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REVIEW

Epigenetic management of major psychosis

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Abstract Epigenetic mechanisms are thought to play a major role in the pathogenesis of the major psychoses (schizophrenia and bipolar disorder), and they may be the link between the environment and the genome in the pathogenesis of these disorders. This paper discusses the role of epigenetics in the management of major psychosis: (1) the role of epigenetic drugs in treating these disorders. At present, there are three categories of epigenetic drugs that are being actively investigated for their ability to treat psychosis: drugs inhibiting histone deacetylation; drugs decreasing DNA methylation; and drugs targeting microRNAs; and (2) the role of epigenetic mechanisms in electroconvulsive therapy in these disorders.

Keywords Bipolar disorder · Epigenetic · Psychosis · Schizophrenia

Introduction

Major psychoses (which refer chiefly to schizophrenia and bipolar disorder) are common, chronic, and recurring mental disorders. Schizophrenia is characterized by impaired social and occupational functioning and manifests as a wide range of abnormalities in perceptual, emotional, cognitive, and motor processes that cluster in three categories (Lewis and Sweet 2009): (1) positive symptoms which include delusions, perceptual disturbances and hallucinations, and abnormalities in the form of thought. (2) Negative symptoms which include asociality, avolition (impaired initiative, motivation and decision making), mood disturbances, alogia (poverty in the amount or content of speech), and anhedonia (reduced capacity to experience pleasure). (3) Cognitive abnormalities like impairment of memory and selective attention. Bipolar disorder is a mood disorder characterized by episodes of mania (extremely elevated mood, energy, unusual thought patterns, and sometimes psychosis) and depression. Schizophrenia and bipolar disorder each affect about 1% of the world's population and cause considerable distress to affected individuals, emotional burden to their families, and economic burden to society (Lewis and Sweet 2009; Martinovich et al. 2009). These disorders are not only a cause of morbidity, but also increased mortality, which results from a relatively high rate of suicide and a shorter life span, due mainly to the medical complications of these illnesses. The average life expectancy of patients with schizophrenia and bipolar disorder is 56.3 years (Insel 2009). These disorders are thought to be due to abnormalities involving the development of the brain leading to disruptions in neural circuits in the brain (Insel 2009).

Family, twin, and adoption studies indicate that major psychosis has a genetic basis. However, the genetic basis of major psychosis is known to be complex, involving both genetic as well as environmental factors (Peedicayil 2010). Considerable efforts have been put into finding the genetic mutations and polymorphisms underlying these disorders by genetic mapping studies. However, to date, no genetic mutation or polymorphism underlying these disorders has been definitively identified by these studies (Cyranoski 2010; Peedicayil 2010). Another possibility for the inheritance pattern of these disorders involves epigenetics. Several lines of evidence, in fact, suggest that major psychosis may be epigenetic disorders (Peedicayil 2007)

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and several laboratories throughout the world are currently attempting to elucidate the epigenetic basis of these disorders.

Epigenetic mechanisms in the central nervous system

Epigenetic mechanisms are known to play a major role in the physiology of the central nervous system (CNS) in humans. This is not surprising, since epigenetic mechanisms are thought to have played a major role in the evolution of the human brain (Peedicayil 2001). During the development of an individual's CNS, the three major cell types in the CNS, neurons, and glial cells (astrocytes and oligodendrocytes), are generated from neural stem cells (NSC), defined as cells that possess the ability to self renew and to differentiate into the three major CNS cell types (Sanosaka et al. 2009). Recent studies have shown that epigenetic effects, in concert with cues from outside the NSC, play an important role in regulating the differentiation potential and fate specification of NSC (Sanosaka et al. 2009; Fig. 1). It is now known that in addition to the periods of fetal life and childhood, neurogenesis takes place even during adulthood in the mammalian brain; and even in neurogenesis during adulthood, epigenetic mechanisms play an important role (Ma et al. 2010). Epigenetic effects are also involved in various aspects of neurophysiology-like cognition (Reichenberg et al. 2009), learning and memory (Jiang et al. 2008), neuronal plasticity (Borrelli et al. 2008), chemical neurotransmission (Stadler et al. 2005), and the circadian clock (Masri and Sassone-Corsi 2010; Fig. 2). Various epigenetic mechanisms including DNA methylation and histone modification (Riccio 2010) and microRNAs (miRNAs; Mehler 2008) are known to play important roles in CNS physiology. Imprinted genes are also important in the functioning of the CNS (Davies et al. 2007). They are thought to play an important role in brain development and behavior, and have been implicated in the pathogenesis of neurological and mental disorders (Davies et al. 2007).

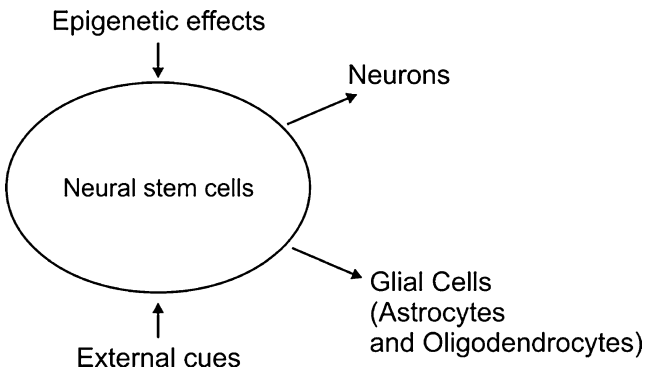

Fig. 1 Regulation of differentiation potential and fate specification of neural stem cells by epigenetic effects and external cues

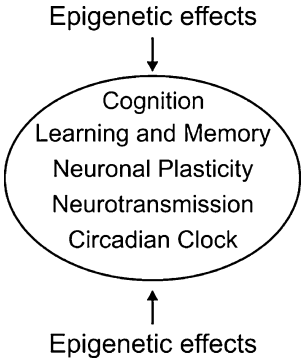

Fig. 2 Epigenetic effects on various aspects of neurophysiology

Epigenetic abnormalities in major psychosis

Epigenetic abnormalities have been detected in patients with major psychosis. However, as mentioned by Mill et al. (2008), at present, it is not clear whether some of these changes are the cause or the effect of the disease process in major psychosis. The epigenetic abnormalities in major psychosis include the following:

Abnormalities involving DNA methylation

Abnormalities of DNA methylation have been the epigenetic abnormality most studied in major psychosis. The genes most widely implicated as being abnormally methylated in major psychosis are the *RELN* gene which encodes the glycoprotein reelin, and the *GAD1* gene which encodes the enzyme GAD_{67}. Reelin is an extracellular matrix glycoprotein that guides neurons and radial glial cells to their positions in the adult brain. GAD_{67} is one of two isoforms of glutamic acid decarboxylase, the enzyme that catalyzes the conversion of the excitatory neurotransmitter glutamic acid to the inhibitory neurotransmitter γ-amino butyric acid (GABA). The promoters of both the *RELN* gene (Veldic et al. 2004; Abdolmaleky et al. 2005; Guidotti et al. 2007) and the *GAD1* gene (Veldic et al. 2004; Veldic et al. 2005) have been found to be hypermethylated in postmortem samples of prefrontal cortex in patients with schizophrenia and bipolar disorder due to over-expression of the enzyme DNA methyltransferase1 (DNMT1), resulting in decreased expression of reelin and GAD_{67}. Similar results were also found in the basal ganglia of patients with schizophrenia but not in patients with bipolar disorder (Veldic et al. 2007). Grayson (2010) has tried to put these data into perspective by proposing that an epigenetic dysfunction that perturbs cortical GABAergic neuron transcription impacts both GABAergic and glutamatergic signaling at the level of

either presynaptic release (GABA) or postsynaptic hypofunction (glutamic acid). The glutamatergic hypofunction could then impact the release of dopamine, a neurotransmitter implicated in the pathogenesis of major psychosis. It has also been suggested by Roth et al. (2009) that although there is strong evidence for epigenetic abnormalities in the *RELN* and *GAD1* genes in major psychosis, it is unlikely that their epigenetic dysfunction alone confers susceptibility to psychosis. Instead, it is likely that many genes are epigenetically dysfunctional in these disorders.

Another gene for which there is preliminary evidence of being epigenetically modified leading to the development of major psychosis is the gene encoding membrane-bound catechol-*O*-methyltransferase (MB-COMT; Abdolmaleky et al. 2006). MB-COMT is one of the two isoforms of COMT, the enzyme which is involved in the catabolism of the neurotransmitters dopamine and noradrenaline. Abnormalities in neurotransmission of both these neurotransmitters have been implicated in the pathogenesis of major psychosis (Sadock and Sadock 2007). A recent genome-wide profiling of DNA methylation in patients with schizophrenia and bipolar disorder found numerous other genes to be abnormally methylated in these disorders (Mill et al. 2008). These included the genes encoding brain-derived growth factor (BDNF) and MARLIN-1, a RNA-binding protein that is widely expressed in the brain and that regulates the production of functional GABA-B receptors. However, the results of this study await confirmation and replication.

Abnormalities involving histone modification

Much less work has been done on histone modifications underlying major psychosis than on abnormalities in DNA methylation. Akbarian et al. (2005) found that patients with schizophrenia as a group showed no alterations in histones as compared to controls. However, in a subgroup of patients, levels of H3-(methyl) arginine 17 exceeded controls and this was associated with decreased gene expression. The authors suggested that histone modifications may contribute to the pathogenesis of prefrontal dysfunction in schizophrenia. Since that report on histone modifications in major psychosis, there have been other reports such as that of Huang et al. (2007) who showed that chromatin remodeling mechanisms at GABAergic gene promoters occur throughout an extended period of normal human prefrontal cortex development and are involved in the pathogenesis of schizophrenia. More recently, Sharma et al. (2008) reported that histone deacetylase1 expression is increased in the prefrontal cortex of patients with schizophrenia, compared to controls.

Abnormalities involving microRNAs

miRNAs have also been studied in major psychosis, so far mainly in patients with schizophrenia. The first study to report abnormal miRNA expression in schizophrenia was that of Perkins et al. (2007) which compared the expression of 264 miRNAs in postmortem prefrontal cortex obtained from 13 patients with schizophrenia and 2 patients with schizoaffective disorder with that in 21 normal controls. These authors found that 16 miRNAs were differentially expressed in the patient group compared with the control group. More recently, Beveridge et al. (2010) found a significant increase in global miRNA expression in postmortem superior temporal gyrus and the dorsolateral prefrontal cortex obtained from patients with schizophrenia as compared to normal controls. The role of miRNAs in disease pathogenesis has also begun to be investigated in postmortem brain samples from patients with bipolar disorder with results suggesting abnormalities of miRNA expression (Kim et al. 2010; Moreau et al. 2011). The study of the role of miRNAs in major psychosis is in its very early stages and needs to be extended, replicated, and confirmed.

Environmental factors in major psychosis

Environmental factors are thought to be involved in the pathogenesis of schizophrenia and bipolar disorder (Lewis and Sweet 2009; Martinovich et al. 2009). It is also now well established that environmental factors modify epigenetic mechanisms of gene expression (Liu et al. 2008). There is evidence that many environmental factors may influence the pathogenesis of major psychosis by altering epigenetic mechanisms. These include psychosocial factors, childhood adversities, migration, urban residence, nutrition, and advanced paternal age (Peedicayil 2010). The study of the means by which environmental factors modify epigenetic mechanisms of gene expression to alter behavior and lead to the development of mental disorders is a very new area of research but is likely to be of great relevance and importance in the future (Rutten and Mill 2009; Peedicayil 2010).

Current management of major psychosis

Currently, there are three major forms of management of patients with major psychosis. One is the use of psychotropic drugs (drugs whose major effects on the body are to correct abnormalities which characterize those found in patients with mental disorders). Another is psychotherapy which refers to the treatment of emotional problems in

patients with mental disorders by psychological means. The third major aspect of treatment of major psychosis is electroconvulsive therapy (ECT), which involves the administration of a small dose of electricity to the scalp of the patient in order to produce a major seizure. ECT was first demonstrated to be useful in the treatment of patients with mental disorders by the Italian scientists Cerletti and Bini in 1938 (Payne and Prudic, 2009). Presently, it is most frequently used to treat patients with severe depressive episodes and is the most effective treatment for such patients. To a lesser extent, it is useful to treat patients with manic episodes and schizophrenia (Payne and Prudic, 2009).

Epigenetic management of major psychosis

Since epigenetic mechanisms are thought to be involved in the pathogenesis of major psychosis, as discussed above, correcting the epigenetic abnormalities involved in major psychosis may lead to clinical improvement of patients with these disorders. Epigenetic management of major psychosis comprises the following: epigenetic therapy using drugs that modify abnormal epigenetic patterns of gene expression, and epigenetic effects of ECT.

Epigenetic therapy of major psychosis

Epigenetic therapy makes use of drugs to change the epigenetic patterns of patients to prevent, cure, or ameliorate disease (Peedicayil 2006; Ptak and Petronis 2008).

Research on the use of epigenetic drugs for a variety of clinical conditions is an active area of epigenetic research at present and a few epigenetic drugs have already been approved for clinical use. Many psychotropic drugs that are currently in use have been shown to influence epigenetic mechanisms of gene expression in addition to other mechanisms of action. The most prominent and best example of this is the mood stabilizer valproic acid or its salt, sodium valproate. Valproic acid, which is a short-chain fatty acid, has been commonly used as an antiepileptic drug since the late 1960s. It was marketed in France in 1969 but was not licensed in the USA until 1978 (Porter and Meldrum 2009). More recently, it was found to have mood-stabilizing effects in patients with bipolar disorder. It has some well-established mechanisms of action as an antiepileptic drug which could contribute to its mood-stabilizing effect: it prolongs the inactive state of sodium channels after depolarization; it potentiates the action of GABA at neuronal synapses where GABA is released, and it blocks T-type calcium channels in thalamic neurons. However, in addition to these actions, it is thought to act epigenetically by inhibiting histone deacetylases (HDACs) and by also causing demethylation of DNA (Dong et al. 2010). Valproic acid, co-administered with typical and atypical antipsychotics, has also been shown to be useful in the management of chronic schizophrenia (Wassef et al. 2000) and treatment-resistant schizophrenia (Kelly et al. 2006). This beneficial effect may be due to activation of DNA demethylation, leading to reversal of a repressed nuclear epigenetic state in cortical neurons (Guidotti et al. 2009; 2011).

Fluoxetine, which is an antidepressant that inhibits the reuptake of serotonin by presynaptic neurons in the brain, in addition, has also been shown by Cassel et al. (2006) to induce expression of the methyl-CpG-binding proteins (MBDs) MeCP2 and MBD1 in normal adult rat brain after repeated injection for 10 days. Induction of the MBDs was accompanied by enhanced HDAC2 labeling intensity and mRNA synthesis and decreased acetylated forms of histone H3. These effects were found in three serotonin projection areas: the caudate–putamen, the frontal cortex, and the dentate gyrus subregion of the hippocampus. These data suggested to the authors that GABAergic neurons are major target cells expressing MeCP2 in response to fluoxetine.

The tricyclic antidepressant imipramine, which is known to inhibit the reuptake of noradrenaline and serotonin by presynaptic neurons in the brain, has also been shown to affect chromatin remodeling. Tsankova et al. (2006) administered chronic social defeat stress (an animal model of depression) followed by chronic imipramine to mice and studied adaptations at the levels of gene expression and chromatin remodeling of five brain-derived neurotrophic factor (*Bdnf*) splice variant mRNAs (I–V) and their unique promoters in the hippocampus. Defeat stress caused lasting downregulation of *Bdnf* transcripts III and IV and robustly increased repressive histone methylation at their corresponding promoters. Chronic imipramine administration reversed this downregulation and increased histone acetylation at these promoters. The hyperacetylation caused by imipramine administration was associated with a selective downregulation of histone deacetylase 5.

miRNAs have also been shown to be affected by currently used psychotropic drugs. Zhou et al. (2009) found hippocampal miRNA changes following chronic administration of valproic acid and lithium to rats. Lithium, like valproic acid, is a mood-stabilizing drug. It is the lightest of the alkali metals and was serendipitously found to have anti-manic effects in 1949. Lithium carbonate and lithium chloride are the lithium salts that are commonly used in clinical practice. The predicted effectors of the miRNAs affected by valproic acid and lithium are known to be involved in neurite outgrowth, neurogenesis, and cell signaling (Zhou et al. 2009). These findings were the first

to show that miRNAs and their predicted effectors are targets for the actions of psychotropic drugs. Chen et al. (2009) showed that there were changes in the expression patterns of 7 of 13 miRNAs in lymphoblastoid cell lines in response to lithium treatment. These authors also showed that there were significant changes in mRNA targets that inversely correlated with changes in the expression of two of the miRNAs.

At present, there are three types of epigenetic drugs that are being investigated for the treatment of major psychosis: drugs inhibiting HDACs, drugs targeting DNA methylation, and drugs targeting miRNAs. Trials of epigenetic drugs in the treatment of major psychosis presently are at preclinical stages. Epigenetic drugs that are being investigated for such a purpose include SAHA (vorinostat), MS-275, and phenylbutyrate (Best and Carey 2010; Grayson et al. 2010).

Drugs inhibiting HDACs

The N-terminal tails of histones are subjected to a variety of post-translational modifications, one of which is acetylation of histones, a reaction catalyzed by a group of histone acetyltransferases. Histones are deacetylated by a group of HDACs. Most work on the use of epigenetic drugs in the management of major psychosis has focused on the use of drugs that inhibit HDACs. Several classes of these drugs are presently being investigated for therapeutic use (Peedicayil 2006; Ptak and Petronis 2008). One of the earliest studies to show the use of HDAC inhibitors in major psychosis was that of Tremolizzo et al. (2002) in which L-methionine was administered for 15 days to mice, which resulted in a marked decrease of reelin and GAD_{67} mRNAs. This effect was associated with an increase in the number of methylated cytosines in the CpG islands of the *RELN* promoter. Valproic acid was found to revert the down-regulation of reelin and GAD_{67} expression. The same group later found that valproate, when administered to mice treated this way, enhanced acetylated histone H3 content and prevented methionine-induced *RELN* promoter hypermethylation, reelin mRNA downregulation, and behavioral deficits (Tremolizzo et al. 2005). More recently, it was shown by Simonini et al. (2006) that the benzamide derivative MS-275 is a potent, long-lasting brain region-selective HDAC inhibitor. They found that MS-275 increased the content of acetylhistone 3 (Ac-H3) in the frontal cortex of mice at a relatively low dose compared to the doses required for the same effect in regions of the brain like the hippocampus and the striatum. Moreover, MS-275 was found to be a much more potent HDAC inhibitor than valproic acid. These authors suggested that benzamide derivative HDAC inhibitors like MS-275 may express greater efficacy than valproic acid as adjunctives to antipsychotics in the treatment of major psychosis.

Covington et al. (2009) showed that chronic social defeat stress in mice caused a transient decrease, followed by a persistent increase, in levels of acetylated histone H3 in the nucleus accumbens, an important limbic region. This persistent increase in H3 acetylation was associated with decreased levels of histone deacetylase 2 (HDAC2) in the nucleus accumbens. These changes in H3 acetylation and HDAC2 expression were found to mediate long-lasting positive neuronal adaptations, since infusion of HDAC inhibitors into the nucleus accumbens exerted robust antidepressant-like effects in the social defeat stress model as well as other behavioral tests. The infusion of MS-275 also reversed the effects of chronic social defeat stress on global patterns of gene expression in the nucleus accumbens as determined by microarray analysis, with marked similarities to the effects of the commonly used antidepressant fluoxetine.

It has also been demonstrated that HDAC inhibition is linked to DNA demethylation. Dong et al. (2007) administered L-methionine to mice for seven days and then measured *RELN* and *GAD1* promoter methylation and MeCP2 bound to methylated cytosines of the *RELN* and *GAD1* promoters. Levels of *RELN* and *GAD1* promoter hypermethylation induced by methionine administration decreased by about 50% after 6 days of methionine withdrawal. When valproate or MS-275 was given after the stopping of methionine administration, these drugs dramatically accelerated the demethylation of both promoters. The authors showed that valproate and MS-275 increased the binding of acetylhistone-3 to the promoters of *RELN* and *GAD1*genes, suggesting that histone-3 covalent modifications modulate DNA demethylation in neurons, supporting the view that directly or indirectly, HDAC inhibitors may facilitate DNA demethylation.

HDACs belong to a family of isozymes and in an interesting and potentially important study, Guan et al. (2009) found that neuron-specific over-expression of HDAC2, but not that of HDAC1, decreased dendritic spine density, synapse number, synaptic plasticity, and memory formation. Conversely, *Hdac2* deficiency resulted in increased synapse number and memory facilitation, similar to what occurs when HDAC inhibitors are administered chronically to mice. Moreover, reduced synapse number and learning impairment of HDAC2-overexpressing mice were decreased by chronic administration of HDAC inhibitors. It was also found that treatment with HDAC inhibitors failed to further facilitate memory formation in *Hdac2*-deficient mice. Moreover, analysis of promoter occupancy showed an association of HDAC2 with the promoters of genes implicated in synaptic plasticity and memory formation. Based on these results,

Guan et al. suggested that HDAC2 functions in modulating synaptic plasticity and long-lasting changes of neural circuits, which in turn negatively regulates learning and memory and that hence HDAC2-selective inhibitors may be useful in human diseases with memory impairment. As mentioned above, memory can be impaired in patients with major psychosis and hence may be usefully treated with such drugs.

Drugs decreasing DNA methylation

DNA methylation is associated with inhibition of gene transcription and is catalyzed by a family of enzymes called the DNMTs. At present, several drugs that inhibit the DNMTs are being investigated for use in clinical practice (Peedicayil 2006; Ptak and Petronis 2008). DNA is thought to be demethylated by a putative demethylase (De Carvalho et al. 2010; Dong et al. 2010).

The first study to investigate the effect of decreasing DNA methylation with regard to major psychosis was that of Kundakovic et al. (2007). These authors found, using cultured NT-2 neuronal precursor cells, that the DNMT inhibitors doxorubicin, azacytidine, and zebularine inhibited DNMT1 leading to the activation of human *RELN* and *GAD1* expression. Later on, Kundakovic et al. (2009) found that the same DNMT inhibitors inhibited the DNMTs, DNMT1, DNMT3A, and DNMT3B, leading to decreased DNA methylation and the reorganization of chromatin surrounding the regulatory regions of the *RELN* and *GAD1* genes, which have been found to be epigenetically modified in postmortem brains of patients with schizophrenia. More recently, Dong et al. (2010) incubated an Sssl methylated mouse *RELN* promoter fragment (−720 to +140) with nuclear extracts from the mouse frontal cortex. They observed DNA demethylating activity which was increased in frontal cortex nuclear extracts from mice treated with valproate. They suggested that valproate up-regulates *RELN* and *GAD1* expression by reducing the methylation of the promoters of these two genes, and that the identification of an enzyme in the brain that facilitates DNA demethylation, and understanding how drugs induce DNA demethylation, are crucial to progress in the epigenetic therapy of mental disorders.

Drugs targeting miRNAs

Since, as described above, miRNAs are thought to be involved in the pathogenesis of the major psychoses, drugs targeting miRNAs may be useful in the treatment of these disorders. Dinan (2010) has recently discussed the possible role of targeting miRNAs in patients with major psychosis. He suggested that the targeting of miRNAs to treat major psychosis involves several hurdles relating to delivery, selectivity, and efficacy, but offers hope as a therapeutic option in the future. Dinan suggested that there are two possible methods that can be used to target miRNAs: inhibiting miRNAs using small molecules, or using smart technologies to administer double-stranded miRNA mimics or antagomirs. A crucial first step in the development of such technologies may be the demonstration that the centrally administered technology is capable of producing behavioral changes in animals. Dinan suggested that evolving technologies employing liposomes, nanoparticles, and specific nucleotide delivery through cell membrane targeting may provide the solution for the targeting of miRNAs in major psychosis. It is apparent from the above that drug targeting of miRNAs in patients with major psychosis is well into the future.

Epigenetic effects of electroconvulsive therapy

Tsankova et al. (2004) used chromatin immunoprecipitation assays to measure in rat hippocampus levels of histones H3 and H4 acetylation and phosphoacetylation at the promoters of the *c-fos*, *BDNF*, and cyclicAMP response element-binding protein (*CREB*) genes, the expression of which is altered by ECT. They found that, with few exceptions, levels of H4 acetylation correlated with mRNA levels for *c-fos*, *BDNF*, and *CREB* throughout the acute and chronic periods of administration of ECT whereas acetylation and phosphoacetylation of H3 were detected more selectively. Their results suggested to the authors that the chronic downregulation of *c-fos* transcription that they observed may be achieved at the level of H4 acetylation, whereas chronic up-regulation of *BDNF* transcription may be sustained by control of H3 acetylation selectively at the *BDNF* P3 and P4 promoters. These results provided for the first time in vivo evidence that ECT causes epigenetic changes in gene expression.

More recently, Ma et al. (2009) employed ECT to study epigenetic changes that may help explain seizure-induced up-regulation of adult neurogenesis in mouse hippocampal neurons. They focused on *Gadd45b*, a gene belonging to the *Gadd45* family and which encodes a protein product, Gadd45b, which links neuronal circuit activity to region-specific DNA demethylation and expression of paracrine neurogenic niche factors from mature neurons in controlling key aspects of activity-dependent adult neurogenesis. They found that ECT-dependent induction of Gadd45b promotes DNA demethylation and adult neurogenesis in mice hippocampal neurons. The results of these two studies suggest that at least a part of the mechanism of action of ECT in patients with major psychosis may be by altering epigenetic mechanisms of gene expression in the brain. The precise role of epigenetic changes induced by ECT in the management of major psychosis may be a good topic for future research.

Conclusions and future prospects

Epigenetics plays a major role in the pathogenesis of the major psychoses. Although at present there are some leads on the epigenetic abnormalities underlying these disorders, the precise epigenetic basis for the pathogenesis of these disorders awaits elucidation The elucidation of the epigenetic abnormalities underlying major psychosis will help in the understanding of the mechanisms by which epigenetic drugs and ECT help in the clinical improvement of patients with these disorders and will help in the development of more effective and safer epigenetic drugs to treat these disorders.

At present, a major drawback in the management of the major psychoses, unlike as in the case of most medical disorders, is that there are no valid biomarkers to aid in the diagnosis and treatment of patients with these disorders. When the epigenetic abnormalities underlying these disorders have been elucidated, epigenetic biomarkers (Peedicayil 2008; Mikkelsen et al. 2010) are likely to help in this regard.

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Conflict of interest The author declares that he has conflict of interest.

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