Epigenetics of bipolar disorder

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Abstract

Bipolar disorder is a common, chronic, and recurring mental disorder with a poorly understood and complex genetic basis. Epigenetic mechanisms refer to the regulation of DNA transcription without alteration of the nucleotide sequence. Epigenetic mechanisms are: DNA methylation, histone modifications and non-coding micro RNAs. Epigenetic information is not stored in the DNA nucleotide sequence; nevertheless it can be transmitted through generations. Recent studies have indicated that epigenetic mechanisms are involved in the pathophysiology of bipolar disorder and also in the mechanisms of action of current medications used for the treatment of bipolar disorder.

Key words: bipolar disorder, epigenetics, DNA methylation, histone modulation, micro RNAs, mood stabilizers.

Introduction

Bipolar disorder is a common, chronic, and recurring mental disorder with a rather poorly understood pathophysiology on the neurobiological level. Family, twin, and adoption studies indicate that bipolar disorder has a genetic basis. However, the genetic basis of bipolar disorder is complex, involving the interplay between genetic as well as environmental factors.1 Several studies have tried to find specific genetic mutations and polymorphisms in association with bipolar disorder; however no genetic mutation or polymorphism underlying this disorder has been definitively identified.1,2 It seems that aberrant nucleotide sequence per se could not be directly linked to the pathophysiology of the bipolar disorder. However, the interplay of different genes and their regulation by environmental factors could better explain the complexity of the bipolar disorder phenomenology and also its unstable course. Beside other mechanisms involved in gene regulation, epigenetic mechanisms by their reversibility, could explain the changing, episodic course of bipolar disorder.

Epigenetic mechanisms

Epigenetic information is defined as information-carrying molecular processes that are inherited through mitosis or meiosis, influencing gene expression independently of the DNA sequence.3 Environmental factors could, via specific intracellular signalling pathways, control neuronal differentiation at multiple levels, such as neuronal precursor cell-cycle control, migration, synaptogenesis, neuronal survival and neurotransmitter phenotype (for review see3). One specific regulation on the cellular level, the induction of timely coordinated cascades of gene expression, controlled by specific and ubiquitous transcription factors, is further regulated by epigenetic mechanisms (Figure 1). Transcription factors, in turn, induce either the expression of structural genes required for specific functions of a given neuronal lineage and/or the expression of non-coding RNAs that play an important further regulatory role.3 However, binding of the transcription factors to the specific regions of the DNA is influenced by different mechanisms such as DNA sequence, especially in the promoter regions on one hand, and epigenetic mechanisms such as histone modulation or methylation of DNA molecule, on the other (Figure 2).4

Histone modification

In association with the DNA molecule, nuclear protein histones are the basic building units of nucleosomes. The DNA molecule is wrapped around a histone protein octamer made of histones. Each histone has a "tail" protruding out of the nucleosome, which can be modified in different ways such as phosphorylation, ubiquitinatation, sumoylation, acetylation, and methylation.5 For example, histones are deacetylated by a group of enzymes known as histone deacetylases (HDACs). When deacetylated the affinity of histones for the DNA molecule is increased. Gene expression is influenced by the chromatin structure via histone modification and chromatin remodelling complexes (remodelers).6 The chromatin structure could switch from a closed or transcriptionally repressive state, to an open or transcriptionally permissive state.7 It could be summarised that this histone modification influences gene transcription in a specific region by changing the affinity between histones and the DNA molecule. Not only histone tail modification but also other processes such as histone post-translational modifications8 and also different histone variants8,9 could influence the packaging of chromosomal DNA and suppress gene expression in a specific DNA region.

DNA methylation

DNA methylation is a stable but reversible covalent modification of the DNA molecule not influencing nucleotide sequence. When the promoter region of the DNA is methylated, the affinity for activators of DNA transcription is, in most cases, decreased, resulting in reduced mRNA production.10 The methylation occurs at the 5' position of the pyrimidine ring of the cytosine in the CpG dinucleotide and is facilitated by different types of DNA methyltransferases (DNMTs). However, cytosines in the CpG dinucleotide are the preferred, but not the exclusive, targets for DNA methylation.11 An interesting observation has been reported for one of the DNMTs, a DNMT1. This DNMT is the main enzyme responsible for the maintenance of DNA methylation. It has also been observed that DNMT1 methylates hemimethylated DNA more rapidly than unmethylated DNA12,13 indicating the possibility that methylation profiles could be inherited from mother to daughter cell10 and from one generation to the next. The establishment and maintenance of CpG site methylation is essential during central nervous system differentiation. DNA methylation has been implicated in synaptic plasticity, learning, and memory.14 Not all CpG dinucleotides are methylated. There is a cell-specific pattern of distribution of methylated CpG dinucleotides15 carrying the epigenetic information in the methylation sequence itself. In contrast to the information stored in the nucleotide sequence, the DNA methylation is not only heritable but also reversible. Furthermore, it has been shown that both described epigenetic mechanisms, histone modulation and DNA methylation, are interconnected. It has been reported that methylated cytosines attract methyl-CpG–binding protein, which recruits chromatin-remodelling proteins to influence the histone structure.16 All these mechanisms could work together to induce transcriptional silencing.16

MicroRNAs

The third known epigenetic mechanisms are micro ribonucleic acids (abbreviated miRNA). MiRNA is a short RNA molecule, on average of 22 nucleotides, found in eukaryotic cells.17 These molecules are involved in post-transcriptional regulation and bind complementary sequences on target messenger RNA transcripts (mRNAs), usually resulting in translational repression or target degradation and gene silencing.17,18 The human genome may encode over 1000 different miRNAs,19 which may regulate numerous genes.20 During the process of translational repression, miRNA bind to specific proteins, such as proteins from the Argonaute family.21

Bipolar disorder and abnormalities in epigenetic regulation

Aberrant epigenetic regulation (epimutations) could have a similar effect to DNA mutations because an epimutation could lead to the abnormal expression of a gene by enhancing or silencing that gene.22 Differences in epigenetic regulation of gene expression have been found in patients with bipolar disorder in comparison to controls. However, it is not clear whether some of these differences are the cause or the effect of the disease process in bipolar disorder.23 Although the understanding

of the role of miRNAs and histone modulation in bipolar disorder is in its very early stages24 several studies have addressed the role of epigenetic mechanisms in this mental disorder.

Epigenetic dysfunction of GABAergic and glutamatergic systems

The main systems for suppressing and activating the activity of the central nervous system are GABAergic and glutamatergic systems respectively. Numerous genes are involved in the regulation of those two systems. However, only recently, differences in epigenetic regulation of specific genes involved in the regulation of these two systems have been reported. For example, it has been reported that the promoter of the GAD1 gene has been found to be hypermethylated in post-mortem samples of the prefrontal cortex in patients with bipolar disorder due to over-expression of the enzyme DNA methyltransferase1 (DNMT1), resulting in decreased expression of GAD67.25 GAD67 is one of two isoforms of glutamic acid decarboxylase, the enzyme that catalyses the conversion of the excitatory neurotransmitter glutamic acid to the inhibitory neurotransmitter gamma-amino butyric acid (GABA), influencing the activity of GABAergic and glutamatergic systems. Furthermore, in a genome-wide profiling of DNA methylation in patients with bipolar disorder it was found that beside other genes abnormalities in the methylation, a gene for RNAbinding protein was involved in the synthesis of functional GABA-B receptors.23

Epigenetic dysfunction of dopaminergic and adrenergic systems

Abnormalities in neurotransmission in the dopaminergic and adrenergic systems have been reported to be involved in the pathogenesis of bipolar disorder. Although GABAergic, glutamatergic, dopaminergic and adrenergic systems are interconnected and dysfunction of one system could affect the others, epigenetic deregulations of genes involved mainly in the regulation of dopaminergic and adrenergic systems have been reported. It has been shown that hypomethylation of membrane bound catechol-O-methyltransferase (MB-COMT) promoter is a major risk factor for bipolar disorder.26 MB-COMT is one of the two isoforms of the COMT enzyme which is involved in the degradation of the neurotransmitters dopamine and noradrenaline. It could be speculated that hypomethylation of MB-COMT promoter could lead to increased expression of the MB-COMT gene and consequently to decreased levels of dopamine and adrenaline.

Neuroplasticity and epigenetic regulation in bipolar disorder

At the cellular level, it has been suggested that abnormal brain derived growth factor (BDNF) gene activity is a leading etiological hypothesis by which early-life adverse experiences persistently modify brain and behavioural plasticity (for review see27). In the genome-wide profiling of DNA methylation in patients with bipolar disorder, abnormalities in the methylation of the BDNF gene have also been found.23 Recently, in a study investigating the degree of DNA methylation at the promoter region of the BDNF gene in peripheral blood mononuclear cells isolated from patients with bipolar type I and type II and healthy controls, a significant BDNF gene expression downregulation in bipolar II patients but not in bipolar I patients in comparison with controls was found.28 Consistently, a hypermethylation of the BDNF promoter region was specifically found in bipolar II patients.28 Another study reported changes in DNA of patients with bipolar disorder associated with hypomethylation and hypermethylation of CpG islands in cyclooxygenase-2 and BDNF promoter regions, respectively.29

Treatment and epigenetic influences

Many psychotropic drugs that are currently in use for the treatment of bipolar disorder have been shown to influence epigenetic mechanisms in addition to other mechanisms of action. Specific epigenetic drugs with their primary mechanism of action influencing directly epigenetic regulation of gene expression are under development.

Mood stabilizers

Valproic acid has mood-stabilizing effects in patients with bipolar disorder. Valproic acid has diverse mechanisms of action. It prolongs the inactive state of sodium channels after depolarization; it potentiates the action of GABA at GABAergic synapses, and it blocks T-type calcium channels in thalamic neurons. In addition to the mechanisms of action as an antiepileptic drug, which could contribute to the mood stabilization, it is thought to influence epigenetic mechanisms by inhibiting HDACs and also by causing demethylation of DNA.30 It has been speculated that beneficial effect of valproic acid may be due to activation of DNA demethylation, leading to reversal of a repressed nuclear epigenetic state in cortical neurons.31 Recently, a study investigating the degree of DNA methylation at the promoter region of the BDNF gene in peripheral blood mononuclear cells isolated from patients with bipolar I and II found higher levels of DNA methylation in patients with bipolar disorder receiving pharmacological treatment with mood stabilizers plus antidepressants in comparison to those exclusively treated with mood-stabilizing agents.28 Moreover, among the different pharmacological therapies, lithium and valproate were reported to be associated with a significant reduction of DNA methylation in comparison to other medications.28 A study using animal models reported that rat hippocampal miRNA changes following chronic administration of valproic acid and lithium.32

Antidepressants

The primary mechanism of action of the tricyclic antidepressant imipramine is inhibition of the reuptake of noradrenaline and serotonin into the presynaptic neurons but it has also been found to influence chromatin remodelling in animal models of five BDNF splice variant mRNAs (I–V) and their promoters in the hippocampus.33 Chronic imipramine administration reversed BDNF transcripts III and IV downregulation induced by stress and increased histone acetylation at the corresponding promoters.33 It was further explained that the observed histone hyperacetylation associated with imipramine administration was also associated with a selective downregulation of histone deacetylase 5.33 Selective serotonin reuptake inhibitors (SSRIs) seem to have similar effects to those of tricyclic antidepressants. Fluoxetine has also been shown to induce expression of the methyl-CpG-binding proteins in adult rat brain after chronic administration.34

Antipsychotics

A preclinical study showed that two atypical antipsychotics, clozapine and sulpiride, but not the typical antipsychotic haloperidol or the atypical antipsychotic olanzapine, administered in mice alone or in association with valproate, in clinically relevant doses for 3 days, down-regulated reelin and GAD67 promoter methylation in the frontal cortex and striatum.35 The authors speculated that these results suggested that clozapine or sulpiride associated with valproate, by increasing DNA demethylation via an unknown mechanism, causes chromatin remodelling that brings about a beneficial change in the epigenetic GABAergic dysfunction typical of patients with bipolar disorder.36

Future specific epigenetic medications

Regarding mechanisms of action, there are three types of epigenetic medications that are being investigated for the treatment of bipolar disorder: compounds inhibiting HDACs, compounds targeting DNA methylation, and compounds targeting miRNAs. Trials of epigenetic medications for the treatment of bipolar disorder are presently at preclinical stages and include compounds such as SAHA (vorinostat), benzamide MS-275 and phenylbutyrate.24,37,38 For example, it was reported that the benzamide MS-275 is much more potent than valproic acid, as a long-lasting and brain-region-selective HDAC inhibitor.39 It was also reported that the infusion of HDAC inhibitors into the nucleus accumbens exerted antidepressant-like effects in the social defeat stress model as well as other behavioural tests in mice.40 On the level of miRNA manipulation, it has been suggested that there are two possible methods that can be used to target miRNAs: inhibiting miRNAs using small molecules, or using smart technologies such as liposomes, nanoparticles, and specific nucleotide delivery systems through the cell membrane to administer double-stranded synthetic RNA which mimics or antagonises the miRNA in the cell.41

Conclusions

Recent research indicates that epigenetic mechanisms are involved in pathophysiology of bipolar disorder and that existing treatments could influence the same mechanisms. Furthermore, data on possible mechanisms of action of medications used in the treatment of bipolar disorder indicate that BDNF regulation might be a crucial target for their effects. Current psychopharmacological drugs, including antidepressants, antipsychotics and mood stabilizers, may exert some of their effects through epigenetic mechanisms. It could be concluded that reversibility of epigenetic changes opens the possibility of evolving new specific treatments for patients with bipolar disorder, from pharmacological approaches to psychotherapy.

GP Comment

What have I learned from this paper?

This is a fascinating area, especially with the advent of personalised medicine, with increasing numbers of patients bringing printouts of their DNA, from commercial companies, to their GP for interpretation - which can be challenging! Although epigenetics is complex, knowing that these mechanisms could account for both environmental and pharmacological effects on the course of bipolar disorder is important. Moreover, pharmacogenomics is a developing area and the GP consultation of the future may include discussions around these themes.

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Figure 1. Transcription and translation of the DNA molecule. Activators are bound to promoter

region of the DNA molecule inducing the transcription of DNA resulting in mRNA production. MRNA is further translated into the protein. Different mechanisms are involved in the regulation of gene expression. The activation of this mechanisms resolve in gene silencing in most cases (Riccio 2010).4

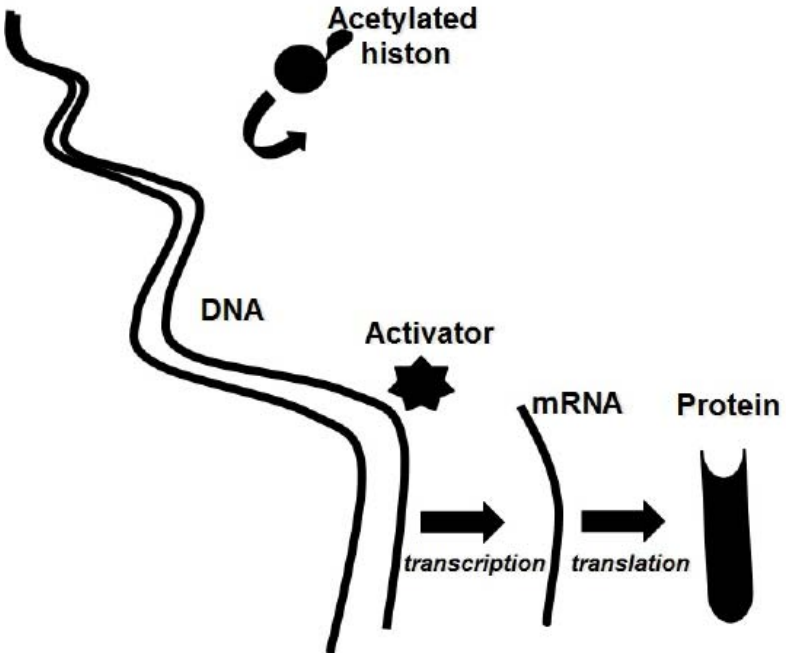

Figure 2. Epigenetic mechanisms involved in the regulation of gene expression. Binding of the transcription factors to the promoter regions of the DNA is influenced by different mechanisms including epigenetic mechanisms such as histone modulation and methylation of DNA molecule.4 The DNA molecule is wrapped around a deacetylated histone proteins resulting in gene silencing. DNA methylation is a stable covalent modification of the DNA molecule. When the promoter region of the DNA is methylated the affinity for activators of DNA transcription is decreased resolving in reduced mRNA production.10 On the post-transcriptional level miRNA molecules are involved in regulation of gene expression. MiRNAs bind complementary sequences on target mRNA transcripts, usually resulting in translational repression or target degradation and gene silencing.17,18