behavior. The postsynaptic serotonin 2A receptor, 5-HT2AR, is the most abundant subtype modulating cortical network activity; it induces synchronized spiking of single units and neuronal ensembles, known as wave oscillation synchronization. It also has a modulatory effect on dopaminergic signaling, another important player in executive function. Importantly, dopamine is now recognized as a potential treatment target for many neuropsychiatric disorders [11].

Conclusion

Metabolic pathways linked to mental health disorders (e.g. social anxiety disorder, a common and disabling disorder, appears to

result from decreased methylation of the oxytocin receptor, OXTR. Oxytocin, a 9-amino acid neuropeptide, is known to increase positive social interactions and pair bonding. Evidence strongly suggests that one cause of SAD is the result of OXTR hypomethylation, conferring increased OXTR expression [12].

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