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REVIEW ARTICLE

Effects of Histone Modification in Major Depressive Disorder

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Abstract: Major depressive disorder (MDD) is a disease associated with many factors; specifically, environmental, genetic, psychological, and biological factors play critical roles. Recent studies have demonstrated that histone modification may occur in the human brain in response to severely stressful events, resulting in transcriptional changes and the development of MDD. In this review, we discuss five different histone modifications, histone methylation, histone acetylation, histone phosphorylation, histone crotonylation and histone β-hydroxybutyrylation, and their relationships with MDD. The utility of histone deacetylase (HDAC) inhibitors (HDACis) for MDD treatment is also discussed. As a large number of MDD patients in China have been treated with traditional Chineses medicine (TCM), we also discuss some TCM therapies, such as Xiaoyaosan (XYS), and their effects on histone modification. In summary, targeting histone modification may be a new strategy for elucidating the mechanism of MDD and a new direction for MDD treatment.

Keywords: Major depressive disorder, histone methylation, histone acetylation, histone phosphorylation, histone crotonylation, histone β-hydroxybutyrylation, HDAC inhibitor.

1. INTRODUCTION

Major depressive disorder (MDD) is a common mental disorder that affects more than 163 million people worldwide [1]. Unlike transitory emotional changes induced by unfortunate events or challenges, MDD can severely affect the daily life of individuals and even threaten their lives. Patients with MDD may have severe symptoms, such as notable, long-term sadness and despair, cognitive issues, loss of interest in activities, reductions in speech and activity, and sleep disturbances [2, 3]. Studies have shown that people who experience serious stressful events, such as divorce, unemployment, severe physical disease, and the death of family members are more likely to develop MDD [4-7]. However, environmental factors are not the only factors that lead to MDD, and genetic, psychological, and biological factors also play important roles in the development of this disease. Recently, researchers demonstrated that the activation of the corticotropin-releasing hormone (CRH)/hypothalamic-pituitary-adrenocortical (HPA) axis, overactivation of the sympathetic nervous system, aberrant secretion of monoaminergic neurotransmitters, hypersecretion of inflammatory cytokines, inhibition of neurotrophic factors, and epigenetic changes are associated with the development of MDD [8-13]. Specifically, the relationship between epigenetics and MDD has attracted scientists' attention in recent years.

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Epigenetics might be one of the bridges that connect environmental and genetic factors. Stressful events might lead to changes in epigenetic modifications, leading to gene expression alterations. The concept of epigenetics, which is the ability to alter gene expression without altering the DNA sequence, was first proposed by Waddington [14]. Epigenetics includes RNA (mRNA and non-coding RNA) editing, genomic imprinting, gene silencing, and X-chromosome inactivation [15]. Epigenetic modifications have been found to be important in nervous system diseases, such as Parkinson's disease, Huntington disease, Alzheimer's disease and MDD [15-17]. Epigenetic modifications include DNA methylation, histone modification and non-coding RNA regulation and can influence the transcription of RNAs, thus inducing phenotypic changes without changing DNA sequences [18-21]. Among these different types of epigenetic modifications, post-translational modifications of histones can influence chromosome conformation, which then changes gene expression.

Currently, antidepressants used in the clinic can be divided into the following seven groups: selective serotonin reuptake inhibitors (SSRIs), serotonin modulators (5-HT_2 blockers), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), heterocyclics, monoamine oxidase inhibitors (MAOIs) and melatonergic antidepressants [22]. These medications work mainly by inhibiting serotonin and norepinephrine activities. However, patients taking the aforementioned antidepressants frequently have serious side effects, and approximately 40% of MDD patients are not sensitive to these medications [23]. The development of highly effective and

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less toxic antidepressants is necessary. Researchers have developed new antidepressants with targets such as the glutamate/gamma-aminobutyric acid systems, the HPA axis pathway, opioid receptors, brain-derived neurotrophic factor (BDNF), and glial-derived neurotrophic factor (GDNF) [23-25]. Moreover, antidepressants that target histone modifications have also attracted the attention of researchers. Histone deacetylase (HDAC) inhibitors have been found to be useful for MDD treatment.

In this review, we focus on histone modification and describe how it affects gene transcription and thus influences the development and treatment of MDD. Furthermore, antidepressants that target histone modifications, especially HDAC inhibitors, are alsodescribed . We also present histone modification studies performed on mice, rats and humans.

2. HISTONE MODIFICATION

Histones and DNA in combination form chromatin. The basic structure of chromatin is the nucleosome, which is formed by two copies of histone 2A (H2A), two copies of histone 2B (H2B), two copies of histone 3 (H3) and two copies of histone 4 (H4) wrapped by a 147-bp piece of DNA [26]. Between nucleosomes, there is an approximately 50-bp DNA segment (linker DNA) that binds with histone H1 [15]. The linker DNA segment and linker histone H1 tightly connect nucleosomes together to form chromatin [27]. Furthermore, the alkaline N-terminal tails of histones protrude from the nucleosome and connect with neighboring nucleosomes to form chromatin of different conformations [26].

All histone modifications occur posttranslationally, which include methylation, acetylation, phosphorylation, crotonylation, β-hydroxybutyrylation, deamination, β-N-acetylglucosamine ADP ribosylation, ubiquitination and SUMOylation, [28]. Different histone modifications can change the conformation of chromatin to euchromatin (active) or heterochromatin (inactive), which then alters gene transcription, DNA repair, DNA replication, DNA recombination and alternative splicing [29-32]. Recent studies have demonstrated that histone modifications can be used to predict gene transcription levels; histone acetylation is always accompanied by transcriptional activation, while histone methylation may be associated with different transcriptional functions [33]. In addition to histone methylation and histone acetylation, histone phosphorylation, histone crotonylation and histone β-hydroxybutyrylation have also been found to regulate the development of MDD. In the following section, we introduce the five histone modifications and their relationships with MDD.

3. HISTONE MODIFICATION IN MDD

Epidemiological analysis has shown that although there are no significant differences in histone modification between identical twins at the time of birth, differences in histone modifications develop with age, leading to differences in the risk for developing MDD [34-36]. This finding suggests that the development environment might alter epigenetic characteristics and thus enhance susceptibility to MDD. In the section below, we focus on how histone modification alters gene transcription and influences MDD progression and discuss whether histone modification could be a biomarker for MDD diagnosis and treatment. Since scientists have discovered that histone methylation, histone acetylation, histone phosphorylation, histone crotonylation and histone β-hydroxybutyrylation may play important roles in gene transcription in MDD, we will discuss these five modifications separately.

3.1. Histone Methylation

Histone methylation is one of the most important histone modifications and is important for signal transmission [37]. First discovered in 1964, histone methylation involves the addition of a methyl group (-CH3) to lysine or arginine residues [38]. Histone methylation is a dynamic process by which a methyl group can be added or removed by specific enzymes. Other proteins can recognize and bind methylated residues to alter phenotypes. Different numbers of methyl groups can be added to the ε-amino group of lysine for monomethylation (me), dimethylation (me2) or trimethylation (me3); arginine can be symmetrically methylated (me2s), asymmetrically methylated (me2a), and monomethylated (me1) [39]. Methylation can occur at different positions and different forms of methylation may be associated with different functions, such as transcriptional activation or transcriptional repression. Histone methylation is catalysed by histone methyltransferases (HMTs), which can add a methyl group donated by S-adenosylmethionine to its target residues [38, 40].

Histone modification of gene regulatory regions may play a role in MDD (Table **1**). One of the most characteristic histone modifications is histone 3 lysine 4 trimethylation (H3K4me3). Enhancement of H3K4me3 at the promoter region of synapsin 1, which results in overexpression of synapsin 1a (SYN1a) and synapsin 1b (SYN1b), was found in the brain tissues of 18 MDD patients who died from suicide, [41]. Studies of mice exposed to chronic unpredictable mild stress (CUMS) have demonstrated that in different epigenetic states, the GDNF gene regulates susceptibility and adaptation to chronic stress. A reduction in the levels of H3K4me3 at the GDNF promoter led to a reduction in GDNF levels in CUMS-exposed mice. This shows that histone modification plays a vital role in the control of behavioural responses to chronic stress [25]. Although H3K4me3 activates gene transcription, other forms of histone methylation, such as H3K9me2 and H3K27me3, inhibit gene transcription. Enhancement of H3K9me2 at the promoter region of calmodulin-dependent protein kinase II α (CaMKIIα) resulted in the inhibition of CaMKIIα in MDD patients and mice exposed to antidepressants compared to that in untreated MDD patients and control mice [42]. RAS-related C3 botulinum toxin substrate 1 (RAC1), a Rho GTPase-related gene known to regulate the synaptic structure, was also shown to be inhibited by the induction of H3K27me3 in the nucleus accumbens (NAc) of mice exposed to chronic social defeat stress compared to that of control mice [43]. Interestingly, enhanced H3K4me3 at the promoter region of SYN1 and reduced H3K4me3 at the promoter region of GDNF were found in MDD patients and animal models [25, 41]. Even in the same disease, the levels of H3K4me3 were disparate at the promoter regions of different genes. Discovering how HMTs and histone demethylase recognize promoter regions of different genes and

determining disparate levels of H3K4me3 in their promoter regions may yield interesting results.

HMTs were also found to be important in MDD (Table **2**). Increased expression and activity of the HMT Setdb1 in forebrain neurons is associated with antidepressant-like phenotypes, including reduced mania, a reduced sense of helplessness in learning, and reduced depression-like behavior in mice in tail suspension and forced swimming tests [44]. Similar to Setdb1 expression and activity, HMT G9a expression and activity were also found to be reduced in a social defeat stress mouse model [45]. Analysis of protein arginine methyltransferase 1 (PRMT1) knockout mice and $PRMT1^{wt/wt}$ mice revealed that deletion of PRMT1 resulted in inhibition of depressive-like behaviour and induction of BDNF, and postsynaptic density protein 95 (PSD95) expression [46]. Expression of JMJD3, a histone lysine demethylase, was also found to be upregulated in the prefrontal cortex and hippocampus of CUMS-induced rats, which resulted in a reduction in pan-H3K27me3 [47]. However, the level of H3K27me3 at the promoter region of RAC1 was increased. This result showed that the level of H3K27me3 might be different in different genes, similar to that observed for H3K4me3. Research on H3K27me3 levels at the promoter regions of specific genes was more precise. Elucidating the underlying mechanism of histone methylation may lead to new methods for treating depression.

3.2. Histone Acetylation

Similar to histone methylation, histone acetylation is a common form of histone modification. Since histone acetylation was first discovered by Allfrey *et al.,* in 1964, it has been found to play important roles in several human diseases [15, 48]. In contrast to histone methylation, histone acetylation may enhance gene transcription. Histone acetylation occurs at lysine residues and can be regulated by histone acetyl-transferases (HATs) and HDACs. HATs weaken the interaction between DNA and histones and expose gene promoter regions, which results in the promotion of gene transcription and expression, while HDACs strengthen these interactions and protect gene promoter regions leading to the inhibition of gene transcription and expression (Fig. **1**) [49, 50]. Normally, histone acetylation and histone deacetylation are under dynamic equilibrium, and diseases can develop if this equilibrium is disrupted.

As shown in Table **1**, Tsankova *et al.,* first discovered that MDD induced by chronic social defeat stress in mice may be related to histone acetylation and that the antidepressant imipramine can effectively induce histone acetylation, thus curing MDD [51, 52]. Moreover, inhibition of BDNF, a factor with antidepressant effects, was observed in the hippocampus of MDD mice, and overexpression of BDNF was found to be accompanied by an increase in H3 acetylation at the P3 and P4 regions of the BDNF promoter following imipramine treatment [51, 52]. Similarly, Fuchikami *et al.,* found that the expression of BDNF was inhibited in the hippocampus when mice was exposed to a single immobilization stress test and that H3 acetylation was inhibited at the P1, P4 and P6 regions of the BDNF promoter in mice exposed to single immobilization stress test compared to that in control mice [53]. Similar to histone methylation, RAC1 expression was also found to be decreased, correlating with the reduction in H3 acetylation of the RAC1 promoter region after exposure to chronic social defeat stress [43]. These results showed that histone methylation and histone acetylation might synergistically control gene expression. H3 acetylation of the promoter region of GDNF is also reduced in CUMS-induced mice, resulting in inhibition of GDNF expression [25]. In addition to alterations in mouse models, changes in the NAc of MDD patients have also been explored. For instance, Robison *et al.,* discovered that H3 acetylation at the CaMKIIA promoter region reduced in patients taking antidepressant drugs compared with patients not taking antidepressants [42].

In addition to pan-acetylation of H3, specific forms of histone acetylation have also been detected. Kenworthy *et al.,* and Montagud-Romero *et al.,* discovered that the levels of H3K9ac, H3K14ac, H4K5ac, H4K8ac, H4K12ac and H4K16ac reduced in the mouse dorsal raphe (DR) nucleus and hippocampus after exposure to social defeat stress [54, 55]. Furthermore, the acetylation levels of H4K12 and H3K14 were also found to be increased 15 or 21 days after exposure to social defeat stress [55, 56]. These discoveries demonstrate that histone acetylation can be inhibited once a mouse is exposed to stress and that histone acetylation is slowly enhanced during recovery, which further shows the important role of histone acetylation in MDD. The above research showed that MDD is highly associated with a reduction in histone acetylation, and analyzing histone acetylation could be a meaningful direction for the study of MDD and for developing MDD treatment strategies.

Currently, HDACs are the main focus of research on the regulation of histone acetylation in MDD (Table **2**). Human HDACs can be divided into the following four classes: class I HDACs, which include HDAC1, 2, 3, 8; class II HDACs, which include HDAC 4, 5, 6, 7, 9, 10; class III HDACs, which include sirtuins (SIRTs); and class IV HDAC, *i.e.*, HDAC11 (Fig. **1**) [57, 58]. Class I HDACs and class II HDACs have been demonstrated to be the most important HDACs in regulating MDD. Convington *et al.,* demonstrated that HDAC2 expression in the mouse NAc can be repressed on both day 1 and day 15 after social defeat in mice to allow recovery from stress, and that HDAC2 expression is also inhibited in postmortem NAc samples from individuals who had been treated with antidepressants [56, 59]. By measuring the levels of 11 HDACs in the mouse striatum (STR), Uchida *et al.,* found that HDAC2 expression can be induced in a CUMS-induced depression model and that depressive behavior developed less often in mice injected with an HDAC2 inhibitor than in control mice [25]. On the other hand, HDAC5 seems to have the opposite function in MDD. Renthal *et al.,* showed that HDAC5 function was decreased in the NAc in a chronic social defeat stress mouse model, while HDAC5 function was increased after imipramine treatment [60]. In addition, HDAC5 knockout mice were also found to be hypersensitive to the development of depressive behavior after chronic social defeat stress [60]. There is still no evidence showing why these two HDACs have distinct functions. We speculate that since HDAC2 and HDAC5 belong to different classes of HDAC, their functions and target genes might also be different. By controlling

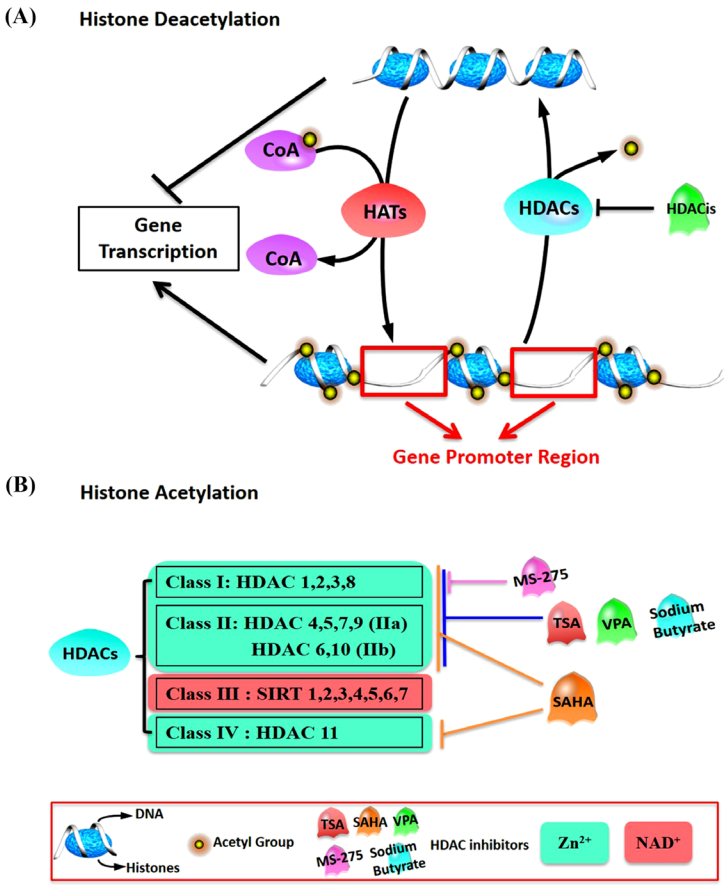

Fig. (1). Regulation of histone acetylation by HATs, HDACs and HDACis in MDD. **A**). Histone acetylation in dynamic equilibrium is controlled by HATs and HDACs. HATs can transfer an acetyl group from acetyl-CoA to a histone, which weakens the interaction between the histone and DNA, exposes the gene promoter region, and ultimately induces the transcription of related genes. On the other hand, HDACs can remove acetyl groups from histone, thus strengthening the interaction between the histone and DNA and inhibiting the transcription of related genes. **B**). Target selectivity of HDACis in MDD. HDACs can be divided into 4 different classes, and Class I and Class II HDACs are the most important HDACs in regulating MDD. HDACis (TSA, SAHA, VPA, MS-275, sodium butyrate) selectively inhibited HDACs, thus maintaining histone acetylation and activation of gene transcription. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

different targeted genes, HDAC2 and HDAC5 synergistically regulate the development and progression of MDD. Moreover, HDAC1 was found to play important roles in redox homeostasis, nitric oxide regulation and inflammatory/anti-inflammatory pathways [61] as we know that the interplay and coordination of redox homeostasis and nitric oxide regulation might exhibit neuroprotection function in neurorelation disease, including MDD [62-64]. Heat Shock Protein 90, a substrate of HDAC6, was also discovered to have a neuroprotection function [65]. Targeting HDACs and redox homeostasis might be promising therapeutics in MDD treatment.

Interestingly, HDAC expression was also detected in peripheral leukocytes, although the pattern of expression was observed to be different. Hobara *et al.* measured the expression of 11 HDACs in the peripheral white blood cells of 20 MDD patients and discovered that HDAC2 and HDAC5 were overexpressed in these patients compared to healthy people, but that there were no significant differences in the expression of the other 9 HDACs [66]. Furthermore, HDAC expression was measured in 39 MDD patients in remission, and it was found that the expressions of HDAC2 and HDAC5 were at normal levels and were not significantly different from those in the healthy groups [66]. Iga *et al.* also obtained similar results: HDAC5 expression was significantly higher in drug-free MDD patients than in healthy controls, but the expression level of HDAC5 returned to normal after 8 weeks of paroxetine treatment [67]. The results reported by Hobara *et al.* and Iga *et al.* suggest that the expression levels of HDAC2 and HDAC5 may be potential biomarkers for MDD and for evaluating the efficacy of MDD therapies [66, 67]. The trend of the change in HDAC5 expression was different in peripheral leukocytes and the NAc. These results suggest that the expression of HDAC5 might be different in different locations in the body.

Apart from Class I HDACs and class II HDACs, SIRTs (class III HDACs) were also discovered to regulate MDD and neurodegenerative disorders [68, 69]. Two genome-wide association studies (GWAS) analyzing 9000 Chinese women with MDD and 4855 Chinese Han population showed that single-nucleotide polymorphism (SNP) rs12415800 (SIRT1) was correlated with risk of MDD and with SIRT1 inhibition

Table 1. Different histone modification types and their associations with MDD.

Histone Modification Types	Modification Position	Transcription Function	Alteration in MDD	Affected Genes in MDD	References
Histone methylation	H3K4me3	Transcription activation	Enhanced at promoter region of SYN1 in MDD patients.	Overexpression of SYN1a and SYN1b	[41]
-	-	-	Reduced at promoter region of GDNF in CUMS-exposed mice.	Inhibition of GDNF	[25]
-	H3K9me2	Transcription repression	Reduced at promoter region of CaMKIIα in MDD patients not taking antidepressants.	Overexpression of CaMKIIα	[42]
-	H3K27me3	Transcription repression	Enhanced at promoter region of RAC1 in NAc of social defeat-stressed mice.	Inhibition of RAC1	[43]
Histone acetylation	Pan H3 Acetylation	Transcription activation	Reduced at BDNF promoter region in MDD mice.	Inhibition of BDNF	[51-53]
-	-	-	Reduced at RAC1 promoter region in social defeat-induced mice.	Inhibition of RAC1	[43]
-	-	-	Reduced at GDNF promoter region in CUMS-induced mice.	Inhibition of GDNF	[25]
-	-	-	Enhanced at CaMKIIα promoter region in MDD patients not taking antidepressants.	Overexpression of CaMKIIα	[42]
-	H3K9ac, H3K14ac, H4K5ac, H4K8ac, H4K12ac, H4K16ac	Transcription activation	Reduced in DR nucleus and hippocampus in social defeat-induced mice.	/	[54-56]
Histone phosphorylation	H3S10p	Transcription activation	Enhanced in ILCx and PrLCx of forced swimming-induced rats.	Promoted H3K14ac, inhibited H3K9ac and H3K9 methylation	[82-85, 91]
-	H3S28p	Transcription activation	／	Promoted H3K27ac, inhibited H3K27 methylation	[86]
Histone crotonylation	Pan Kcr	Transcription repression	Reduced in PFC of social defeat-induced mice.	Overexpression of CDYL	[107]
Histone β-hydroxybutyrylation	H3K9bhb	Transcription activation	Reduced in spatial restraint-induced MDD mice.	Inhibition of BDNF	[112-115]

[70, 71]. Research on a Japanese population showed similar results that SNP rs1245800, rs4746720 (SIRT1) and rs10997875 (SIRT1) were discovered to be associated with suicide and MDD [72, 73]. Not only SIRT1, SNPs in SIRT2 were also found to be related to the risk of postpartum depressive symptoms [74]. Studies have shown that MDD is a disease relevant to inflammation and redox homeostasis. And SIRTs were discovered to involve in the regulation of inflammation, redox homeostasis, and cell senescence [75]. Thus, SIRTs might be potential therapeutic targets in MDD treatments. SIRT1 activator resveratrol has been found to alleviate depressive-like behaviors in LPS (lipopolysaccharide)-induced mice [76]. Another SIRT1 activator, SRT2104 was also discovered to exhibit neuroprotective ability in CUMS-treated mice [77]. Interestingly, SIRT2 seems to have an opposite function in MDD compared to SIRT1. SIRT2 inhibitor 33i showed antidepressant function in CUMS mice [78]. Analyzing the function of different SIRTs and their relationship with MDD might help develop new therapies.

Histone methylation and histone acetylation are the two most common histone modifications in MDD. However, in recent years, histone phosphorylation, histone crotonylation and histone β-hydroxybutyrylation have also been found to be associated with MDD.

3.3. Histone Phosphorylation

Histone phosphorylation is another type of histone modification. Most histone phosphorylation takes place on serine and threonine residues, although tyrosine residues can also be phosphorylated [79]. Similar to histone acetylation, histone phosphorylation is under dynamic equilibrium and regulated by protein kinases (PKs) and protein phosphatases (PPs) [80]. PKs can transfer a phosphate group from ATP to an amino acid residue of histone and thus change the conformation of chromatin, while PPs can remove a phosphate group from histones [81]. Moreover, interactions between histone phosphorylation and histone acetylation and between histone phosphorylation and histone methylation have been found in cells. For example, phosphorylation of H3S10 was demonstrated to promote the acetylation of H3K14 but inhibit both the acetylation and methylation of H3K9, resulting in the activation of gene transcription [82-85]. In addition, H3S28p was found to promote H3K27 acetylation and inhibit H3K27 methylation, resulting in enhanced gene expression [86].

Histone phosphorylation has been found to play important roles in the human nervous system. Crosio *et al.* discovered that treatments targeting dopamine, acetylcholine or glutamate enhance H3S10 phosphorylation in the mouse hippocampus [87]. H3S10p expression was also found to be upregulated in the hippocampus in mice subjected to fear conditioning or drug addiction models [88, 89]. H3S10 phosphorylation at the c-fos promoter region was also found to be induced in rats exposed to novelty stress [90]. To date, there have been very few studies on the function of histone phosphorylation in MDD. Morello *et al.* first demonstrated that rats subjected to forced swimming tests showed a significant increase in H3 phosphorylation in the infralimbic (ILCx) and prelimbic (PrLCx) areas of the prefrontal cortex compared to mice not subjected to stress (Table **1**) [91]. However, no other researchers have focused on the relationship between histone phosphorylation and MDD. Since histone phosphorylation plays an important role in the human nervous system, the mechanism by which histone phosphorylation influences MDD might also be a valuable new future research direction.

3.4. Histone Crotonylation

Histone crotonylation is another uncommon histone modification that was first identified by Tan *et al.*, who identified 67 novel histone marks by analyzing mass spectrometry (MS) data using PTMap software (which can locate post-translational modification sites) and found 28 histone marks that are likely to be crotonylated [92, 93]. Histone crotonylation is similar to histone acetylation as this modification always occurs on lysine residues and is dynamically controlled by crotonyltransferases and decrotonylases [94]. Crotonyltransferases transfer a crotonyl group from crotonyl-CoA to an amino acid residue of histone, and decrotonylases remove the crotonyl group. HATs also regulate histone crotonylation, while class I HDACs (HDAC1, 2, 3, 8) act as decrotonylases [95-100]. Moreover, the concentration of crotonyl-CoA was found to be one of the restrictive factors of histone crotonylation [99, 100].

In human somatic and mouse male germ cell chromosomes, histone crotonylation was found to occur at the promoter regions or enhancer regions of active genes, resulting in the regulation of gene transcription [93, 99]. In addition, the crotonylation of histones was found to play critical roles in the regulation of processes such as acute kidney injury, spermatogenesis, telomere maintenance, HIV latency, and cancer development [101-106]. Liu *et al.* demonstrated that MDD induced by chronic social defeat stress is correlated with inhibition of histone crotonylation accompanied by induction of chromodomain Y-like protein (CDYL) expression (Table **1**) [107]. This is the first and only study demonstrating the relationship between MDD and histone crotonylation. More studies analyzing histone crotonylation regulation of other MDD-related gene expression levels and the relationship between histone crotonylation and other histone modifications in the regulation of gene transcription are necessary.

3.5. Histone β-hydroxybutyrylation

Histone β-hydroxybutyrylation is a newly discovered histone modification described by Xie *et al.* in 2016 [108]. Histone β-hydroxybutyrylation was found to be dynamically influenced by the cellular level of β-hydroxybutyryrate, but the mechanism by which a β-hydroxybutyryl group is transferred from β-hydroxybutyrate to a histone is still unknown [108, 109]. Moreover, RNAseq and Kyoto Encyclopedia of Genes and Genomes analysis (KEGG) revealed that β-hydroxybutyrylation of H3K9 is highly correlated with enhancement of gene expression [108].

β-Hydroxybutyrate, a ketone body, has already been demonstrated to be important in nerves- and nerve-related diseases. β-Hydroxybutyrylation was found to protect neurons from toxicity and prevent dopaminergic neurodegeneration in Alzheimer's and Parkinson's disease [110, 111]. Recent studies also showed that β-hydroxybutyrate might exert an antidepressant effect in MDD resulting from chronic unpredictable stress [112-114]. Chen *et al.* first linked the antidepressant effect of β-hydroxybutyrate to histone modification [115]. They found that β-hydroxybutyrylation of H3K9 reduced in mice with MDD induced by spatial restraint stress and that injection of β-hydroxybutyrate could increase the levels of β-hydroxybutyrate and H3K9 β-hydroxybutyrylation without changing H3K9 acetylation levels (Table **1**) [115]. Furthermore, BDNF expression was found to be upregulated after β-hydroxybutyrate injection, suggesting that H3K9 β-hydroxybutyrylation might also be an important regulator of BDNF expression [115]. Since β-hydroxybutyrate does not exert its antidepressant effect by altering the histone acetylation level, we believe that histone β-hydroxybutyrylation is a promising direction for understanding the mechanisms of MDD. Research on the mechanism by which β-hydroxybutyryl groups are transferred to histones might provide a better understanding of histone β-hydroxybutyryl modifications.

4. TARGETING HISTONE MODIFICATION FOR MDD THERAPY

4.1. HDAC Inhibitors

Although there are several histone modifications involved in MDD, the main histone modification that has been targeted for MDD therapy is histone acetylation, specifically, the use of HDAC inhibitors (HDACis). HDACis can be divided into the following four groups on the basis of their

Table 2. Histone modification enzymes and their functions in MDD.

Enzymes	Types	Function	Catalytic Site	Association with MDD	References
Setdb1	Histone methylatransferase	Adding methyl to targeted residuces	H3K9	Reduced mice depression-like behaviors.	[44]
G9a	Histone methylatransferase	Adding methyl to targeted residuces	H3K9	Reduced in social defeat stress MDD model.	[45]
PRMT1	Protein arginine methyl-transferase 1	Adding methyl to arginine	H4R3	$PRMT1^{-/-}$ mice inhibited LPS-induced depressive-like behavior.	[46]
JMJD3	Histone lysine demethylase	Removing methyl from lysine	H3K27	Overexpressed in prefrontal cortex and hippocampus of CUMS-induced rats.	[47]
HDAC2	Histone deacetylases (Class I)	Removing acetyl from targeted residuces	/	Enhanced in MDD patients not taking antidepressants and CUMS-induced mice. Enhanced in MDD patient peripheral leukocytes.	[59, 60, 66]
HDAC5	Histone deacetylases (Class II)	Removing acetyl from targeted residuces	/	Reduced in NAc of social defeat-induced mice. Enhanced in MDD patient peripheral leukocytes.	[60, 66, 67]

Table 3. Overview of HDACis used to treat MDD in animal models.

HDACi	Classification	Targeted HDAC	Targeted Genes	References
Trichostatin (TSA)	Hydroxamates	Class I, II	BDNF	[118, 128]
Vorinostat (SAHA)	Hydroxamates	Class I, II, IV	GDNF, CORT, BDNF	[25, 119, 120]
Valproic Acid / Valproate (VPA)	Aliphatic acid	Class I, II	BDNF, GSK-3β, β-catenin, CORT, MC4R	[121-123]
MS-275	Benzomide	Class I	CREB, BDNF, CORT, RAC1, GJA5, *etc*.	[43, 89, 124, 128]
Sodium butyrate	Aliphatic acid	Class I, II	BDNF, TTR, HTR2A	[126-128]

chemical structures: hydroxamates, cyclic peptides, aliphatic acids and benzomides [116, 117]. The abilities of different HDACis to exert an antidepressant effect and target HDACs and the genes that encode them have been investigated in MDD animal models (Table **3**).

Weaver *et al.* discovered that the HDACi trichostatin A (TSA) could reverse the hippocampal transcriptome changes induced by maternal care in early life in rats [118]. Another HDACi, vorinostat (also known as suberoylanilide hydroxamic acid, SAHA), which was the first HDACi to be approved for clinical use by the U.S. FDA, was discovered to reverse the induction of MDD-related behavior and GDNF expression by CUMS exposure in mice [25]. Moreover, Kv *et al.* and Meylan *et al.* found that SAHA could affect corticosterone (CORT) and BDNF levels in an MDD mouse model [119, 120]. Valproic acid (VPA), an HDACi widely used to treat epilepsy and bipolar disorder, was also discovered to have antidepressant properties. VPA was found to affect BDNF, glycogen synthase kinase 3β (GSK-3β), β-catenin, CORT, and melanocortin-4 receptor (MC4R) expression in MDD animal models [121-123]. MS-275, a selective HDACi that target class I HDACs, was found to influence the expression of proteins including cAMP-response element-binding protein (CREB), BDNF, CORT, RAC1, and gap junction protein α 5 (GJA5) in mice subjected to chronic social defeat stress [43, 56, 124]. Furthermore, in mice subjected to chronic restraint stress, sodium butyrate was shown to cause significant remission of MDD-related behaviors [125, 126]. Sodium butyrate was found to exert an antidepressant effect by regulating BDNF, transthyretin (TTR) and serotonin 2A receptor (HTR2A) expression [126, 127]. Additionally, the HDACis TSA, sodium butyrate and MS-275 were shown to increase acetylation at the BDNF promoter region, thus increasing BDNF transcription in mice with MDD induced by maternal separation in infancy [128]. In addition, the combination of the antidepressant agent fluoxetine and HDACis was found to obviously decrease MDD-related behaviors, suggesting that HDACis may be used with common antidepressant drugs in the future [125, 128].

Although HDACis have been shown to have antidepressive characteristics in animal models, there are still some limitations to be resolved before wide application in the clin-

ic. In addition to acting on histones, HDAC can also suppress the acetylation of other proteins, such as α-tubulin, hypoxia-inducible factor-1α (HIF-1α), signal transducer and activator of transcription 3 (Stat3), and β-catenin [129-132]. Accordingly, the application of HDACis for MDD treatment might result in severe side effects. For example, an FDA-approved HDACi named Farydak used to treat multiple myeloma was found to exhibit side effects such as serious gastrointestinal toxicity, thrombocytopenia, myelosuppression, fatal cardiac ischaemic events, arrhythmias, electrocardiogram (ECG) changes, localized and systemic infections, and hepatic dysfunction [133]. There is a dire need to discover new HDACis that can selectively target the promoter regions of MDD-related genes and exhibit low toxicity . Moreover, investigating dual inhibitors that target both HDAC- and MDD-related factors (*e.g.*, serotonin and monoamine oxidase) might be a new direction to cure MDD.

Furthermore, studies have shown that only SAHA, VPA and sodium butyrate can cross the blood-brain barrier (BBB), while some of the other HDACis have difficulty in penetrating the BBB [134]. To cure MDD, researchers had to increase the drug concentration administered; this might also lead to enhancement of the side effects, thus discovering HDACis that can easily penetrate the BBB is urgent. Coupling HDACis with BBB substrates might be a new direction to explore new HDACis for treating MDD. Hiranaka *et al.* discovered that exploiting new drugs that consist of a hybrid of an HDACi and substrate of pyrilamine-sensitive proton-coupled organic cation antiporter (PYSOCA) could increase the permeability of BBB [135]. In addition to BBB substrates, HDACis have been hybridized with other antidepressants that can penetrate the BBB, which is another way to facilitate delivery into the brain. In addition, encapsulating HDACis into nanoparticles might be another way to transport HDACis into the brain. Li *et al*. injected coating miRNAs using nanoparticles *via* the mouse tail vein and successfully cured mice with traumatic brain injury [136]. Similarly, packaging of HDACis into nanoparticles might also help them pass through the BBB, which then helps cure MDD.

4.2. Common Antidepressants and Histone Modification

Apart from HDACis, common antidepressants used in the clinic were also found to regulate histone modification during MDD treatment. Ookubo et al., analyzed 11 antidepressants and discovered that most of them could enhance H3 acetylation levels in different brain areas [137]. Quetiapine restored H3K9me3 levels in the prefrontal cortex (PFC), which then helped relieve MDD-related behavior in socially isolated mice [138]. Lithium was also discovered to reduce HDAC1, 3, 4, 5, 7, 8, 10 expressions [137, 139]. H3 histone acetylation was also found to be enhanced at the promoter region of BDNF in the hippocampus of MDD rats treated with olanzapine, accompanied by inhibition of HDAC5 [140].

Fluoxetine, an SSRI, was discovered to decrease pan H3 acetylation levels and increase H3K9me2 levels at the promoter region of CaMKIIα in mice with social defeat stress [141]. Pan H3 acetylation was also increased at the HDAC4 promoter region in the hippocampus of fluoxetine treated rats, which resulted in HDAC4 enrichment and decreased H4 acetylation at the mammalian target of rapamycin (mTOR) promoter and G Protein Subunit Alpha I1 (Gnai1) promoter region [142]. Moreover, HDAC2 expression was also decreased in the spinal dorsal horn in fluoxetine treated female mice, accompanied by increased H3 acetylation levels [143]. Venlafaxine, an SNRI, was also found to inhibit HDAC5 expression and increase H3K9ac levels in a chronic unpredicted stress (CUS) rat model [144]. Heterocyclic antidepressants could also regulate histone modification. Amitriptyline could significantly increase H3K4me3 and H3K9ac levels at the promoter region of activating transcription factor 3 (Atf3) and H3K4me3 levels at the promoter region of heme oxygenase 1 (Hmox1) in mouse neuronal cells [145]. Imipramine was also found to promote H3K9ac, H3K14ac and H3K4me2 levels at the BDNF promoter region in the hippocampus of mice with social defeat stress [52]. HDAC activity was also inhibited in the NAc of imipramine-treated rats [146].

Most of the antidepressants discussed above could inhibit HDAC and induce histone acetylation in MDD treatment. Some antidepressants, such as lurasidone, exhibit opposite functions. Lurasidone was discovered to enhance HDAC1, 2 and 5 expressions [121]. This result suggested that the combination of lurasidone with HDACis might have a better antidepressant effect. Researchers have paid attention to the combination of common antidepressants and HDACis for the treatment of MDD. Lithium and valproate cotreatment induced BDNF expression and exhibited a neuroprotective effect in MDD [147, 148].

4.3. Anti-depressant Effect of Alternative Traditional Chinese Medicine (TCM) Therapies on Histone Modification

In addition to commonly used antidepressants, traditional alternative therapies have been widely used to treat MDD patients worldwide. Traditional alternative therapies are medical practices that are distinct from standard therapies, and include Ayurvedic medicine, TCM, homeopathy, and naturopathic therapies [149]. Traditional alternative therapies are essential for most of the world's population and are more popular in developing countries. Currently, various traditional alternative therapies, especially TCM therapies, play valuable roles in the treatment of psychiatric patients. TCM originated in ancient China and has been widely used in Asian countries for over two thousand years. The main TCM therapies include Chinese herbal medicines, acupuncture, *Tai Chi* and massage. Among these therapies, Chinese herbal medicines are commonly used for regulating mood and preventing mental diseases, such as depression, anxiety and insomnia.

Xiaoyaosan (XYS), a classic Chinese herbal medicine formula used in TCM, was first recorded in *Taiping Huimin Heji Jufang* in the Song Dynasty. XYS comprises eight Chinese herbs: Radix *Bupleuri*, Radix *Paeoniae Alba*, Radix *Angelicae Sinensis*, Rhizoma *Atractylodis*, Poria, Radix *Glycyrrhizae*, Herba *Menthae*, and Rhizoma *Zingiberis*. XYS has been used clinically to treat depression in China for more than 2000 years. It has been demonstrated that XYS can decrease Hamilton scale (HAMD) and self-rating depression-scale (SDS) scores in depression patients [150, 151]. XYS has also been demonstrated to ameliorate depression-like

behaviors in CUMS-treated rats, rats subjected to chronic immobilization stress and mice subjected to CUMS [152, 153]. Studies have shown that the antidepressant effect of XYS may be associated with histone modification. Wang *et al.* demonstrated that XYS could decrease the expression of H3 in the hippocampus of mice subjected to CUMS [154]. Pretreatment of methyl-4-phenylpyridinium (MPP^+)-treated SH-SY5Y cells with extract of *Paeonia lactiflora,* a Chinese herb that is a component of XYS, impedes the changes in H3K9 and H3K27 of H3, thus increasing the expression of HDAC5 without changing HATs [155]. The active compounds of XYS, namely, luteolin, quercetin, saikosaponin D (SSD), ferulic acid and curcumin, have been identified by HPLC [156-158]. Ferulic acid has been demonstrated to ameliorate CUMS-induced depression-like behaviors in mice by inhibiting SIRT6, which can deacetylate H3 at lysine 9 and lysine 56 [159]. Li *et al.* found that SSD can increase the expression of HSP-90 and decrease the expression of HDAC6, which is a member of the HDAC family, in CORT-treated PC12 cells [160, 161]. Aggarwal *et al.* found that quercetin supplementation for 4 weeks ameliorated cognitive impairment in ovariectomy (OVX) mice by restoring HAT/HDAC homeostasis through ERK activation and reversing alterations in the levels of neuroplasticity markers in the cortex and hippocampus [162]. Quercetin enhances p16INK4α gene expression by decreasing methylation and increasing histone acetylation of the p16INK4α gene [162]. In addition, luteolin has been reported to stimulate HDAC activity and inhibit HAT activity during inflammation and hyperglycaemia [163, 164]. Curcumin is also involved in histone modification in chronic obstructive pulmonary disease, heart failure and type I diabetic nephropathy [165-167]. However, whether luteolin and curcumin play a role in histone modification in depression remains to be studied. Overall, these findings suggested that the antidepressant effect of XYS may be related to histone modification.

5. TARGETING HISTONE MODIFICATION IN OTHER NERVOUS SYSTEM DISEASES

Apart from MDD, histone modification could also be a therapeutic target in other nervous system diseases, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and spinal muscular atrophy (SMA).

PD is a neurodegenerative disease accompanied by abnormal dopaminergic neurons. HDAC inhibitors TSA, SAHA, VPA and sodium butyrate have been found to upregulate the expression of the neurotrophic factors GDNF and BDNF in a PD rat model, which then protects dopaminergic neurons and increases dopamine levels [168-171]. α-Synuclein, a neuronal protein that induces neurotoxicity in PD, could also be inhibited by HDACis which then alleviated PD symptoms [172]. Levodopa, a drug commonly used in PD, was found to reduce the acetylation of histone H4 [173].

AD, another neurodegenerative disease that affects thousands of elderly individuals, could also be treated with HDACis. β-Amyloid (Aβ), a peptide that is highly correlated with AD, could be inhibited by VPA [174, 175]. Hyperphosphorylation of tau protein is also a diagnostic marker of AD. The HDAC inhibitors tubastatin A and ACY-1215 have been found to reduce tau phosphorylation in AD [176]. Donepezil, a commonly used anti-AD drug, was found to inhibit the binding between HDAC6 and the BDNF promoter in the cortex, which then leads to overexpression of BDNF [177].

Another neurodegenerative disease, HD, could also be affected by histone modification. HDACis such as TSA, SAHA, sodium butyrate, RGFP966, and LBH589 were found to reduced HD symptom in an HD mouse model [178-181]. Survival motor neuron gene 1(SMN1), a key factor involved in SMA, was also found to be induced by various HDACis in the SMA model [182-187].

Currently, most drugs that target histone modifications of nervous system diseases are HDACis. This might be due to the neuroprotective effect of HDACis. Once scientists solve the problem of HDACis penetrating the BBB, an increasing number of HDACis might be used for treating nervous system diseases in the future.

CONCLUSION

MDD is a disease that involves a combination of genetic and environmental factors, and alterations in histone modifications induced by different environmental factors may influence the development of MDD. Exploring the changes in histone modification may help elucidate the mechanisms of MDD and identify new directions for treating MDD. Among the different histone modifications, histone methylation, and especially histone acetylation, have been found to be critical in MDD. Histone crotonylation and histone β-hydroxybutyrylation are newly discovered histone modifications. Although there have been few studies on the effects of histone crotonylation and histone β-hydroxybutyrylation on MDD, we believe that these two modifications may also play significant roles in MDD.

HDACis and alternative TCM therapies have been demonstrated to exert antidepressant effects to treat MDD. Unfortunately, studies on the antidepressant effect of HDACis have only been performed in animal models; clinical trials evaluating the effect of HDACis in humans have not yet been conducted. However, many clinical trials evaluating HDACis in cancer have been performed, and HDACis have been approved by the US. FDA for clinical use; thus, we believe that HDACis could also be applied for the treatment of MDD in the future.

Traditional alternative therapies have been increasingly used to treat MDD. The TCM therapy XYS is a classical formula used to treat MDD in China. We have found that active compounds of XYS can alter histone modifications, leading to the amelioration of MDD. We believe that TCM therapies can treat MDD by acting as critical regulators of histone modifications.

SEARCH STRATEGY

We divided our reference search into multiple small parts and used PubMed (https://pubmed.ncbi.nlm.nih.gov/) as our main search tool. We first searched the keywords '(histone methylation) AND (depression [Title/Abstract])' in PubMed and obtained 156 results. By excluding reviews and unrelated research, we obtained 68 papers. Similarly, we also searched for the keywords '(histone acetylation) AND (depression [Title/Abstract])' and obtained another 76 papers

that were not duplicates of the papers related to histone methylation. Moreover, we obtained 5 papers related to histone phosphorylation, 2 papers related to crotonylation and 1 paper related to histone β-hydroxybutyrylation. The keywords '(histone modifications) AND (antidepressant)' were also searched and 27 papers were obtained. There were no papers on the association between MDD and histone deamination, β-N-acetylglucosamine, ADP ribosylation, ubiquitination or SUMOylation. All received papers were carefully read, selected and summarized.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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