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Review

Plasticity of the epigenome during early-life stress

S. Barnett Burns[a], J. Kasia Szyszkowicz[b], Giamal N. Luheshi[b], Pierre-Eric Lutz[a,1], Gustavo Turecki[a,*]

[a] McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada
[b] Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Early life adversity remains a significant risk factor for the development of a host of negative behavioural and pathological outcomes in adulthood long after the stressor is over. Recent evidence indicates that these lasting effects of ELS may occur via alterations in the epigenetic landscape. Here, we review the main findings of the effects of early life adversity on DNA methylation, histone post-translational modification, and non-coding RNAs in the context of psychiatric disease in animal models and human cohorts. We specifically explore how early life adversity alters epigenetic patterns in both a global manner, and in specific candidate genes that play a role in relevant systems such as the hypothalamic-pituitary-adrenal axis, as well as neurotransmitter and neuroendocrine signalling. We also discuss how individual factors, such as genetics, sex, and age, as well as the type, and timing of early life adversity, can create differential susceptibility and significantly moderate outcomes. Although challenges remain in deciphering the complexity of how the early environment interacts with individual factors to determine epigenetic patterns, as well as how to translate these mechanistic findings into clinically relevant populations, the reviewed literature sheds light on the potential of the field to identify effective interventions for vulnerable individuals.

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* Corresponding author.
E-mail address: gustavo.turecki@mcgill.ca (G. Turecki).
[1] Current address: Institute of Cellular and Integrative Neuroscience, CNRS, UPR3212, Strasbourg, France.

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1. Introduction

Despite the remarkable development human fetuses undergo in utero, further postnatal maturation depends on a multitude of crucial experiences and environmental cues to calibrate fundamental systems [1]. Multiple time windows exist in early postnatal life, known as experience-dependent events, when developing systems become especially sensitive to environmental cues [2]. In addition, as development occurs in a hierarchical manner, both the timing and the temporal coordination of these events are vital [3]. Thus, the early life environment can modify fundamental systems in ways that persist into adulthood.

This plastic response allows for the environmental regulation of physiological and behavioural systems and thus can be viewed as an overall adaptive response. Indeed, some alterations during development, although atypical, may result in adaptations that confer resilience to specific circumstances in adulthood [4,5]. However, when expected experiences are completely absent, or the environment is otherwise extreme, or there is simply a mismatch between the developmental cues and the adult environment [6,7], this early-life 'programming' can become a liability.

Stressful experiences during early life have a potent, yet complex, impact on the developmental programming of the stress response and multiple other signalling systems. Although often assumed to be wholly negative, it is important to note that stress exposure is not deterministic, and can have contradictory effects on adult outcomes, in some cases even being associated with increased resilience to later stressors. The line between beneficial and toxic stress exposure is not yet clear and may depend on multiple individual factors, which we will discuss later in this review. The majority of studies thus far, however, have focused on the negative outcomes of developmental stress exposure. This is largely due to the evidence that early life adversity (ELA) (such as child abuse, neglect, parental loss, low socioeconomic status) is a major risk factor for multiple negative health outcomes later in life, including adult psychopathology, and therefore represents a significant public health concern. For example, ELA has been associated with cognitive, interpersonal, and behavioural impairments, PTSD, ADHD, autism, addiction, anxiety disorders, depression, suicide, as well as multiple chronic health issues, such as cardiovascular and respiratory diseases, diabetes, obesity, and cancer [8–11]. This wide variety of outcomes may be due to many factors, including the fundamental nature of the developmental exposure. Indeed, exposure during experience-dependent events may allow perturbations to become biologically embedded in basic systems that subsequently have far reaching effects [12–14]. In general, ELA has large scale impacts on stress and immune reactivity, as well as reductions in gray and white matter volume in many brain regions, and alterations in connectivity and function, (for in-depth reviews see [2,3]). Although the molecular processes underlying these large-scale changes are not fully elucidated, growing evidence suggests that epigenetic mechanisms, which allow the environment to modulate gene expression, mediate the processes by which ELA becomes biologically embedded in the brain.

1.1. Epigenetics: from Waddington to a modern definition

The concept of epigenetics (epigenesis + genetics = epigenetics) was first described by C.H. Waddington in 1940 [15,16] and provided a mechanism for cell differentiation during early development [17]. Waddington was the first to propose that phenotypes occurred as an interaction between genes and the environment. Although, there are many types of gene regulatory mechanisms that are essential to normal brain and stress response development, including as long-term recruitment and action of transcription factors [18], and alternate splicing of functional gene variants [19], epigenetic marks are distinct in that they are sequence-independent regulation of genetic function and expression that is stably heritable [20]. The epigenetic mechanisms that have been most studied in the context of ELA are: DNA methylation, post-translational histone modifications (PTMs), and noncoding RNAs (ncRNA) [21], and will be the focus of this review. However, this list is by no means exhaustive. Many other epigenetic mechanisms have been described, such as chromatin loops and long-range chromatin interactions [22]. More work will need to be done to determine how these mechanisms potentially interact and alter gene expression in the context of ELA.

1.1.1. DNA methylation

DNA methylation is a dynamic process that occurs during development and throughout life, even in post-mitotic cells, such as neurons [23]. Traditionally, DNA methylation has been defined as the addition of a methyl group to the 5th carbon of a cytosine base (5mC) and reported at CpG islands at gene promoters in the mammalian genome, where it is functionally associated with gene silencing (Fig. 1 a–c). However, 5mC methylation in other parts of the genome besides the promoter has also been described and the transcriptional effect in those areas is not consistent.

1.1.1.1. Hydroxymethylation. In contrast to 5mC, hydroxymethylation (5hmC), is often found in the gene body and exhibits global positive correlations with gene expression [24,25]. 5hmC occurs when ten-eleven translocation methylcytosine dioxygenases (TET1, 2 and 3) converts 5mC to 5-hydroxymethylcytosine (5hmC), possibly as a stepping stone to demethylation [26]. 5hmC has been described in neural tissue and was first identified in Purkinje and granule cells [27]. However, the functional significance of 5hmC, as either a separate functionally important mark or a demethylation stepping stone, remains to be elucidated. It is especially important to note that traditional bisulfite sequencing cannot distinguish between 5mC and 5hmC. Thus, it is therefore possible

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