

A Brief Review on Epigenetic Aspects involved in Depression

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Abstract

It is known that external environmental or internal physiologic factors interact with an individual's genetic constitution to determine risk for depression throughout life. This can be possible through epigenetic mechanisms that lead to changes in gene expression – with transgenerational abilities - that do not involve a change in the DNA sequence. Here we briefly summarize the link between depressive disorders and epigenetics, considering stressful events as important triggers for these modifications. The increasing knowledge in this issue is relevant for updating and expanding comprehension in the molecular basis of this mood disorder.

Keywords: Depression; Epigenetics; Stress; Environmental factors

Abbreviations:

CNS: Central Nervous System; HPA: Hypothalamic-Pituitary-Adrenal; CRH: Corticotrophin Releasing Hormone; PVN: Paraventricular Nucleus; ACTH: Adrenocorticotrophic Hormone; GC: Glucocorticoid; MRs: Mineralocorticoid Receptors; BDNF: Brain Derived Neurotrophic Factor

Epigenetic aspects involved in depression

Growing evidences support the hypothesis that epigenetics is a key mechanism through which environmental exposures interact with our genetic constitution and this interaction is able to cause depression throughout life. The term epigenetics (“epi” means above in Greek) is used to denote transgenerational transmission of traits without a change in the nucleotide sequence of DNA [1-4]. It had emerged as a mechanism initiated by environmental cues and cellular events mediated by various cellular mechanisms that originate phenotypes during the development. However, recently, it has been postulated that these cellular modifications can be converted into alterations in chromatin structure - non related with DNA sequence alteration - that finally lead to expression or suppression of altered gene programs [5].

While the genome defines the potential genetic information, the epigenome defines which genes are actually expressed. This regulation over the gene expression without altering the sequence of the DNA is possible by epigenetic modifications including microRNAs (small RNA molecules that can negatively control their target gene expression posttranscriptionally), covalent modifications of histone proteins, mechanisms controlling higher order chromatin organization and DNA methylation. Among numerous epigenetic processes, DNA methylation is one of the major mechanisms studied in the context of early life adversities as a potential via to explain the long-term effects on gene transcription [3]. It is a stable mark that is important for diverse cellular processes [6]. Methyl group is added to the C5 position catalyzed by DNA methyltransferases (DNMTs) [7]. Considering all cytosines in the human genome, about 3% is methylated and proper cytosine methylation is required for cell differentiation, genetic

imprinting and suppression of repetitive elements. In the central nervous system, DNA methylation is a physiological process, relevant for normal brain development, differentiation and maintenance of function [8,9]. Indeed, during development, pluripotent stem cells undergo division and differentiate into different cell types that ultimately become different organs and tissues with specific patterns of gene expression [10].

Epigenetics refers to how both the external environment and internal physiologic environment can interact with the nuclear DNA of every single cell in the body, to alter how these cells function. This knowledge carries profound implications for how we live our lives or even how we comprehend the other. In mood and anxiety disorders, it is difficult to assume that there is a gene responsible for the depression or anxiety framework [11,12]. One inherits a susceptibility to these conditions through multiple different genes, but the genes alone do not cause the illnesses [13]. The genetic material within the nucleus of brain cells must first be influenced by factors that come from outside the brain, such as external environmental or influenced by physiologic factors that come from inside the body that can interact with these susceptibility genes to cause several psychiatric disorders [14].

Mood disorders including depression are at the most present psychiatric disorders in present society. It is described that 16% population is estimated to be affected by major depression once during their life time [15]. All symptoms of these mood disorders are collectively called ‘depressive syndrome’ and they are characterized by anxiety, feelings of guilt, long-lasting depressed mood and recurrent thoughts of death and suicide involving several brain areas and a large amount of neurotransmitters [16-18]. For instance, the presence of polymorphism in the serotonin transporter gene evidencing a “gene-by-environment interaction” involving stressful events has been associated with depression since the last decade. Interestingly, these reports suggest the contribution of epigenetics mechanisms in the genesis of this mood disorder, though “epigenetics” term was not clearly described by the authors [14,19,20]. However, it is worthy of note that nearly half these manifestations has genetic or epigenetic contribution and may involve the combination of multiple factors once a defect in a single gene generally is unable to induce the multifaceted symptoms of depression [21].

A substantial body of research using state-of-the-art interview measures of episodic life events has found higher levels of many stressors prior to the onset of major depressive episodes in patients compared to controls, and in community samples [22]. Though not all people who encounter a stressful life experience succumb to its depressogenic effect, most recent evidences strongly suggest that most episodes of major depression are preceded by stressful life events [23-26].

Stressful life events have been shown to alter stress susceptibility in subsequent generations. Studies of epigenetic mechanisms originated by some stressful event are revealing fundamentally new insight into the range of genes and biochemical pathways within specific brain regions. These affected areas are related with the appearance of depression and with the reversal of symptoms under antidepressant treatment [27-30]. In fact, all organisms are routinely under stressful events and changes in their environment that will affect their homeostasis. Stress responses arise from these challenges and include changes in both central and peripheral nervous system to restore the initial homeostasis [31,32]. The perception of a stressful event can activate the neural circuitry, in particular, the hypothalamic-pituitary-adrenal (HPA) axis. In response to an external or internal stressor, there is release of the corticotrophin release hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus. This release in turn elicits production and release of the adrenocorticotrophic hormone (ACTH) from the pituitary gland into the blood. Glucocorticoids (GCs) are finally produced by the adrenal cortex and released in the bloodstream (i.e. cortisol in primates) [33]. GCs bind to two types of receptors: the GC receptors (GRs) found throughout the brain and the mineralocorticoid receptors (MRs) found largely in the limbic system, particularly in the hippocampus [34,35]. Under basal conditions, the MRs are mainly occupied owing to their higher affinity compared with GRs. However, when levels of GCs increase during stress, higher occupancy of the lower affinity GCs can be observed, and a negative feedback signal is sent to decrease HPA activity and restore homeostasis [35]. However, if the GCs are released, they interact with their receptors, that act as 'ligand inducible transcription factors' [36] that can activate or repress gene transcription and thus alter gene expression.

It is described that early affective experiences will lead to individual differences in later stress responsivity. Experiments with rodents have demonstrated that licking behavior (LB) of mother is critical for shaping stress responsivity of adult offspring. Offspring born to mothers who exhibit high levels of licking behavior are less anxious in a novel environment and have an attenuated corticosterone response to stressful event compared with offspring of low-LB mothers [37]. These behavioral and physiological characteristics are related with expression of hippocampal glucocorticoid receptors (GRs), such that adult offspring of low-LB mothers have reduced levels of GRs compared with offspring of high-LB mothers [37]. This reduced level of GRs will compromise the negative feedback of cortisone in response to stress, maintaining the levels of this hormone high in the bloodstream.

Several studies have demonstrated associations between susceptibility for depression and changes in the HPA axis function that can occur at different levels. Dekker et al. reported that rs11119328, a polymorphism of the HSD1 gene, is associated with higher cortisol levels and greater susceptibility for depression [38]. The literature has consistently shown that maternal affection has long-lasting effects on the expression of NR3C1, the gene encoding for the GC receptor, with associated anxious- and/or depressive-like behaviors in animals and

humans. Seemingly, early repeated stress can impact this gene and this altered gene expression leads to altered susceptibility to subsequent stressors [39]. Male mouse pups subjected to maternal separation exhibit permanent increases in stress susceptibility and generate offspring that display the same enhanced stress susceptibility for next generations [40].

The internal and external factors that are interacting over the genetic material (epigenetics) within our brain cells to initiate the onset of an emotional disorder need to be more explored. In the brain, an important function of the DNA that makes up our genes and chromosomes is to code messenger RNA, which finally will induce the production of neuroprotective proteins. These protective proteins, for instance BDNF (Brain Derived Neurotrophic Factor), protect and support brain cell structure and function. It has been strikingly implicated in the genesis of depressive disorders [41-48]. The neurotrophin BDNF is a molecule extremely sensible to stress, and its expression or production is reduced in key brain regions of animal model of depression [49-51] and also in the blood of depressed patients [52-54]. In order to better understand the possible mechanisms underlying these changes, researchers have investigated the role of DNA methylation within BDNF promoter regions. The decrease of BDNF observed in depression may be associated with the reduction in hippocampal volume seen in depressed patients. Reduced levels of hippocampal BDNF are observed in both acute [55] and chronic [56] stress paradigms in animals. Antidepressant treatment in both humans and animals causes an increase in hippocampal BDNF, and antidepressant responses are abolished upon BDNF knockout, suggesting that this molecular adaptation is relevant for part of the symptomatology of depression [57-59].

Conclusion

Depressive disorder is a growing condition around the world and the increasing knowledge about several factors involved in its origin is highly relevant. Through epigenetic mechanisms, traumatic or stressful experiences in early stages of life predispose to greater susceptibility to depression in adulthood and future generations (Figure 1). These data demonstrate how our daily life and our experiences can deeply impact our health and our behavior for a long time.

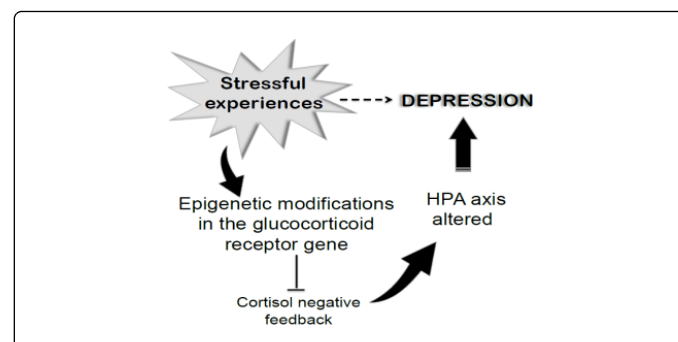


Figure 1: The scheme represents the possible way stressful events of life can lead to depression. Stressful experiences are able to cause methylation in the promoter region of the glucocorticoid receptor gene characterizing an epigenetic (over genetic) modification; then, the negative feedback by cortisol released by adrenal will be disrupted altering the hypothalamic-pituitary-adrenal (HPA) axis increasing the risk to develop depression.

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