Epigenetic mechanisms of stress and depression

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Summary

The etiopathogenesis of mood disorders is not fully understood. Among different possible causes, the involvement of genetic factors is taken into account. The manifestation of clinical symptoms cannot be assigned to a single gene mutation, thus the epigenetic association in the origin of those illnesses is suggested. The epigenetic regulation of gene expression, evoked by environmental stimuli rests upon producing persistent changes in its expression. There are several epigenetic mechanisms that change the accessibility of DNA to transcriptional factors such as acetylation/deacetylation and methylation/demethylation of the histones or an introduction of methyl groups to the cytosine of the DNA. Early and adult stress exposure is believed to have an association with epigenetic alteration of genes involved in mood regulation, for example, genes involved in the regulation of the HPA axis activity (NR3C1) or responsible for the serotonergic neurotransmission (SLC6A4). The data coming from epigenetic research indicate that mechanism of action of some antidepressants such as fluoxetine and escitalopram or mood stabilizers such as valproic acid, is at least partly associated with the epigenetic processes. Moreover, the epigenetic changes in some genes are believed to be promising diagnostic tools. These changes may help to identify the groups of patients particularly vulnerable to mental disorders and may have potential utility as biomarkers facilitating diagnosis and treatment of psychiatric disorders. Taken together, the epigenetic research will reveal neurobiological underpinnings of affective disorders and may open a new pharmacological avenue for patients suffering from mood disorders and other mental disorders.

Key words: epigenetics, mood disorders, epigenetic modification as a therapeutic

Introduction

Affective disorders such as anxiety disorders, depression or trauma-related disorders are among the most common mental illnesses, affecting 220, 322 and 44 million people in the world respectively [1]. Despite significant differences in their
clinical presentation, the pathogenesis of those groups of mental illnesses is highly interrelated. It is postulated that the changes in the serotonergic, noradrenergic and glutamatergic transmission as well as alterations in the hypothalamic-pituitary-adrenal (HPA) axis activity may be responsible for the clinical presentation. It is believed that disturbances in neurotransmission may be evoked by many factors, including genetic factors. However, so far, despite the application of human genome-wide association studies (GWAS) in clinical studies, no single loci that is directly linked to anxiety and/or depressive disorders has been identified [2]. Nevertheless, the interaction between specific genes and external factors, such as adult or early life stress, has been linked with increased vulnerability to anxiety and depression. Taking into consideration that etiology of mental illnesses has not been assigned to a single gene mutation, epigenetic mechanisms are believed to take part in the origins of psychiatric disorders [3].

Epigenetics refers to pathways that could modulate gene expression and change the phenotype of the cells. The Greek prefix ‘epi’ means ‘above’ and indicates that epigenetics is not associated with alterations in the sequence of the DNA but is linked to acquired modification of chromatin and/or nucleotides instead. It is also postulated to be a potential mechanism by which environmental factors can create persistent changes in the genes expression and can increase the vulnerability to illnesses, e.g., stress-related psychiatric disorders [3]. The epigenetic modifications are characterized by unique properties. On the one hand, it is believed that epigenetic pattern could be persistent and heritable. On the other hand, it has been shown that several antidepressants and mood stabilizers that are used in the treatment of psychiatric disorders, like valproate, amitriptyline, fluoxetine, escitalopram, apart from the different pharmacodynamics properties, exert their therapeutic effect at least in part via epigenetic mechanisms [4].

In this review, we will attempt to discuss the influence of early adverse experiences and severe adult stress on epigenetic alterations that are associated with the occurrence of anxiety or depressive disorders, with special attention paid to components of the HPA axis, serotonergic and dopaminergic systems. We will also shortly describe the epigenetic-like mechanisms of antidepressants and mood stabilizers currently used in the treatment.

**Overview of epigenetic mechanisms**

Chromatin remodeling

Chromatin consists of DNA, histones and non-histone proteins and, by condensing a DNA strand into higher order structures, serves as an organizer of the genome. The basic unit of chromatin is nucleosome. It includes about 146 base pairs of DNA coiled on a core histone octamer (that is created by duplicates of histones: H2A, H2B, H3, and H4). H1 is a fifth histone molecule which decreases the distance between the nucleosomes and facilitates the creation of a DNA compact structure [5]. Chromatin
remodeling plays a pivotal role in keeping the balance between effective storage and functional utility of the DNA. Condensed chromatin is a physical barrier for processes associated with gene expression and is perceived as a transcriptionally inactive form. Conversely, uncondensed chromatin is in ‘open state’ which allows individual genes to be transcribed. There are several epigenetic mechanisms that affect compact chromatin structure and change the accessibility of DNA to transcriptional factors such as acetylation/deacetylation and methylation/demethylation of the histones.

Histone acetylation is the introduction of an acetyl group to the histone (N-terminal tails) that facilitates transcription through neutralization of their positive charge and in turn disrupts interaction with the negatively charged DNA and ultimately leads to relaxation of the chromatin structure and activation of transcription processes [6] (Figure 1). Histone acetylation is catalyzed by histone acetyltransferases (HATs). Deacetylation is the opposite reaction, associated with the removal of acetyl residues and decreased transcriptional activity that is catalyzed by histone deacetylases (HDACs) [7]. The appropriate balance between HATs and HDACs is pivotal for proper histone core function and is believed to contribute to the regulation of transcription [7]. Important role in the regulation of HDACs activity plays a well-established, strong gene repressor – repressor element-1 silencing transcription factor (REST). REST binds to repressor element-1 motif (RE1 motif) of target genes and owing to intermediate proteins recruiting HDAC1 and HDAC2 leads to gene silencing [8].

Other form of epigenetic modifications, mediated by histone methyltransferases (HMTs) is methylation of histones, which add methyl groups to specific lysine residues of histones. Histone methylation creates specific docking sites that enable recruitment of transcriptional regulator to the loci of the specific genes. Histone methylation may be associated either with gene silencing or gene activation. The example of activating methylation is the methylation of K4 residue in histone 3-H3K4 and repressing are methylations of histone 3 in the position of K9 (H3K9) or K27 (H3K27) (Figure 1). The methylation of histone lysine residue is believed to be the most stable modification of histone, however, the discovery of histone demethylases (HDMs) indicates that there is a possibility to reverse this alteration [9].

DNA methylation

The next methylation-related epigenetic mechanism is associated with an introduction of methyl groups to the cytosine of the DNA in a specific cytosine-phosphate-guanine rich region (CpG). This reaction is catalyzed by DNA methyltransferases (DNMTs) and is thought to repress gene transcription due to the prevention of recognition by activated transcription factors (Figure 1). DNA methylation was initially supposed to be irreversible. ‘Passive’ demethylation, when methyl residues were lost after replication in the absence of DNA methyltransferases, was thought to be the only way of demethylation. However, in in vitro study, it was demonstrated that the DNA
demethylase can demethylate CpG sites as well as fully methylated and hemimethylated DNA.

The role of the non-coding RNA in the regulation of epigenetic mechanisms

Non-coding RNA (ncRNA) refers to nucleotide molecules that are not translated to protein but possess functional role in the regulation of translation. NcRNAs are divided into two major groups based on their size, i.e., small ncRNAs (shorter than 200 nucleotides) and long ncRNAs (longer than 200 nucleotides) [10]. The most studied ones are small micro RNAs (miRNAs). They bind to complementary regions of mRNA and regulate translation, mostly by repressing synthesis of the protein due to enzymatic degradation of the mRNA or by acting as a steric hindrance for translational factors [11]. miRNA are important regulators of enzymes controlling epigenetic alteration, i.e., DNMTs and HDACs. A number of nervous system miRNAs may be regulated by REST [12]. Furthermore, it has been found that some miRNAs are able

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**Figure 1.** The schematic presentation of the involvement of epigenetic mechanisms in the regulation of chromatin remodeling processes: H3K9, H3K27 – the examples of histone methylation linked with gene repression; H3K4 – the example of histone methylation linked with gene activation; Me – methylation of the DNA cytosines; Ac – histone acetylation
Epigenetic mechanisms of stress and depression

Epigenetic mechanisms of early childhood trauma and adult stress

The epigenetics of stress

Early life adversities, such as parental deprivation, violence either physical or sexual are linked with greater vulnerability to mood and anxiety disorders in later life [16, 17]. Childhood and adult adverse experience may influence biological systems activity through epigenetic mechanisms [18]. It is clearly proved that traumatic events can modulate the activity of the HPA axis. An increase in secretion of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) leads to release of glucocorticoids. Activated glucocorticoid receptors (GR) translocate to the nucleus and regulate the transcription of many genes, including those involved in epigenetic processes. Moreover, stress events could influence epigenetic mechanisms by activation of transcription factors, e.g., cAMP response element binding protein (CREB), REST, Fos, Jun family proteins [19].

The effect of early life adversities on epigenetic modification

Early life unfavorable factors are associated with greater susceptibility to mood, anxiety and trauma-related disorders in adulthood [16, 17]. Furthermore, the illness in these patients with early adverse history is usually characterized by earlier onset, longer duration, increased severity as well as a higher risk of resistance to pharmacological treatment [20]. This greater susceptibility is believed to be evoked by the changes in the HPA activity. Early life adversities may evoke epigenetic modifications of the HPA axis that in turn may not work properly in response to environmental stressors. In depressed patients who experienced early sexual abuse, an increased methylation of GR gene promoter – NR3C1, was observed [21]. Severity of maltreatments (duration, frequency, number, and the nature of the abuse) positively correlated with the level of NR3C1 promoter methylation [21]. Interestingly, an increase in NR3C1 methylation was also observed in healthy adults with disruption of parental ties and child maltreatment in a medical history. Similarly, in suicide completers with a history of maternal deprivation, increased cytosine methylation of the NR3C1 gene promoter was noted [16]. Moreover, in population with increased NR3C1 methylation, a diminished cortisol response in the dexamethasone suppression test and the CRF stimulation test was found [22]. It is hypothesized that
the altered expression of GR resulting may predispose to increased susceptibility to depression, anxiety and PTSD [21, 22].

The epigenetic alterations refer to genes whose protein products are involved in the regulation of the HPA axis activity. Increased demethylation of the FKBP5 gene that encoded FK506 binding protein, an important modulator of GR, was observed in patients with early adverse history [23]. FK506 binding protein has been found to decrease GR ligand binding and diminish translocation of the receptor complex to the nucleus. Bearing in mind that GR mediates the negative feedback response, invalid function of this protein may lead to dysregulation of the HPA axis and could have long-term consequences [23]. These findings suggest that the early life traumas may persistently influence the HPA axis through epigenetic modifications of human GR-related genes.

Moreover, the hyperactivation of the HPA axis evoked by early life adversity is suggested to be one of the suicide causes [24]. For example, increased methylation of GR1B and 1C variants in the hippocampus of suicides with history of abuse, compared to those without adverse early life experience, was observed [25]. Furthermore, increased methylation of GR receptor variants may contribute to the dysregulation of negative feedback loop in stress axis (HPA).

Another study carried out in 85 healthy people assessed the relationship between the methylation of gene encoding KIT tyrosine kinase ligand (KITLG) and cortisol response to stress stimuli. It was shown that KITLG methylation is responsible for the relationship between the occurrence of traumatic experiences in childhood and cortisol levels in response to stress [26]. The results of the analysis indicate that disorders of the HPA axis function leading to a changed reaction to stress stimuli may result from epigenetic changes caused by childhood trauma.

In another study, the gene methylation status was compared between males with and without childhood abuse history using a GWAS (the promoter methylation of over 20,000 genes and 489 microRNAs was assessed). It was found that almost 1,000 gene promoters were differentially methylated (311 hypermethylated and 686 hypomethylated) in association with childhood abuse. These results indicate that childhood abuse may cause profound epigenetic changes [27].

It is worth noting that early life adversities induce long-lasting changes not only in the HPA axis function but also could influence the serotonergic system, the malfunction of which may contribute to mood and anxiety disorders [28]. In the area of interest is a serotonin transporter gene (SLC6A4), a key regulator of serotonergic neurotransmission. In patients with a history of child abuse, increased methylation of the SLC6A4 gene or SLC6A4 promoter was reported [28, 29]. The methylation status correlated with worse clinical presentation and with the presence of early life adversities [28]. In twins study, higher SLC6A4 gene DNA methylation at age 5, 7 and 10 was reported in bullied twins compared to not-bullied ones. Furthermore, children with higher
methylation of SLC6A4 had a blunted cortisol response to stress [30]. This suggests that child abuse, through the epigenetic alteration of serotonin transporter gene, may have lasting effects on neurotransmission in later life.

The impact of adult stress on epigenetic alteration

Human epigenetic research in adults is limited and comes from PTSD cases. Epigenetic modifications after adult stress involve mostly the HPA system regulators. Decreased methylation of the SKA2 gene (its protein product is involved in the transport of GR into the nucleus) in the military personnel deployed to Afghanistan was associated with elevated susceptibility to PTSD after deployment. The exposure to stress by itself, however, caused an increase in the methylation of the SKA2 gene [31]. It has been shown that increased SKA2 methylation is associated with greater PTSD severity in Afghanistan veterans [32].

In adults, similarly to children, the epigenetic alterations of the genes associated with the regulation of the monoaminergic system activity are observed. Serotonin receptor 3A gene promoter (HTR3A) was found to be differentially methylated in women with PTSD caused by interpersonal violence exposure. Lower percentage of methylation was observed in promoter region 2 and 3 and higher percentage of methylation was noted in other 4 and 5 promoter regions. Furthermore, decreased methylation of 2 and 3 regions was linked with lifetime violence exposure and severity [33]. Moreover, it was demonstrated that changes in methylation of promoter of HTR3A has consequences for the proper function of medial prefrontal cortex, which is a structure engaged in the PTSD pathogenesis [33].

These findings were confirmed by a study that assessed the degree of methylation of the 5-HT3A receptor gene in patients with bipolar disorder, borderline personality and attention deficit hyperactivity disorder. It was demonstrated that patients with a higher symptom severity have a traumatic childhood history and accompanying epigenetic changes in the form of increased methylation of 5-HT3A receptor gene [34].

The next gene of increased vulnerability to PTSD after its epigenetic modification was found to be the dopamine transporter (SLC6A3-DAT1). Elevated status of SLC6A3 methylation was associated with increased risk of PTSD, but only in conjunction with high methylation at specific locus of the promoter (cg13202751) [35]. It is suggested that increased methylation status of the SLC6A3 gene promoter may be associated with decreased expression of the dopamine transporter and increased level of dopamine in the synaptic cleft. The obtained results are in agreement with the previous works, where the elevated plasma and urinary levels of dopamine in patients with PTSD were observed [35].

These data indicate that a single common epigenetic cause of mood disorders and depression has not yet been identified. It seems that the increased risk of depression as a consequence of exposure to stress stimuli may result from the strong influence
of stress on the activity of many neurotransmitter systems and the HPA axis, which causes permanent changes in their activity [36]. Moreover, exposure to stress during the developmental period may cause neuroplasticity disorders, which in turn may lead to changes in the development of brain structures such as: orbito-frontal cortex, prefrontal cortex or limbic system, whose proper function is crucial in mood regulation. It seems, therefore, that the pathogenesis of depression, although still not fully explained, may be related also to epigenetic mechanisms.

**Epigenetic mechanisms and treatment of depression and bipolar disorder**

**Epigenetic changes and antidepressants**

An increasing amount of clinical data indicates that the analysis of epigenetic changes in patients with mental disorders may be not only a marker of clinical improvement, but also a predictor of response to pharmacological treatment. The most promising epigenetic markers include the methylation of the SLC6A4 gene promoter and the monitoring of the peripheral level of BDNF, which is directly related to the methylation level of its gene.

The clinical data suggest that hypomethylation of the SLC6A4 gene promoter was linked to impaired response to escitalopram [37]. It is believed that insufficient response to treatment could be elicited by increased expression of serotonin transporters and consequently a decrease in serotonin availability in the synaptic cleft. Okada et al. [4] found that initially increased methylation level of the SLC6A4 gene promoter predicted better therapeutic responses of different antidepressants (paroxetine, fluvoxamine or milnacipran). Therefore, methylation status of SLC6A4 may have a predictive value for effective antidepressant treatment.

Other important element is brain derived neurotrophic factor (BDNF), which has been recognized as one of the most important mediators of neuroplasticity in stress-related disorders [38, 39]. In untreated depressed patients, plasma BDNF concentration was decreased [39, 40]. Furthermore, it has been found that relapsed depressed patients had much lower BDNF plasma concentrations than during the illness onset [41]. Several studies (preclinical and clinical) have reported that decrease in BDNF level (central and peripheral) is a consequence of higher methylation of BDNF gene promoter. Therefore, the methylation of BDNF gene is postulated to be a possible diagnostic marker of mood disorders. It is worth noting that effective antidepressant treatment increases plasma BDNF [40, 42]. It has been found that absence of plasma BDNF increase within the first week of treatment may predict resistance to antidepressants [41]. The expression of BDNF mRNA was increased in brains of patients with a history of antidepressant treatment, whereas in non-treated patients it was decreased. Furthermore, treated patients had lower level of repressive histone methylation H3K27me3 in BDNF promoter [43]. In depressed patients, increased BDNF mRNA in treatment
responders was observed. This effect correlated with a decrease in repressive histone H3K27 methylation. Furthermore, repressive methylation negatively correlated with changes in depression severity [44].

Histone deacetylase inhibitors

It is suggested that the use of HDACs inhibitors (HDACsI) may became a novel strategy treatment for depression and other psychiatric disorders. HDACsI are natural or synthetic small molecules that can inhibit activity of HDACs and influence chromatin availability for transcription factors. Currently available HDACsI are divided into four groups: (1) short chain fatty acids (e.g., sodium butyrate, phenylbutyrate, valproate, entinostat – MS-275); (2) hydroxamic acids (e.g., trichostatin A); (3) epoxyketones (trapoxin); and (4) beznamides [45].

Almost all data regarding the HDACsI mechanisms derives from animal studies. The HDACsI presented antidepressant-like activity in different animal models of stress and depression. For example, administration of sodium valproate, which besides other mechanisms is the HDACsI, abolishes the anxiety and depressive-like behaviors in animals. Furthermore, it is able to reverse changes in the H3, H4 and HDAC5 expression caused by stress [46]. Entinostat (MS-275), another HDACsI, induces antidepressant-like behavior in mice, such as reduced immobility time in forced swim test (FST) and tail suspension test (TST) [47].

Another first class HDACsI, sodium butyrate, exerts its antidepressant-like behavior through causing short-lasting histone hyperacetylation and increasing BDNF mRNA [48, 49]. In chronic stress study, the mechanism of sodium butyrate action was also associated with increased histone H4 and H3 acetylation and normalized level of HDAC2 [49]. Sodium butyrate combined with fluoxetine potentiates its effects, decreasing immobility scores in TST [48]. The effect was limited when the drugs were administrated separately, which reveals advantages of using an antidepressant with HDACsI co-treatment [48].

In preclinical study, imipramine reversed behavioral and neurobiological changes caused by predator exposure and FST stress [50, 51]. After imipramine treatment the levels of HDAC5 and HDAC2 returned to the control values [50, 52]. Limited human study revealed that histone modification may be one of antidepressants mechanisms. In post-mortem brains of depressed patients treated with fluoxetine, reduced global histone H3 acetylation at the CaMK2A (calcium-/calmodulin-dependent protein kinase II alpha; pivotal for synaptic plasticity) gene promoter in the nucleus accumbens (NAc) was observed [53]. These epigenetic changes were accompanied by decreased CaMK2A mRNA level and increased repressive histone dimethylation – H3K9. Authors have linked the antidepressant mechanism of action with downregulation of CaMK2a in mouse model and extrapolated this conclusion to human studies, suggesting a new mechanism of fluoxetine [53].
Different HDACsI with variable pharmacokinetics and affinity to HDACs are being tested for their antidepressant potency in animal model of depression. Similar alterations in histones and histone-related enzymes have been found in human brain and in animal model. Consequently, it is proposed to use HDACsI particularly in the treatment of resistant depression [54]. At present, however, only valproic acid is commonly used in the treatment of bipolar disorder [55]. Other HDACsI may have different unknown targets and unspecific side effects [56]. Nevertheless, the histone modification may become a promising strategy as a target for treatment of affective disorders.

Epigenetic markers facilitating diagnosis and treatment monitoring

The diagnosis of many psychiatric disorders is based on the assessment of patients’ symptoms. At present, beside the dexamethasone suppression test there is no objective laboratory test which could improve the diagnosis of affective disorders.

It is postulated that analysis of methylation in the peripheral blood cells may serve as a marker of some symptoms of psychiatric disorders. Among the various epigenetic changes that are considered as potential, peripheral biomarkers for mental illness, the most promising are: methylation of the BDNF gene; SKA2 gene methylation; NR3C1 gene methylation; SLC6A4 gene methylation; FKBP5 gene methylation. The assessment of methylation of BDNF gene promoter has been found as a useful biomarker because depressed patients presented a significant increase in methylation of BDNF gene promoter in peripheral blood. It was also shown that the higher level of BDNF and SKA2 genes methylation correlates with suicidal thoughts in depressed patients [57, 58]. Similarly, the NR3C3 gene was indicated as a marker of PTSD development in war veterans; lower methylation correlated with greater susceptibility to the illness development [59].

Because antidepressants may have the potential to reverse epigenetic alterations, methylation status of some genes has been proposed to be an indicator of response to the treatment of stress-related disorders. In patients with depression, poorer methylation of the SLC6A4 gene predicted impaired antidepressant treatment efficiency [37]. In PTSD patients, methylation of the NR3C1 gene assessed at pre-treatment, predicted treatment outcome, but it did not differ in responders compared to non-responders. Conversely, methylation of the FKBP5 gene was not able to predict treatment response at pre-treatment, however, decreased with recovery [59].

Besides the methylation status of particular genes, the histone modification machinery status is also considered as a marker of depression. A higher level of mRNA for HDAC2 and HDAC5 has been found in peripheral leukocytes of patients with depression in depressive than in remitted state [60, 61]. Moreover, in patients with bipolar disorder, increased level of HDAC4 mRNA was found compared to the control group [61]. On the other hand, mRNA for HDAC6 and HDAC8 were decreased in depressed patients regardless of depression state. A relatively new concept in the
biomarker searching is the analysis of the mRNA level for sirtuins 1, 2 and 6 [62]. The list of potential biomarkers are presented in Table 1. Nevertheless, despite intensive studies, the identification of useful biomarker in clinical practice in psychiatry is still not concluded and requires further studies.

<table>
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<tr>
<th>Epigenetic modification</th>
<th>Potential marker</th>
<th>Epigenetic pattern</th>
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<td>Lower methylation</td>
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<td>Prediction of antidepressant treatment response</td>
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<td>BDNF</td>
<td>Increased methylation</td>
<td>Peripheral blood leukocytes</td>
<td>Marker of depression</td>
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<td>BDNF</td>
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<td>HDAC8</td>
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Conclusions

In the recent years, a meaningful role of epigenetic mechanisms in etiology of psychiatric disorders is postulated. Epigenetic changes may influence availability of many proteins (e.g., transporters, receptors) through altered transcriptional and translational processes. This may in turn have impact on neurotransmission and contribute to the manifestation of clinical symptoms of mental illnesses. Some antidepressants and mood stabilizers used in psychiatric treatment are associated with the influence on the epigenetic mechanisms. Fluoxetine or escitalopram can be examples of antidepressants with such potential. In addition, HDACsI, valproic acid, is commonly used in bipolar disorder treatment. Other HDACsI have also been recently recognized as promising antidepressants, which was demonstrated in numerous animal models. Unfortunately, due to not fully understood mechanism of action, none of these HDACsI has found the application in the
treatment of psychiatric disorders. Further studies on epigenetic mechanisms that expand our understanding of engagement of epigenetic mechanisms in the etiopathogenesis of mental illnesses are necessary to create new therapeutic opportunities in the near future.

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