

The Potential Role of Epigenetic Drugs in the Treatment of Anxiety Disorders

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Abstract: There is increasing evidence that abnormalities in epigenetic mechanisms of gene expression contribute to the pathogenesis of anxiety disorders (ADs). This article discusses the role of epigenetic mechanisms of gene expression in the pathogenesis of ADs. It also discusses the data so far obtained from preclinical and clinical trials on the use of epigenetic drugs for treating ADs. Most drug trials investigating the use of epigenetic drugs for treating ADs have used histone deacetylase inhibitors (HDACi). HDACi are showing favorable results in both preclinical and clinical drug trials for treating ADs. However, at present the mode of action of HDACi in ADs is not clear. More work needs to be done to elucidate how epigenetic dysregulation contributes to the pathogenesis of ADs. More work also needs to be done on the mode of action of HDACi in alleviating the signs and symptoms of ADs.

Keywords: anxiety disorders, epigenetic, histone deacetylase, histone deacetylase inhibitor

Introduction

Anxiety disorders (ADs) are common disorders having a current global prevalence of 7.3%, with a range of 4.8% to 10.9%.¹ The age of onset of these disorders is usually in the mid-twenties, and women are twice as likely than men to be diagnosed to have these disorders.² In patients with ADs there is anxiety in situations where there is no external reason or cause for such distress, and the patient's daily functioning is affected.³ Such patients experience a diffuse, unpleasant, and vague feeling of apprehension, often accompanied by autonomic symptoms like headache, sweating, palpitations, tightness in the chest, mild abdominal discomfort, and restlessness.⁴ There is a high amount of co-morbidity between ADs and depressive disorders⁵ and drug addiction.⁶

ADs form a group of related but distinct psychiatric disorders including panic disorder (PD), agoraphobia, specific phobia, social anxiety disorder (SAD), and generalized anxiety disorder (GAD).⁴ PD involves acute intense attacks of anxiety with feelings of impending doom. Regarding PD, there can be many attacks in one day, or only a few attacks in a year. Agoraphobia refers to fear or anxiety about places from which escape may be difficult. Specific phobia involves an excessive fear of a specific object, circumstance, or situation. SAD (social phobia) refers to the fear of social situations which involve scrutiny or interaction with strangers. GAD involves anxiety about everything, for most days during at least a six-month period.⁴ The different subtypes of ADs often occur together in the same patient.⁵

Pathogenesis of Anxiety Disorders

Both psychological and biological factors are thought to contribute to the pathogenesis of ADs.⁴ Psychological factors involved in the pathogenesis of ADs comprise

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traumatic and stressful life events, especially during childhood.⁷ There is consistent evidence that many types of psychosocial stress increase the synthesis and release of cortisol.⁴ Cortisol helps to mobilize and restore energy stores and contributes to changes like increased arousal, vigilance, focused attention, and memory formation.⁴ However, excessive and sustained cortisol secretion can lead to serious adverse effects like hypertension, dyslipidemia, insulin resistance, and cardiovascular disease.⁴ In addition to psychological factors, biological factors play a crucial role in the pathogenesis of ADs. For example, family and twin studies have shown that genetic factors are involved in the pathogenesis of ADs.⁷ Segregation analysis has shown that ADs are not Mendelian disorders, but complex traits involving multiple genes interacting with environmental factors resulting in the development of the disorders in affected individuals.⁷ However, linkage and candidate gene studies have produced inconclusive results, and genome-wide association studies (GWAS) have so far not reached genome-wide significance.⁸ Hence, at present, the results of genetic mapping studies are equivocal and inconclusive.⁸ The autonomic nervous system of some patients with ADs, especially those suffering from PD, shows raised sympathetic tone, slow adaptation to repeated stimuli, and excessive response to moderate stimuli.⁴ Abnormal functioning of three neurotransmitters, noradrenaline, serotonin, and γ -aminobutyric acid (GABA) has been implicated in the pathogenesis of ADs.⁴ Neuroimaging studies have commonly implicated the amygdala, insula, and prefrontal cortex (PFC) in the pathophysiology of ADs.⁹

Current Pharmacotherapy of Anxiety Disorders

Many of the currently used drugs for ADs modify the functioning of noradrenaline, serotonin, and GABA by enhancing their actions. Currently used antianxiety (anxiolytic) drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), benzodiazepines, buspirone, and β -adrenergic receptor blockers.¹⁰ The histamine-1 receptor blocker hydroxyzine which causes short-term sedation, is used in treating patients in whom other anxiolytic drugs are not recommended.¹⁰ The anticonvulsant drug pregabalin may be useful in the treatment of ADs, as in some patients with GAD, SAD, and PD.^{4,11} The monoamine oxidase inhibitor

moclobemide may be helpful in treating severe cases of SAD.^{4,11}

The drug of choice for treating ADs depends on the subtype of the disorder and the clinical need for acute anxiolytic effects.¹¹ Among the drugs, only the benzodiazepines and the β -adrenergic receptor blockers are effective acutely. For the treatment of chronic anxiety SSRIs and SNRIs are used. For situational anxiety, the β -adrenergic receptor blockers are used. For example, propranolol, in conjunction with psychological intervention, has been shown to decrease anxiety in subjects who develop situational anxiety due to spiders.¹² For immediate effects, the benzodiazepines are used.¹¹ In conjunction with pharmacotherapy, psychotherapy is essential for the effective control of symptoms of patients with ADs.⁶

Outline of Epigenetics

Epigenetics, which literally means above, or in addition to, genetics, is presently an active area of research in both biology and medicine. It refers to heritable changes in gene expression not involving changes in DNA sequence. It involves molecular mechanisms like DNA methylation, DNA hydroxymethylation, histone modifications, and non-coding RNA (ncRNA)-mediated regulation of gene expression.¹³ Regarding ncRNAs, they can be considered to be a part of epigenetics, when epigenetics is considered in a broad sense.¹³ For example, epigenetic mechanisms of gene expression like DNA methylation can regulate ncRNA expression.¹⁴ Conversely, ncRNAs can regulate epigenetic mechanisms of gene expression. For example, ncRNAs can regulate the expression of genes encoding proteins like DNA methyltransferases (DNMTs) that are involved in the epigenetic regulation of gene expression.¹⁴ ncRNAs can be classified based on size into long ncRNAs (lncRNAs) which are more than 200 base pairs long and short ncRNAs which are less than 200 base pairs long.¹³ The most extensively studied short ncRNAs are microRNAs (miRNAs).¹³

Epigenetic mechanisms of gene expression are known to interact with each other. Unlike the DNA sequence, epigenetic mechanisms of gene expression are relatively easily modified by the environment.¹⁵ Epigenetic mechanisms of gene expression are known to vary between cells and tissues and also show temporal variation.^{16,17} There is increasing evidence that abnormalities in epigenetic mechanisms of gene expression contribute to the pathogenesis of disease, especially common disease. Indeed, epigenetics has been referred to as the epicenter of modern

medicine.¹⁸ There is also increasing evidence that epigenetic mechanisms of gene expression are dysregulated in virtually every type of psychiatric disorder and that dysregulated epigenetic mechanisms contribute to their pathogenesis.^{16,17,19}

Role of Epigenetics in the Pathogenesis of Anxiety Disorders

Scope of Epigenetics in Anxiety Disorders

Several lines of evidence suggest that abnormalities in epigenetic mechanisms of gene expression contribute to the pathogenesis of ADs: 1. As alluded to above, no genetic mutation or polymorphism underlying these disorders has been conclusively identified. 2. The concordance rate of identical twins for ADs is only 30 to 40%, supporting the idea that there are environmental factors involved in their pathogenesis.^{20,21} 3. Environmental factors, especially psychosocial stress, are known to influence the pathogenesis of ADs.²² 4. There are gender differences in the epidemiology of ADs: The lifetime prevalence of ADs in women is 30.5% whereas in men it is 19.2%.⁴ 5. As given below, there is experimental evidence that epigenetic mechanisms of gene expression are dysregulated in patients with ADs.

To date, no study has investigated epigenetic changes in the post-mortem brain of patients with ADs. The reason for this is the practical difficulty of obtaining suitable post-mortem brain tissues from patients diagnosed to have ADs. However, studies have been conducted on peripheral cells and tissues obtained from patients with ADs as proxies for brain tissues.

Roles of DNA Methylation and Histone Modifications in Anxiety Disorders

Changes in DNA methylation and histone modifications in animal models of ADs are listed in Table 1 and in peripheral cells in patients with ADs in Table 2. It is interesting that in two studies^{24,25} hypermethylation of the GAD1 gene, which encodes the enzyme glutamic acid decarboxylase1, the enzyme that catalyzes the decarboxylation of glutamic acid to GABA, was found. Hypermethylation of DNA correlates with inhibition of gene expression.¹³ Hence hypermethylation of GAD1 would lead to reduced expression of GAD1, and hence reduced formation of GABA, the major inhibitory neurotransmitter in the brain. In this context, it is known that patients with PD have been found to have lower brain concentrations of

Table 1 Epigenetic Changes in Animal Models of Anxiety Disorders

Tissue	Epigenetic Change	References
Rat developing hippocampus, amygdala	DNA methylation changes	[23]
Rat basolateral amygdala	Hypermethylation in <i>GAD1</i> gene	[24]
Mouse basolateral amygdala	Hypermethylation of <i>GAD1</i> gene	[25]
Rat hippocampus	Hypermethylation of <i>Nr3c1</i> gene	[26]
Rat amygdala	Hypermethylation of developing brain	[27]
Rat amygdala	BDNF gene hypermethylation	[28]
Rat amygdala	Aberrant HDAC2-mediated histone modifications	[29]
Rat hippocampus	Differential histone acetylation and methylation	[30]
Rat hippocampus	H3 histone acetylation; modulation of methyl-CpG-binding	[31]
Mouse cerebral cortex	Down-regulation of HDAC2 associated with <i>BDNF</i> gene	[32]
Rat hippocampus	Reduces H3K14 acetylation due to prenatal dexamethasone	[33]
Rat hippocampus	Decreases H3K9 and H4K12 acetylation due to social isolation	[34]
Rat PFC	Reduces H3/H4 acetylation after extinction training	[35]
Rat nucleus accumbens	Inhibition of G9a/GLP HMT	[36]
Mouse medulla oblongata	Histone modifications of genes affecting neurodevelopment and emotionality	[37]
Mouse hippocampus and amygdala	Dysregulation of miR-132/212	[38]
Rat amygdala	Over-expression of miR-101a and its target <i>Ezh2</i>	[39]
Rat PFC and hippocampus	Changes in miRNA-135a and miRNA-16	[40]
Rat amygdala and PFC	Microbial regulation of miRNA expression	[41]
Mouse PFC	lncRNA Gomafu associated with anxiety	[42]

Abbreviations: BDNF, brain-derived neurotrophic factor; GAD1, glutamic acid decarboxylase1; HDACi, histone deacetylase inhibitor; HMT, histone methyltransferase; lncRNA, long non-coding RNA; miRNA, microRNA; PFC, prefrontal cortex.

Table 2 Epigenetic Changes in Human Peripheral Cells in Anxiety Disorders

Tissue	Epigenetic Change	References
Whole blood	183 differentially methylated loci	[46]
Blood cells	<i>GAD1</i> gene hypomethylation	[47]
Buccal cells	Hypomethylation of <i>SERT</i> gene	[48]
Whole blood	<i>MAOA</i> gene hypomethylation	[49]
Whole blood	Several CpG sites hypomethylated	[50]
Saliva cells	Hypomethylation of <i>MAOA</i> gene	[51]
Whole blood	Hypomethylation of oxytocin receptor gene	[52]
Saliva	Hypermethylation in AA genotype of <i>OXTR</i> rs53576	[53]
PBMCs	Global DNA hypermethylation	[54]
Leukocytes	Glucocorticoid receptor gene hypermethylation	[55]
Whole blood	Hypermethylation of <i>FOXP3</i> promoter	[56]
Whole blood	Hypermethylation of <i>HECA</i> gene in females	[57]
Saliva cells	Neurodevelopmental pathway gene hypermethylation	[58]
Whole blood	Hypermethylation of <i>STK32B</i> promoter	[59]
Peripheral venous blood	Hypermethylation of <i>BDNF</i> gene	[60]
Peripheral blood	Hypermethylation of <i>NR3C1</i> gene	[61]
Saliva	Hypermethylation of <i>NR3C1</i> gene	[62]
Peripheral blood	Hypermethylation of <i>FKBP5</i> gene	[63]
Saliva	Hypermethylation of <i>BDNF</i> and oxytocin receptor genes	[64]
Whole blood	hsa-miR-579-3P upregulates fear and anxiety	[65]
PBMCs	Increases miR-663 expression	[66]
Sperm	Reduces levels of miRNAs 449 and 34	[67]
Peripheral blood	Moderating effect of miRNAs on workplace bullying	[68]

Abbreviations: *GAD1*, glutamic acid decarboxylase1; miRNA, microRNA; PBMCs, peripheral blood mononuclear cells.

GABA than healthy controls.^{43,44} However, the data on GABA concentrations in plasma and cerebrospinal fluid of patients with anxiety is contradictory, possibly due to differences between studies in study design and methodology, tissues where sampling was done, and patient populations. Supporting a direct role for GABA in ADs is the recent finding of He et al⁴⁵ that repeated oral administration of GABA to emotionally stressed rats was found to reduce anxiety. These authors subjected the rats to stress using the open field and elevated plus maze models.

Stressful life events, especially those during childhood, are known to increase the risk for adult-onset ADs.⁶⁹ Stress is known to activate many neuronal circuits, like those in the hippocampus,⁷⁰ and the hypothalamic-pituitary-adrenal (HPA) axis. Genes encoding proteins associated with the HPA axis like the glucocorticoid receptor (GR or *NR3C1*), corticotropin releasing factor (CRF), FK506 binding protein 5 (*FKBP5*; a co-chaperone of the glucocorticoid receptor), proopiomelanocortin (POMC), and vasopressin have been found to show abnormalities in DNA methylation by previous studies.⁶⁹ These studies suggest that excessive stress due to dysregulation of the HPA axis caused by changes in DNA methylation of such

genes can upregulate the HPA axis and increase anxiety.⁶⁹ A consistent epigenetic change appears to be hypermethylation of the *Nr3C1* gene, the gene encoding the GR. Such findings have been seen in animal models of ADs,²⁶ and in peripheral tissues of patients with ADs.^{61,62} Indeed, there is converging evidence that in individuals who experience stress during early life hypermethylation of the *Nr3C1* gene could contribute to the development of stress during adulthood.⁷¹

The GR is also known to interact with histone deacetylase 6 (HDAC6) in the brain. Lee and co-workers,⁷² showed that acute stress, via the GR, increases glutamatergic signaling in the PFC of rats. The authors found that inhibition or knockdown of HDAC6 prevents the enhancement of glutamatergic signaling by acute stress. The same treatment of the GR chaperone protein HSP90, a substrate of HDAC6, produced similar results. These results suggested to the authors that HDAC6 is a key enzyme regulating the synaptic effects of acute stress in the PFC. Espallergues et al⁷³ showed that selective knockout of HDAC6 in the dorsal raphe neurons in mice reduces the anxiogenic effects of glucocorticoids in mice. These authors found that in mice exposed to chronic social

defeat, HDAC6 depletion in serotonergic neurons prevents social avoidance. HDAC6 depletion was associated with decreased interaction between HSP90 and the GR.

FKBP5 is a chaperone protein that negatively regulates GR sensitivity by reducing binding affinity and restricting nuclear translocation.⁶⁹ Roberts et al⁶³ found that the FKBP5 gene in peripheral venous blood is hypermethylated in patients with agoraphobia with or without PD and that this is corrected by psychotherapy. These findings support the previous data of the same group⁷⁴ that children with ADs had hypermethylation in the FKBP5 gene and that this was corrected by psychotherapy.

Brain-derived neurotrophic factor (BDNF) is a member of a family of neurotrophins which also includes nerve growth factor. BDNF is a key regulator of neuronal differentiation, structure, and function.⁷⁵ Moreover, there is evidence that BDNF modulates neuronal activity to impact complex human phenotypes like memory, anxiety, and depression.⁷⁵ BDNF levels appear to be reduced in patients with ADs.⁷⁶ However, this is not consistent across all the different subtypes of ADs.⁷⁶ The gene encoding BDNF has been found to be epigenetically modified, with reports of hypermethylation in the rat amygdala,²⁸ and peripheral venous blood,⁶⁰ and saliva⁶⁴ of patients with ADs. Since hypermethylation is associated with reduced gene expression, this would lead to reduced levels of BDNF. The oxytocin neuropeptide system plays a role in social behavior and cognition.⁶⁹ In this regard, the gene encoding the oxytocin receptor has shown changes in DNA methylation in patients with ADs.^{52,53,64}

Role of Non-Coding RNAs in Anxiety Disorders

ncRNAs play a major role in neurogenesis and the regulation of normal neuronal function in the brain.⁷⁷ For example, they regulate neuronal plasticity, learning and memory.⁷⁸ There is also increasing evidence that ncRNAs, especially miRNAs, are involved in the pathogenesis of neuropsychiatric disorders including ADs.⁷⁸ For example, experimental up- or down-regulation of candidate miRNAs associated with neurocircuits associated with anxiety can modulate anxiety-related behavior in animal models of ADs.⁷⁷

Studies on animal models of ADs suggest that specific miRNAs may play various roles in the development and progression of anxiety in a brain region-specific manner.⁷⁸ Transposable elements (TEs) are mobile genetic elements (pieces of DNA capable of moving to new locations).⁷⁹ They make up to two-thirds of the human genome.⁸⁰ There is growing evidence of a close association between TEs and ncRNAs, and many small ncRNAs originate from TEs.⁷⁹ TEs have been associated with disease pathology in patients with ADs. For example, stress can interact with the epigenome to regulate the expression of TEs in a region-specific manner to alter stress responsiveness, anxiety, and brain plasticity.⁸¹ Compared to changes in DNA methylation and histone modifications relatively few studies to date have investigated the role of ncRNAs in the pathogenesis of ADs (Tables 1 and 2).

Trials of Epigenetic Drugs in Anxiety Disorders

Table 3 lists preclinical drug trials that have evaluated epigenetic drugs for treating ADs. As shown, most of the trials have evaluated the use of HDAC inhibitors (HDACi) in

Table 3 Preclinical Trials of Epigenetic Drugs in Anxiety Disorders

Drug	Class	HDAC Class Target of Drugs	Effect	References
MS-275	HDACi	I, III	Reduces anxiety in S1 mice	[82]
TSA	HDACi	I, II	Has anxiolytic effects in rats	[83]
TSA	HDACi	I, II	Reduces anxiety-like behavior in rats	[84]
TSA, SAHA	HDACi	I, II,IV	Reduces anxiety-like behavior in Fischer rats	[85]
SAHA	HDACi	I, II,IV	Reduces stress-related behavior in rats	[86]
MS-275	HDACi	I,III	Rescues enhanced innate anxiety in mice	[87]
TSA	HDACi	I,II	Reverses anxiety due to maternal binge drinking	[88]
SB,VA	HDACi	I,IIa	Reduces anxiety in mice	[89]
SAHA	HDACi	I,II, IV	Reduces corticosterone-induced stress in mice	[90]
Lactate	Natural drug	–	Promotes resilience to stress in C57BL/6 mice	[91]

Abbreviations: HDACi, histone deacetylase inhibitor; SAHA, suberoylanilide hydroxamic acid; SB, sodium butyrate; TSA, trichostatin A; VA, valproic acid.

preclinical studies of the use of epigenetic drugs for treating ADs. All the preclinical drugs trials that evaluated the use of HDACi listed in Table 3 found that these drugs alleviate stress or anxiety. The HDACi that were evaluated (MS-275, trichostatin A (TSA), vorinostat, sodium butyrate, and valproic acid) belong to different classes of HDACi. However, it is to be noted that most of them inhibit HDACs I and/or II, both of which are class I HDACs.⁹² One study⁹¹ evaluated the use of the naturally occurring compound lactate which was found to promote resilience to stress in mice by modulating the activity of HDACs.

Table 4 lists the clinical trials of epigenetic drugs in the treatment of anxiety. As listed, all the clinical trials made use of valproate, which is known to function as a HDACi. Five of the 6 trials tested the anxiolytic effect of valproate on patients with ADs, and all found valproate to give beneficial effects.^{93–97} One trial⁹⁸ was conducted to determine whether valproate reduces anxiety in healthy subjects and it found that valproate reduces anxiety in such subjects. It must be noted that valproate in addition to acting as a HDACi, also inhibits nerve conduction, which could also contribute to its antianxiety effects.

miRNA-directed therapy is another option in the treatment of ADs.⁹⁹ miRNAs in patients with ADs can be targeted to lead to an upregulation of the targeted miRNA. Another possible therapy involves the inhibition of miRNAs in order to reduce their effects in target areas. Antagomirs and antisense oligonucleotides are being investigated for inhibiting miRNAs in preclinical drug trials.⁹⁹ However, miRNA-directed therapy in psychiatric disorders including ADs is in its early stages, and much more research needs to be done in order to take this field forward.⁹⁹

Table 4 Clinical Trials of Epigenetic Drugs in Anxiety Disorders

Drug	Class	HDAC Class Target of Drugs	Finding	References
Valproate	HDACi	I, IIa	Decreases panic disorder	[93]
Valproate	HDACi	I, IIa	Ameliorates panic disorder	[94]
Valproate	HDACi	I, IIa	Decreases panic disorder	[95]
Valproate	HDACi	I, IIa	Decreases social anxiety	[96]
Valproate	HDACi	I, IIa	Reduces anxiety	[97]
Valproate	HDACi	I,IIa	Decreases anxiety in healthy subjects	[98]

Abbreviation: HDACi, histone deacetylase inhibitor.

Implications of Trials of Epigenetic Drugs in Anxiety Disorders

There are several classes of drugs that are effective for the treatment of ADs. However, there are problems with the currently available drugs. For example, about one third of patients with ADs do not adequately respond to the current drugs.² A related problem is treatment-resistant ADs.¹⁰⁰ Another problem is adverse effects that include habituation, dependence, and abuse.¹⁰ In this light, new drugs could be useful in the treatment of patients with ADs. One potential class of new drugs for treating ADs is epigenetic drugs. As shown in Tables 3 and 4, preclinical and clinical drug trials using HDACi for the treatment of ADs are showing favorable results.

HDACs are a group of enzymes that belong to two families and four classes.¹⁰¹ The two families are the HDAC family and the Sir2 regulator family. In humans HDACs are divided into four classes based on sequence similarities. The class I enzymes are HDAC1, HDAC2, HDAC3, and HDAC8. The class II enzymes are HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10. The class III enzymes have sequence similarity to the yeast Sir2 protein and are SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7. Class IV HDACs has one enzyme, HDAC11.

When compared to histone acetyltransferases (HATs), the quest for specific histone substrates for HDACs has proved to be arduous. The problems encountered include very low measurable HDAC activity when HDACs are purified to homogeneity, and functional redundancy of many HDACs.¹⁰¹ HDACs also have non-histone substrates in addition to histones. Using high-resolution mass spectrometry, it was demonstrated that there are more than 3600 acetylation sites on 1750 proteins. The acetylation sites are present on nuclear, cytoplasmic, and mitochondrial proteins involved in many different cellular processes.¹⁰² The broad spectrum HDACi, SAHA and MS-275, were found to up-regulate about 10% of all the sites by at least a factor of 2, indicating that many of these acetylation reactions are regulated by classical HDACs. Computational models suggest that many more acetylation sites occur. These findings suggest that acetylation due to HDACs is common in histone and non-histone proteins.

Clinically useful HDACi are classified according to their chemical structure⁹² into hydroxamic acids (vorinostat or SAHA, panobinostat, belinostat, TSA, quisinostat, rocilinosat, and abexinostat), short chain fatty acids

(butyrate and valproic acid), cyclic peptides (romidepsin), and benzamides (mocetinostat or MGCD0103 and entinostat or MS-275). Most currently available HDACi inhibit classes I, II, and IV of the HDACs, but not SIRT enzymes. HDACi, like HDACs, affect several targets in addition to HDACs and have mechanisms of action other than inhibition of HDAC. Many targets of HDACi are involved in anti-tumor pathways. HDACi cause accumulation of acetylated forms of histone and non-histone proteins that regulate gene expression, cell proliferation, and cell death.¹⁰³ Although HDACi can up-regulate global histone acetylation levels, they do not always cause histone hyperacetylation, particularly at regions near gene promoters.¹⁰⁴ These drugs up-regulate or down-regulate an equal number of genes. Hence, at present, the possible mechanism of action of HDACi in the treatment of the ADs is unclear. However, it has been shown that HDACi in addition to causing histone acetylation, also cause DNA demethylation, possibly due to increased levels of the demethylating enzyme ten-eleven translocation methylcytosine dioxygenase 1 (TET1).^{105,106} Since several genes have been shown to be hypermethylated in animal models of ADs (Table 1) and in human peripheral cells in patients with ADs (Table 2), DNA demethylation of such genes by HDACi may contribute to the mechanism of action of HDACi in ADs.

As mentioned in the introduction, co-morbidity exists between ADs and depressive disorders. Since HDACi are giving favorable results in preclinical and clinical trials of depressive disorders,¹⁰⁷ these drugs could be useful for treating patients with ADs who also have depressive symptoms. Since HDACi are known to have cognition-enhancing effects, this property of these drugs may also make them suitable for treating patients with ADs some of whom can experience cognitive deficits.¹⁰⁸

Conclusions

Several lines of evidence suggest that disrupted epigenetic mechanisms of gene expression contribute to the pathogenesis of ADs. However, the study of the role of abnormal epigenetic mechanisms of gene expression in ADs is in its early stages, and more work needs to be done to clarify issues in this area. Preclinical and clinical drug trials suggest that HDACi give favorable results in the treatment of ADs. However, at present the mode of action of HDACi in ADs is not clear. More work needs to be done on elucidating the mode of action of HDACi in alleviating the signs and symptoms of ADs.

Disclosure

The author alone is responsible for the content and writing of this paper and he reports no conflicts of interest.

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