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A Brief Review on Epigenetic Aspects involved in Depression

Catarine Lima Conti* **and Adriana Madeira Alvares da Silva-Conforti**

Department of Biology, Federal University of Espirito Santo, Alegre, ES, Brazil

***Corresponding author:** Catarine Lima Conti, Department of Biology, Federal University of Espirito Santo, Alegre, ES, Brazil, Tel: +55-27-3552-8903; Fax: +55-27-3552-8991; E-mail: catarineconti@hotmail.com

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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: Adrenocorticotropic 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 adrenocorticotropic 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 off- spring 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 neurothrophin 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.

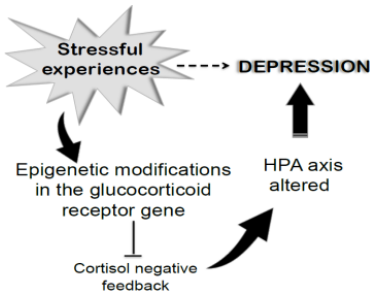

Figure 1: The scheme represents the possible way stressful events of life can lead to depression. Stressful experiences are able to cause methylation in the promoter region of the glucocorticoid receptor gene characterizing an epigenetic (over genetic) modification; then, the negative feedback by cortisol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

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References

1. Xin F, Susiarjo M, Bartolomei MS (2015) Multigenerational and transgenerational effects of endocrine disrupting chemicals: A role for altered epigenetic regulation? Semin Cell Dev Biol 43: 66-75.
2. Babenko O, Kovalchuk I, Metz GA (2015) Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev 48: 70-91.
3. Bale TL (2015) Epigenetic and transgenerational reprogramming of brain development. Nat Rev Neurosci 16: 332-344.
4. Nilsson EE, Skinner MK (2015) Environmentally induced epigenetic transgenerational inheritance of disease susceptibility. Transl Res 165: 12-17.
5. Bonasio R, Tu S, Reinberg D (2010) Molecular signals of epigenetic states. Science 330: 612-616.
6. Cedar H, Bergman Y (2012) Programming of DNA methylation patterns. Annu Rev Biochem 81: 97-117.
7. Bestor TH (2000) The DNA methyltransferases of mammals. Hum Mol Genet 9: 2395-2402.
8. Nafee TM, Farrell WE, Carroll WD, Fryer AA, Ismail KM (2008) Epigenetic control of fetal gene expression. BJOG 115: 158-168.
9. Bird A (2008) The methyl-CpG-binding protein MeCP2 and neurological disease. Biochem Soc Trans 36: 575-583.
10. Reik W (2007) Stability and flexibility of epigenetic gene regulation in mammalian development. Nature 447: 425-432.
11. Costello EJ, Pine CS, Hammen C, March PS, Plotsky PM, et al. (2002) Development and natural history of mood disorders. Biol Psychiatry 52: 529-542.
12. Monroe SM, Simons AD (1991) Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychol Bull 110: 406-425.
13. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, et al. (1995) Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 152: 833-842.
14. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, et al. (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301: 386-389.
15. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, et al. (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62: 593-602.
16. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, et al. (2002) Neurobiology of depression. Neuron 34: 13-25.
17. Treadway MT, Pizzagalli DA (2014) Imaging the pathophysiology of major depressive disorder - from localist models to circuit-based analysis. Biol Mood Anxiety Disord 4: 5.
18. Demic S, Cheng S (2014) Modeling the dynamics of disease states in depression. PLoS One 9: e110358.
19. Silberg J, Pickles A, Rutter M, Hewitt J, Simonoff E, et al. (1999) The influence of genetic factors and life stress on depression among adolescent girls. Arch Gen Psychiatry 56: 225-232.
20. Garnefski N, van Egmond M, Straatman A (1990) The influence of early and recent life stress on severity of depression. Acta Psychiatr Scand 81: 295-301.
21. Burmeister M (1999) Basic concepts in the study of diseases with complex genetics. Biol Psychiatry 45: 522-532.
22. Cohen BE, Edmondson D, Kronish IM (2015) State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens 28: 1295-1302.
23. Armour C, Contractor A, Elhai JD, Stringer M, Lyle G, et al. (2015) Identifying latent profiles of posttraumatic stress and major depression symptoms in Canadian veterans: Exploring differences across profiles in health related functioning. Psychiatry Res 228: 1-7.
24. Sawchuk, CN, Roy-Byrne P, Noonan C, Bogart A, Goldberg J, et al. (2015) The Association of Panic Disorder, Posttraumatic Stress Disorder, and Major Depression With Smoking in American Indians. Nicotine Tob Res 18: 259-66.
25. Slavich GM, Irwin MR (2014) From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull 140: 774-815.
26. Foland-Ross LC, Kircanski K, Gotlib IH (2014) Coping with having a depressed mother: the role of stress and coping in hypothalamic-pituitary-adrenal axis dysfunction in girls at familial risk for major depression. Dev Psychopathol 26: 1401-1409.
27. Bagot RC, Labonté B, Peña CJ, Nestler EJ (2014) Epigenetic signaling in psychiatric disorders: stress and depression. Dialogues Clin Neurosci 16: 281-295.
28. Golden SA, Christoffel DJ, Heshmati M, Hodes GE, Magida J, et al. (2013) Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. Nat Med 19: 337-344.
29. Moriam S, Sobhani ME (2013) Epigenetic effect of chronic stress on dopamine signaling and depression. Genet Epigenet 5: 11-16.
30. Mann JJ, Currier DM (2010) Stress, genetics and epigenetic effects on the neurobiology of suicidal behavior and depression. Eur Psychiatry 25: 268-271.
31. Swan CL, Sistonen L (2015) Cellular stress response cross talk maintains protein and energy homeostasis. EMBO J 34: 267-269.
32. Mao B, Gao Y, Bai Y, Yuan Z (2015) Hippo signaling in stress response and homeostasis maintenance. Acta Biochim Biophys Sin (Shanghai) 47: 2-9.
33. Ulrich-Lai YM, Herman JP (2009) Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10: 397-409.
34. Brunton PJ, Russell JA (2011) Neuroendocrine control of maternal stress responses and fetal programming by stress in pregnancy. Prog Neuropsychopharmacol Biol Psychiatry 35: 1178-1191.
35. De Kloet ER, Vreugdenhil E, Oitzl MS, Joëls M (1998) Brain corticosteroid receptor balance in health and disease. Endocr Rev 19: 269-301.
36. Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009) Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 10: 434-445.
37. Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, et al. (1997) Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science 277: 1659-1662.
38. Dekker MJ, Tiemeier H, Luijendijk HJ, Kuningas M, Hofman A, et al. (2012) The effect of common genetic variation in 11Î²-hydroxysteroid dehydrogenase type 1 on hypothalamic-pituitary-adrenal axis activity and incident depression. J Clin Endocrinol Metab 97: E233-237.
39. Booij L, Wang D, Lévesque ML, Tremblay RE, Szyf M (2013) Looking beyond the DNA sequence: the relevance of DNA methylation processes for the stress-diathesis model of depression. Philos Trans R Soc Lond B Biol Sci 368: 20120251.
40. Franklin TB, Russig H, Weiss IC, Gräff J, Linder N, et al. (2010) Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry 68: 408-415.
41. Golimbet VE, Volel' BA, Kopylov FIu, Dolzhikov AV, Korovaitseva GI, et al. (2015) [Anxiety and polymorphism Val66Met of BDNF gene predictors of depression severity in ischemic heart disease]. Kardiologiia 55: 9-13.
42. Li YJ, Xu M, Gao ZH, Wang YQ, Yue Z, et al. (2013) Alterations of serum levels of BDNF-related miRNAs in patients with depression. PLoS One 8: e63648.

43. Lee Y, Lim SW, Kim SY, Chung JW, Kim J, et al. (2013) Association between the BDNF Val66Met Polymorphism and Chronicity of Depression. Psychiatry Investig 10: 56-61.
44. Kalueff AV, Avgustinovich DF, Kudryavtseva NN, Murphy DL (2006) BDNF in anxiety and depression. Science 312: 1598-1599.
45. Pei Y, Smith AK, Wang Y, Pan Y, Yang J, et al. (2012) The brain-derived neurotrophic-factor (BDNF) val66met polymorphism is associated with geriatric depression: a meta-analysis. Am J Med Genet B Neuropsychiatr Genet 159B: 560-566.
46. Hashimoto K (2006) [Depression and BDNF]. Nihon Yakurigaku Zasshi 127: 201-204.
47. Groves JO (2007) Is it time to reassess the BDNF hypothesis of depression? Mol Psychiatry 12: 1079-1088.
48. Kerman IA (2012) New insights into BDNF signaling: relevance to major depression and antidepressant action. Am J Psychiatry 169: 1137-1140.
49. Elfving B, Plougmann PH, Müller HK, Mathé AA, Rosenberg R, et al. (2010) Inverse correlation of brain and blood BDNF levels in a genetic rat model of depression. Int J Neuropsychopharmacol 13: 563-572.
50. Molteni R, Cattaneo A, Calabrese F, Macchi F, Olivier JD, et al. (2010) Reduced function of the serotonin transporter is associated with decreased expression of BDNF in rodents as well as in humans. Neurobiol Dis 37: 747-755.
51. Qiao H, An SC, Ren W, Ma XM (2014) Progressive alterations of hippocampal CA3-CA1 synapses in an animal model of depression. Behav Brain Res 275: 191-200.
52. Vinberg M, Bukh JD, Bennike B, Kessing LV (2013) Are variations in whole blood BDNF level associated with the BDNF Val66Met polymorphism in patients with first episode depression? Psychiatry Res 210: 102-108.
53. Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, et al. (2013) Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology 38: 377-385.
54. Molendijk ML, Spinhoven P, Polak M, Bus BA, Penninx BW, et al. (2014) Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484). Mol Psychiatry 19: 791-800.
55. Barrientos RM, Sprunger DB, Campeau S, Higgins EA, Watkins LR, et al. (2003) Brain-derived neurotrophic factor mRNA downregulation produced by social isolation is blocked by intrahippocampal interleukin-1 receptor antagonist. Neuroscience 121: 847-853.
56. Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 15: 7539-7547.
57. Coppell AL, Pei Q, Zetterström TS (2003) Bi-phasic change in BDNF gene expression following antidepressant drug treatment. Neuropharmacology 44: 903-910.
58. Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, et al. (2005) Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57: 1068-1072.
59. Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, et al. (2007) Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. Biol Psychiatry 61: 187-197.