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REVIEW

EARLY-LIFE EXPERIENCES AND THE DEVELOPMENT OF ADULT DISEASES WITH A FOCUS ON MENTAL ILLNESS: THE HUMAN BIRTH THEORY

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Abstract—In mammals, early adverse experiences, including mother–pup interactions, shape the response of an individual to chronic stress or to stress-related diseases during adult life. This has led to the elaboration of the theory of the developmental origins of health and disease, in particular adult diseases such as cardiovascular and metabolic disorders. In addition, in humans, as stated by Massimo Fagioli's *Human Birth Theory*, birth is healthy and equal for all individuals, so that mental illness develop exclusively in the postnatal period because of the quality of the relationship in the first year of life. Thus, this review focuses on the importance of programming during the early developmental period on the manifestation of adult diseases in both animal models and humans. Considering the obvious differences between animals and humans we cannot systematically move from animal models to humans. Consequently, in the first part of this review, we will discuss how animal models can be used to dissect the influence of adverse events occurring during the prenatal and postnatal periods on the developmental trajectories of the offspring, and in the second part, we will discuss the role of postnatal critical periods on the development of mental diseases in humans. Epigenetic mechanisms that cause reversible modifications in gene expression, driving the development of a pathological phenotype in response to a negative early postnatal environment, may lie at the core of this programming, thereby providing potential new therapeutic targets. The concept of the Human Birth Theory leads to a comprehension of the mental illness as a pathology of the human relationship immediately after birth and during the first year of life.

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Key words: epigenetics, animal models, annulment drive, vitality, Human Birth Theory, ''*anaffettività*".

Contents

CRITICAL LIFE PERIODS AND PROGRAMMING

Perinatal life, infancy, childhood, adolescence and aging are periods particularly sensitive to stressors (McEwen, 2012). Indeed, during these critical periods, adverse experiences may affect behavioral and physiological functions such as growth, metabolism, reproduction and the inflammatory/immune response (Seckl and Holmes, 2007; Seckl, 2008).

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Abbreviations: CNS, central nervous system; DOHaD, developmental origins of health and disease; EEG, electroencephalography; HPA, h ypothalamic–pituitary–adrenal; IGF, insulin/insulin-like growth factor; PRS, perinatal stress; SATs, Spontaneous Activity Transients.

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Non-genetic factors occurring early in life, such as intrauterine growth restriction and low birth weight or poor maternal care, are known to act as perinatal "*programming*" because they critically contribute to several aspects of the adult phenotype. This has led to the elaboration of the theory of the developmental origins of health and adult diseases (DOHaD), such as cardiovascular and metabolic disorders (Barker, 1995; Harris and Seckl, 2011; Santos and Joles, 2012; Barker and Thornburg, 2013; Entringer and Wadhwa, 2013). Moreover, in the field of psychiatry, the postnatal period has been found to be crucial for the development of diseases. In fact, as stated by Fagioli's *Human Birth Theory* (Fagioli, 1972), mental illnesses develop essentially during the '*postnatal period*', i.e. in the first year of life, and are expressed later in life and in adulthood. According to this theory, birth is healthy and equal for each individual. As major stress hormones, glucocorticoids are potential candidates for the role of '*programming factors*' in different paradigms of perinatal stress (Painter et al., 2012; Maccari et al., 2014). In particular, glucocorticoids have powerful brain-programming properties and may underlie the association between low birth weight and adult stress-related cardiovascular, metabolic and neuroendocrine disorders such as hypertension and type-2 diabetes (Barker, 1995). The prenatal diagnosis of these metabolic disorders represents significant progress in fetal medicine (Painter et al., 2012).

In the central nervous system (CNS), the stress response, which is partially evoked by glucocorticoids, includes both the facilitation of neural pathways that support time-limited adaptive functions (arousal, vigilance and focused attention) and the inhibition of neural pathways that support time-limited non-adaptive functions, such as eating, growth and reproduction, in order to ensure the central coordination of the stress response and the 'fight or flight' reaction (Chrousos, 2009). The hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic adrenomedullary system are generally considered to be the two key players in the stress response (De Klöet et al., 2005; Lupien et al., 2009). Within this context, it is also important to consider the inhibitory role of the hippocampus on the activity of the HPA axis (Sapolsky et al., 1985). Three fundamental elements form the multidimensional architecture of the stress response (Fig. 1): (i) the stimulus-stressor (positive or negative); (ii) its cognitive evaluation by the organism (strongly related to life experience and predictive abilities); and, (iii) the resulting neuroendocrine and behavioral responses of the individual. Allostatic processes, which result from these three steps, are engaged in order for the organism to find a new equilibrium in response to the specific stressor. The individual either reaches this new equilibrium and shows successful adaptation to stress, or cannot reach a new equilibrium and shows an unsuccessful response (no adaptation). In this latter situation, an inappropriate stress response, especially after chronic stimulation, might impair growth, development and body composition, and might account for many behavioral, endocrine, metabolic, cardiovascular and autoimmune disorders (McEwen, 2008).

In the literature, one of the main issues is to understand the nature of the increased vulnerability to physical and mental disorders in response to a negative early-life environment. It is known that maternal care shapes long-term environmental epigenetic programming, which establishes and sustains the phenotype of the offspring. Weaver et al. (2004) have shown that the development of the HPA axis in the offspring is influenced by the extent of maternal care *via* epigenetic mechanisms based on DNA methylation and histone acetylation. These mechanisms lie at the core of the programming that shapes the vulnerability of an individual to developing stress-related diseases, such as metabolic or neurodegenerative disorders, and determines the severity of such diseases (Nestler, 2014; Turecki and Meaney, 2016) (Fig. 2). "Epigenetics", from the Greek prefix "epi" literally means "above genetics", and refers to chemical changes in DNA and histones that do not change the genetic code but cause long-lasting and reversible modifications in gene expression that control cell differentiation during development and, more generally, cell adaptation to the external environment. Epigenetic changes include DNA methylation, post-translational modifications of histones (acetylation, methylation, phosphorylation and glycosylation), and production of non-coding RNA species (e.g. microRNAs). DNA methylation at CpG islands of gene promoters, a process catalyzed by DNA methyltransferases (DNMTs), usually leads to a long-lasting suppression of gene expression. The molecular processes leading to DNA demethylation are less well established and may involve retroviral restriction enzymes, such as APOBEC. Histone acetylation drives the opening of chromatin, resulting in the activation of gene expression, whereas deacetylation suppresses gene expression. Histone acetylation is catalyzed by histone acetyltransferases (e.g. p300), whereas deacetylation is catalyzed by histone deacetylases (HDACs), which form a large family of enzymes subdivided into four classes (Gräff et al., 2011). Histone deacetylation and methylation have been implicated in the pathophysiology of mood disorders and drug addiction (Nestler, 2014). Epigenetic changes are inherited mitotically in somatic cells (Martos et al., 2015), suggesting that environmental cues may have long-term consequences on the developing brain. Interestingly, epigenetic marks can be transmitted transgenerationally, and the "adaptive" phenotype may thus become dissociated from the initial environmental trigger, which can influence the progeny. Obviously, this could generate unexpected and unpredictable changes in the resilience to stress of the progeny. Thus, the epigenome is the key to interpreting how an individual will react to its environment and transmit the resulting phenotype to its progeny. It is worth noting that epigenetic processes are dynamic and reversible, as opposed to genetics, which is based on irreversible changes in DNA sequence.

This review will focus on the importance of the epigenetic programming triggered by early-life events on the developmental trajectory of the CNS, emphasizing the importance of postnatal events in the pathophysiology of mental disorders in adult life. In the