Epigenetics and depression: current challenges and new therapeutic options

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Purpose of review

Epigenetics comprises heritable but concurrent variable modifications of genomic DNA defining gene expression. The aim of this publication is to review the field of epigenetics in depression. Within this scope, we outline potential therapeutic options evolving in this young field of psychiatric research.

Recent findings

Recently published papers show that epigenetic mechanisms like histone modifications and DNA methylation affect diverse pathways leading to depression-like behaviors in animal models. Adverse alterations of gene expression profiles, including glucocorticoid receptor or brain-derived neurotrophic factor, were shown to be inducible by early life stress and reversible by epigenetic drugs. Postmortem studies revealed epigenetic changes in the frontal cortex of depressed suicide victims. There exists profound evidence for histone deacetylase inhibitors to be a novel line of effective antidepressants via counteracting previously acquired adverse epigenetic marks.

Summary

Because of the complex causal factors leading to depression, epigenetics is of considerable interest for the understanding of early life stress in depression. The current research regarding epigenetic pharmaceuticals is promising and deserves further attention in depression and psychiatry in general, and may strike out new ways towards individually tailored therapies.

Keywords

depression, DNA methylation, epigenetics, homocysteine, treatment

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Introduction

The Global Burden of Disease Study predicted major depression to become the second leading cause of disability until 2020, and the lifetime prevalence was estimated to be approximately 17% in the United States, with similar rates being reported on the European level [1]. Major depressive disorder (MDD) displays a variety of psychopathological symptoms and diverse clinical manifestations with at least depressed mood and/or a loss of interest or pleasure as core symptoms. Additional symptoms encompass changes regarding weight, appetite, sleep, psychomotor and thinking disturbances with excessive worrying, guilt, and possibly suicidal ideation [2]. Although there exist numerous hints toward a neurobiological understanding of depression [3] and environmental effects such as adverse life events merged into a model of gene–environment interactions (G × E), they still do not provide the required answers concerning individual risk assessment, history of disease, and pharmacological or psychological treatment options [4]. Therefore, the epigenetic perspective may add new insights into the G × E findings that were shown to be applicable to depression. Caspi *et al.* [5] were the first to suggest that it might be applicable to depression. They showed that childhood maltreatment and later stressful life events predicted the onset of depressive symptoms only in genetically predisposed individuals with a short (s) allele of the serotonin transporter promoter polymorphism (5-HTTLPR), while the long allele carriers were more resilient to depression after adverse life events. Moreover, incidences of childhood maltreatment were found to be predictive for adult depression only among s allele carriers.

In rat, Weaver *et al.* [6] first showed that differences in maternal care can lead to less fearful offspring raised by well-caring mothers and more fearful offspring raised by low tactile stimulating mothers. These distinct behaviors can be traced back to epigenomic changes in the hippocampal glucocorticoid receptor gene, through different histone acetylation and DNA methylation, which were

reversible by cross-fostering or by the infusion of a histone deacetylase (HDAC) inhibitor (HDACi). This first proof of behavioral programming of the epigenome due to early life stress was shown to be reversible not only during the first weeks of life, but also in adulthood, through the application of the amino acid methionine, which serves as a donor for methyl groups in DNA methylation [7]. Thus, epigenetic mechanisms are not only essential for normal cellular development, differentiation, and a nonmutagenic tissue-specific translation of the genome, but also may serve as a novel and promising approach to psychiatric diseases.

The present review focuses on the latest developments in the field of epigenetics with respect to depression. Due to only a limited number of articles published within the last 18 months, we also refer to earlier pioneering publications regarding this topic for further reading. The latest literature of special interest in the field of epigenetics and depression comprises nine papers published between February 2009 and April 2010. They are briefly summarized and discussed in the respective context of a neurobiological approach to depression, early life stress and abuse research, brain-derived neurotrophic factor (BDNF), homocysteine and potential epigenetic therapy options.

Mechanisms of epigenetic regulation in the genome

Epigenetics comprises mechanisms of gene expression modifications that do not alter the genomic code itself. Therefore, these mechanisms are 'epi', which means alongside the coding sequence of the genome consisting of the four nucleobases adenine, guanine, thymine, and cytosine. Besides the sequence of nucleobases in the genome, gene expression in different types of cells and tissues is modulated by two major mechanisms that are currently crucial for the understanding of epigenetics in psychiatric disorders. The first is 'DNA methylation', which means that the expression of a gene is silenced through the modification of the gene's promoter region, which initiates the transcription of the adjacent gene. The methylation of promoter cytosines in repetitive dinucleotide sequences of cytosines and guanines (CpG) allows further methyl-CpG binding proteins, like methyl CpG-binding protein 2 (MeCP2), to bind and repress expression of the gene [8]. Secondly, epigenetic marking is achieved through physical changes in the formation of tightly packed DNA, which is normally folded into nucleosomes around proteins, so-called histones. These can be modified through either acetylation, methylation, or phosphorylation at their NH_2-termini, which may lead to an unfolding of the DNA/histone unit. This formation allows the transcription of the genomic DNA and subsequent protein expression. The state of packaging of DNA through histones and therefore the accessibility of DNA in different tissues is heritable and known as the 'Histone code' [9]. Although epigenetic marking is heritable, it is not stable throughout the lifespan, and interactions between enzymes mediating either DNA methylation, DNA methyltransferases (DNMTs), or histone changes (HDACs) exist [10].

Epigenomic stress memory through DNA methylation

The early findings of maternal behavior determining the stress response in rats via epigenomic programming of the glucocorticoid receptor gene in the hippocampus was recently also shown to be true for humans. McGowan *et al.* from the Meaney group [11••] studied methylations of the neuron-specific glucocorticoid receptor (NR3C1) promoter in hippocampi from suicide victims with and without a history of sexual and nonsexual child abuse compared with control subjects who had died from causes other than suicide and had not been abused as children. The level of DNA methylation at the NR3C1 promoter sites was significantly higher in the hippocampi of abused suicides compared with nonabused and control subjects. Glucocorticoid receptor expression measured by the amount of mRNA was also found to be reduced in hippocampi of abused suicide victims compared with nonabused and control subjects. Due to previous findings showing an association of decreased hippocampal glucocorticoid receptor expression with depression [12] and the heritability of the epigenome, the authors interpreted their findings as an indicator for a possible parent-to-offspring transmission of depression via an epigenetic modification of stress response.

A recent study conducted by Murgatroyd *et al.* [13••] investigated early life stress and DNA methylation of the arginine vasopressin (*AVP*) gene enhancer region and its consequences regarding MeCP2 occupancy in the hypothalamic paraventricular nucleus. The separation of newborn mice pups from their mothers for the first 10 postnatal days resulted in a persistent upregulation of AVP due to hypomethylation of the *AVP* gene enhancer region. As AVP increases the release of corticotropin-releasing hormone (CRH) inducing a sustained hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, early stressed mice showed deficits in the forced-swim test and in step-down avoidance learning tasks. These behavioral and cognitive deficits were partly reversible by an AVP receptor antagonist. A further interesting finding was that the hypomethylation of the *AVP* gene enhancer region remained unchanged despite intermediate behavioral changes due to short-term AVP receptor blockade. Furthermore, MeCP2 as a possible connection between different epigenetic mechanisms is

believed to restore previously stress-affected DNA hypomethylation through recruiting DNMTs. Thereby, MeCP2 might help to protect DNA methylation patterns over time [14•].

A recent study conducted by Daniels *et al.* [15•] found differences in plasma corticosterone and hippocampal nerve growth factor levels in a rat pup separation model but no changes in methylation patterns of the exon 1_7 glucocorticoid receptor promoter in the hippocampus. Even without epigenetic alterations, behavioral differences between early stressed and control rats were observed shortly after the completion of separation in an open field test.

Brain-derived neurotrophic factor

The transcription of the *BDNF* gene was previously shown to be regulated by epigenetic modifications involving DNA methylation, MeCP2 and chromatin remodeling [16]. According to the neurotrophin hypothesis of depression, BDNF expression is decreased in depression and stress states. This hypothesis could be tested on the epigenomic level in a mouse chronic defeat stress model. It was shown that the down-regulation of BDNF messenger RNA (mRNA) was accompanied by long-lasting histone dimethylation (leading to gene suppression) in the hippocampus [17].

Recently, Roth *et al.* [18••] reported *BDNF* gene silencing in the prefrontal cortex (PFC) of early maltreated rat pups due to DNA methylation processes that lasted into adulthood (postnatal day 90). Furthermore, offspring derived from maltreated females exhibited the same abusive behaviors as their mothers and greater DNA methylation in the PFC and hippocampus, indicating a generation-to-generation transmission of previously acquired DNA methylation patterns. Interestingly, further cross-fostering experiments showed no significant change in DNA methylation patterns, in the direction of either maltreated offspring to normally caring mothers or normally treated offspring to maltreating mothers. Thus, the changes in DNA methylation acquired through maltreating experiences are not easy to reverse by switching to a well-caring environment. Maternal maltreatment in this study comprised a relatively high proportion of rough handling like stepping on, dropping, dragging and actively avoiding the offspring.

Epigenetics and suicide

In addition to findings of a stress-induced downregulation of BDNF at the epigenetic level, one of its mediating receptors in astrocytes, TrkB.T1 (a truncated splice variant of tropomyosin-related kinase B), was recently found to be epigenetically reduced in the frontal cortex of suicide completers [19]. Although six out of ten suicide completers with an epigenetic down-regulation of TrkB.T1 suffered from MDD, further analyses found no association of MDD or substance abuse with hypermethylation of the TrkB.T1 promoter. MDD was also present in 10 out of 18 subjects with no apparent DNA methylation changes at the TrkB.T1 promoter.

A study conducted by the McGill Group for Suicide Studies [20] was designed to investigate the expression of an RNA-binding protein in oligodendrocytes (QKI) that is involved in myelination processes. It showed no evidence for epigenetic control (DNA hypermethylation at the promoter site) of the QKI gene. However, decreased levels of QKI-mRNA and QKI-protein were observed in the orbitofrontal cortex (OFC) of suicide completers who died during an episode of MDD when compared to control subjects who died of either heart attack or accidents.

Homocysteine

The homocysteine hypothesis of depression reviewed by Folstein *et al.* [21] centering around hyperhomocysteinemia leading to an increased risk of stroke, heart disease, neurotransmitter imbalances and thereby depression was further extended by a brief comment in the American Journal of Psychiatry in 2007 [22]. The authors herein stated that homocysteine is metabolized to S-adenosylmethionine, a methyldonor, which might influence DNA methylation. Secondly, homocysteine itself was shown to affect global and gene promoter DNA methylation, and the administration of acute homocysteine usually leads to demethylation of promoter DNA with a subsequent increase in gene expression [23]. A further study supported the hyperhomocysteine hypothesis of depression, reporting significantly higher homocysteine levels in patients with moderate depressive symptoms and eating disorder diagnoses [24].

Current treatment options: histone deacetylase inhibitors

The consequence of the epigenetic changes due to defeat stress in mice investigated by Tsankova *et al.* [17] (see BDNF above) resulting in a down-regulation of BDNF could be reversed by chronic imipramine (a tricyclic antidepressant) treatment. Although the imipramine recovery of BDNF expression was due to histone acetylation and not a reversal of the previously stress-induced histone methylation, the antidepressant-induced histone acetylation was shown to be long-lasting and mediated by selective HDAC down-regulation. Therefore, the antidepressant effects of imipramine may be mediated, amongst other pathways, by the inhibition of specific HDACs.

The above-cited study by Roth *et al.* [18••] also showed that adverse effects on BDNF expression induced by early maltreatment regimens can be modified, even in adults, by acting on the level of DNA methylation. Here, a treatment of early defeated adult rats with zebularine, a DNA methylation inhibitor, restored BDNF expression through decreasing the promoter methylation. Even though zebularine is not a classical DNMT inhibitor [25], this study brought a first proof of concept that changes in the level of DNA methylation are drug-inducible.

Nowadays, epigenetic drug treatment options most commonly concern cancer therapy using HDACis to induce previously affected tumor suppressor and metastasis-inhibitory gene activity by shifting the acetylation–deacetylation reactions towards acetylation, as reviewed by Szyf [26•]. Thus, the first clinically approved HDACi 'Vorinostat' (suberoylanilide hydroxamic acid, SAHA) is now used in the treatment of cutaneous T-cell lymphoma, with good response rates exceeding 30% [27].

The above-summarized studies clearly demonstrate that epigenetic alterations are potentially reversible and accessible for drug treatment. Furthermore, epigenetics has the potential to influence hippocampal and non-hippocampal brain neurogenesis even in the adult brain. This fact applies, for example, to the anticonvulsant and mood stabilizer valproic acid, which is a potent HDACi with impact on neuronal differentiation [28•]. In 2007, the HDACi sodium butyrate was shown to exert antidepressant effects in a continuous dosage regimen in a depression mouse model, either alone or in conjunction with the selective serotonin reuptake inhibitor fluoxetine [29]. Accordingly, epigenetic alterations that found their way into the epigenome via DNA methylation or histone/chromatin modifications in early infancy, young or later adulthood leading to psychiatric disorders including depression are potential objectives of epigenetic drugs, such as DNMTs and HDACis.

In a recent study conducted by Covington *et al.* [30•], site-specific continous infusion of the HDACis 'MS-275' and 'SAHA' in the nucleus accumbens (NAc) of mice previously put under defeat stress showed antidepressant effects that were equivalent to the effects of systemic fluoxetine application. Interestingly, besides the unique increase of acetylated histones in the NAc, treatment with the HDACi 'MS-275' also showed fluoxetine-like gene expression modifications, proving partly shared antidepressant actions by both agents [30•].

Considering the future use of DNMTs and HDACis as well as other substances addressing the epigenetic profile in the treatment of depression or further psychiatric disorders, issues regarding the selectivity, mode of action, toxicity and brain permeability of drugs have to be addressed. With respect to rational drug design, one should consider that the currently available HDACis usually block a range of HDACs with impact on different cellular mechanisms involving cytotoxicity, cell cycle control, or immune modulation. Here, first promising results have been achieved with the development of 'MS-275', which was shown to be selective for a specific HDAC, namely HDAC1, and to cross the blood–brain barrier [31••]. Furthermore, the interdependent epigenetic mechanisms orchestrating histone modifications, DNA methylation and moderating proteins like MeCP2 have to be considered in future research [14•]. Besides considerations regarding personalized medicine with epigenetic drug choice taking the respective patient's histone or DNA methylation code into consideration, the combination of established antidepressants with novel epigenetic drugs deserves particular attention. As HDACis such as 'MS-275' themselves exert antidepressant effects comparable to established antidepressants such as fluoxetine in animal models [30•], the mutual complementation of different pharmacological effects now including epigenetic mechanisms is showing promising trends towards combined standard/epigenetic treatment choices [31••]. The rationale behind this hypothesis refers to the potential of epigenetic drugs to relax the physical formation of the genome, to restore illness-conditioned or stress-conditioned gene expression, and thereby to facilitate the action of other yet established treatment options in depression.

Conclusion

In the present review, we aimed to summarize the current results regarding epigenetics and depression. Herein, we emphasized research results showing epigenetic changes due to early stress research and promising treatment options employing HDACis as novel antidepressants. In addition, we support ideas in the field of epigenetic pharmaceuticals that HDACis and DNMT, thus histone and DNA methylation interfering drugs, might have the potential to restore previously shut-down chromatin structure for subsequent treatment interventions. However, it appears feasible that the physical opening of the genome itself exerts antidepressant effects in particular brain areas like the hippocampus, PFC, and NAc.

Furthermore, we consider the methyl donor homocysteine, besides its hypothesized impact on the development of depression via neurotransmitter modifications [21], as a promising new research target regarding DNA methylation and depression.

From the perspective of G × E with genes mediating an individual's risk to stressful life events, epigenetics

may have the potential to understand the underlying molecular processes of G × E with hopeful benefits for future personalized diagnostics and therapies for depression and other psychiatric disorders.

References and recommended reading

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