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Review article

Histone deacetylases (HDACs) as therapeutic target for depressive disorders

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ABSTRACT

Major depressive disorder (MDD) represents approximately 40% of the disability caused by mental illnesses globally. The poorly understood pathophysiology and limited efficiency of pharmacological treatment (based primarily on the principles of the monoaminergic hypothesis) make depression a serious medical, public and socio-economical problem. An increasing number of studies suggest that epigenetic modifications (alterations in gene expression that are not due to changes in DNA sequence) in certain brain regions and neural circuits represent a key mechanism through which environmental factors interact with individual's genetic constitution to affect risk of mental disorders. Accordingly, chromatin-based epigenetic regulation seems to be a promising direction for the development of new, more effective antidepressant drugs. Recently, several inhibitors of histone deacetylases (HDAC) have been extensively studied in the context of antidepressant action. So far, none of them has been used to treat depression in humans due to the low selectivity for specific HDAC isoforms, and consequently, a risk of serious adverse events. In this review, we focus on the HDAC inhibitors (HDACi) with the greatest antidepressant efficacy and their activity in the preclinical studies. Moreover, we discuss their potential therapeutic usefulness in depression and the main limitations.

Contents

Introduction

Depression is a common mental disorder manifested by low mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, poor concentration and anxiety symptoms [1]. According to the Global

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Burden of Disease (GBD) study [2] depressive disorders will become the second leading cause of disability worldwide by the year 2020 and a significant contributor to the burden of suicide and ischemic heart disease. The lifetime prevalence of depressive disorders is estimated to be approximately 17% in the United States, with a similar level being reported for European countries [3]. Depressive disorders often begin in adolescence and can become chronic or recurrent; thus, leading to substantial impairments in an individual's ability to take care of his or her everyday responsibilities [4]. Because the etiology of depression is not fully understood, the development of useful diagnostic tests as well as highly effective and rapid-acting antidepressant treatment strategies has been very challenging [5].

A variety of environmental factors has been shown to contribute to mental disease, especially during the early stages of life. For example, exposure to chronic stress may result in permanent functional alterations in gene expression, inducing functional changes in the neural circuit, and consequently affecting behavior [6,7]. Some of these alterations are known to be maintained by epigenetic modifications in specific brain regions [8–11]. In general, epigenetics refers to covalent modification of DNA, protein, or RNA, resulting in alterations to the function and/or regulation of these molecules, without changing their primary sequences. In some cases, these modifications are stable and passed on to future generations, while in other situations they are dynamic and change in response to environmental stimuli. Epigenetic regulation is fundamental for many cellular (both physiological and pathological) processes and allow to explain some phenomena in which medical observations confront traditional genetics. The major mechanisms in epigenetic regulation include chemical modifications to the cytosine residues of DNA (DNA methylation; long-term changes) and histone proteins associated with DNA (histone modifications – HMs; more flexible and short-term changes) [12]. Out of many post-translational modifications of histone proteins that control the chromatin architecture around specific genes thereby regulating their transcription, histone acetylation and deacetylation are the best studied and most common forms of HMs in neuropsychiatric diseases [13–16]. Overall, histone acetylation leads to the activation of the transcription machinery while deacetylation results in its inhibition. The key regulatory enzymes involved in these post-translational modifications are histone acetyltransferases (HATs) and histone deacetylases (HDACs) [17].

HDAC enzymes oppose the effects of HATs by reversing lysine acetylation, an action that restores the positive charge of the lysine thus stabilizing the local chromatin structure. By removing acetyl groups from ε-amino lysines of proteins, HDACs not only alter transcription, but also promote either the establishment or erasure of alternative posttranslational lysine modifications including methylation, ubiquitination, and sumoylation [18]. Furthermore, they can alter the dynamics of histone modification "cross talk" [19]. Like many other important enzymes in the cell, HDACs are subject to a variety of controlling mechanisms, such as protein–protein interactions and posttranslational modifications [20]. Dysregulation of HDACs (especially an increase in their activity) which consequently leads to impaired acetylation and deacetylation may result in the development of many diseases, including depression [11,21,22]. Accordingly, compounds with modulatory action on these enzymes may be innovative and promising tools in the fight against depression. Recently, several inhibitors of HDACs (HDACi) have been intensively investigated as possible agents for the treatment of cancer, parasitic, inflammatory and other diseases [23–27]. Some preclinical studies have also indicated that HDACi possess antidepressant-like activity [28–33].

In this manuscript, we first review the importance of HDACs in the pathophysiology and treatment of depression followed by an overview of HDACi with the greatest antidepressant potentials and their activities in preclinical studies. Finally, we discuss their potential therapeutic use in depression and limitations.

HDACs: classification, characteristic and biological activity

HDACs (also named lysine deacetylases; KDAC) are multi-subunit protein complexes occurring in yeast cells and higher *Eukaryota* [34]. Based on their structural similarity to the yeast HDACs, enzyme activity, and location within the cell, the 18 currently known human histone deacetylases are grouped into two families and four classes [35]. Class I HDACs (HDACs I; HDAC1, −2, −3 and −8) are related to the yeast *rpd3* gene; class II HDACs (HDACs II; IIa: HDAC4, −5, −7 and 9; IIb: HDAC6 and −10) are related to the yeast *hda1* gene; class III HDACs (HDACs III) also known as the sirtuins (SIRTs) are related to the *sir2* gene and includes SIRT1-7. Phylogenetically SIRTs are further divided into four subclasses (SIRT1, SIRT2, and SIRT3 belong to subclass I, SIRT4 is the sole member of subclass II, SIRT5 to subclass III, and SIRT6 and SIRT7 to subclass IV). Class IV (HDAC IV), contains only HDAC11 with features of both Classes I and II [19].

Enzymes of classes I, II and IV belong to the classical HDACs family and are metalloproteins which require zinc (Zn) ions as cofactor and whose activities are inhibited by trichostatin A (TSA). On the other hand, HDACs from class III are nicotinamide adenine dinucleotide (NAD^+)-dependent and are not affected by TSA [36]. The HDAC I class are mostly nuclear enzymes (except HDAC 8) involved in cell proliferation and survival [37]. The major subclasses, i.e. HDAC 1 and HDAC 2 have a high sequence homology (85%) and have different functional roles during the development of the central nervous system [38]. These enzymes form both homo- and heterodimeric complexes as well multi-protein complexes with many transcription factors, like REST corepressor 1 (CoREST), nucleosome remodeling and deacetylase (NuRD) complex, mitotic HDAC (MiDAC) complex, nuclear receptor corepressor (N—CoR) or silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) [39,40]. Currently, the class I HDACs are the best characterized among all the HDACs because of their involvement in *cancerogenesis* and the development of several types of cancer (for example see [26]). Unlike HDACs I, class II HDACs are primarily localized to the cytoplasm (depending on phosphorylation status, may be shuttled between the cytoplasm and nucleus) and consist of enzymes with tissue-specific expression and function [41]. HDAC IIa is associated with MEF2 (myocyte enhancer factor 2)-regulated process while HDAC IIb is involved in the control of microtubule and actin-dependent cell motility [42]. HDAC11 is the only member of the Class IV family located in the nucleus and it is involved in the regulation of interleukin-10 expression [43–45], OX40L (CD252) surface expression [46] and expression of the chromatin licensing and DNA replication factor 1 (Cdt1) [47]. Conversely, the SIRTs having powerful anticancer, anti-aging and anti-neurodegenerative potentials and are found in the nucleus, cytoplasm, and mitochondrion. They carry out very important physiological functions of cell survival, metabolism and ATP regulation, apoptosis and much more [48].

Understanding the mechanisms of histone deacetylase action has been primarily accelerated by the availability of HDACi. A good number of compounds that inhibit HDAC activity have been developed and well characterized [26]. Their beneficial effects in the regulation of many cellular processes have been proved. Along the same line, research is increasingly showing that epigenetic abnormalities are closely associated with a large number of human diseases (including psychiatric disorders), providing a rationale for the use of epigenetic-based therapies such as HDACi [49–54] (see also [13] for review).

Role of HDACs in the pathophysiology and treatment of depression

Recent studies on the mechanisms of depression have revealed some possible gene-environment interactions which may explain why after decades of study, no specific genes or loci have been indicated as risk factors for depression. Furthermore, the majority of clinical trials estimate that even after successive treatments with different antidepressants, almost 35% of patients do not achieve full remission [55], suggesting that there could be an epigenetic component to depression that is not being addressed by current pharmacological treatments [56].

An increasing amount of evidence indicates that major depressive disorders (MDD) and depression-like behavior in animal models are associated with alterations in the expression of some HDACs (Tables 1 and 2, respectively). One of the HDACs is overexpressed, while the other is reduced in expression, which probably depends on the HDAC function in the cell, as well as the stage of disease [57,58] (see Table 1). For example, Hobara et al. [58] observed an increase in HDAC2 and HDAC5 mRNA levels in leucocytes in the depressive stage (but not in the remission stage) of MDD patients, while other authors showed a decline in the HDAC2 protein in the nucleus accumbens (NAc) in clinical depression [30]. In patients with bipolar disorder (BD), an elevated HDAC4 expression (only in the depressive stage), and reduced HDAC6 and HDAC8 expression (both in the depressive and remissive stages) were noted. It is interesting to note that in the study by Hobara et al. [58], first-degree relatives of the patients did not show any significant alterations in HDACs expression levels. Furthermore, there were no significant differences in HDAC mRNA levels among affective disorder patients receiving any type of antidepressants, such as tricyclics, tetracyclics, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or mood stabilizers (e.g. lithium, valproate), which suggests that the observed alterations of HDAC expression in patients are unlikely to be due to the effects of medication [58]. A 3-week treatment with clomipramine and paroxetine or lithium chloride and valproate did not affect HDAC2, 5, 4, 5 and 8 mRNA expression levels [58]. In another clinical study, a decrease in SIRTs (especially: SIRT1, 2 and 6) expression in the depressive stages of both MDD and BD patients was observed. These changes were normalized in the remissive stage and were comparable to those in healthy controls, implying that SIRT1, 2 and 6 mRNA levels could be potential state markers of mood disorders [57]. Interestingly, a study carried out in a large Japanese population indicated association between rs10997875 (single nucleotide polymorphism; SNP) in the *SIRT1* gene and MDD with no apparent correlation between the *SIRT1* gene and SSRI therapeutic response in MDD patients [59].

Immunochemical studies of the brain revealed cell- and region-specific expression of HDACs. HDAC 10 is primarily found in some neurons, while HDAC 2, 3, 4, 5, 11 are found in oligodendrocytes. Both HDAC1, 2 (but not HDAC3, 4, 5, 6, 7, 8, 9, 11) are expressed in astrocytes and also in neurons [60,61]. A detailed analysis of changes in the level of acetylation of histone H3 and HDACs expression after antidepressants treatment was carried out by Ookubo et al. [61]. The study showed that lithium (200 mg/kg), carbamazepine (CBZ; 40 mg/kg), olanzapine (OLZ; 15 mg/kg), clomipramine (CLM; 50 mg/kg), (*S*)-citalopram (ECM; 30 mg/kg), duloxetine (DLX; 5 mg/kg) and mirtazapine (MIR; 20 mg/kg) administered for 14 days in C57BL/6 male mice induced significant increases in acetylated histone H3 (AcH3) levels, especially in NAc. The observed alterations correlated with changes in HDACs expression in different brain regions and were drug-specific (for more details, see Table 2 and [61]).

Based on the available studies (especially preclinical), we conclude that HDAC2 is the most investigated HDAC in the context of the pathophysiology and therapy of depression. Han et al. [21], showed that both mRNA and protein levels of HDAC2 were reduced in the hippocampus (HP) in a chronic restraint stress (CRS) model in mice. Treatment with sodium butyrate (SB; 0.6 g/kg; HDAC inhibitor) prevented and normalized the CRS-induced changes (Table 2). In the chronic social defeat stress model, a decrease in HDAC2 (but not HDAC1 and 3) mRNA level was demonstrated in NAc and chronic fluoxetine administration did not reverse the changes [30].

Table 1
Summary of clinical studies on the HDACs in depressive disorders.

Authors' names	Controls	Patients [n]	Samples	Methods	Findings
Hobara et al. [58]	n = 28	MDD: Depressive phase = 20 MDD: Remission = 39	Peripheral white blood cells	qPCR	↑ HDAC2, 5; ↔ HDAC1,3,4,6,7,8,9,10,11 ↓ HDAC8,9 ↔ HDAC1,2,3,5,7,9,10,11
		BD: Depressive phase = 12 BD: Remission = 33 Relatives BD = 13			↑ HDAC4; ↓ HDAC6,8 ↔ HDAC1,2,3,5,7,9,10,11 ↓ HDAC5,6,7,8,9,10 ↔ HDAC1,2,3,4,11 ↔ HDAC6,8
Iga et al. [104]	n = 25	MDD: Depressive phase = 25; Remission = 20	Peripheral white blood cells	qPCR	↑ HDAC5 in depressive phase; normalization in remission phase
Abe et al. [57]	n = 28	MDD: Depressive phase = 20; Remission = 39	Peripheral white blood cells	qPCR	↓ SIRT1,2,6 in depressive phase; normalization in remission phase ↔ SIRT3,4,5,6,7 both in depressive and remission phase
		BD: Depressive phase = 12; Remission = 32			↓ SIRT1,2,6 in depressive phase; normalization in remission phase ↔ SIRT3,4,5,6,7 both in depressive and remission phase
Kishi et al. [59]	n = 766	MDD = 450	Peripheral white blood cells	SNP genotyping	association between rs10997875 in SIRT1 gene and MDD in Japanese patients; lack of association between SIRT1 gene and SSRI therapeutic response in MDD
Covington et al. [30]	n = 8	Depressed = 8	Nucleus Accumbens	Western blot	↓ HDAC2 protein in depressed humans

MDD, major depressive disorder; BD, bipolar disorder; HDAC, histone deacetylase; SIRT, sirtuin; ↑ increase; ↓ decrease; ↔ no changes

Table 2
Influence of stress and/or antidepressant treatment on the histone modifications and HDACs expression. Summary of preclinical studies.

Authors' names	Species/ Strain	Model/Treatment	Brain region	Methods	Findings
Liu et al. [11]	Sprague-Dawley rats	Chronic unpredictable stress (28 days)	Hippocampus	Western blot	↓ acetylation of H3 (Lys9) and H4 (Lys 12) ↑ HDAC5
Tsankova et al. [22]	BL6/C57 mice	Chronic social defeat stress (10 days) + imipramine (4 weeks)	Hippocampus	ChIP assay	↓ acetylation of H3 at *Bdnf* P4 promoter and ↔ H4 acetylation levels at the *Bdnf* P3 promoter in defeated mice; Imipramine induced H3 hyperacetylation in these mice
				qPCR	↔ HDAC 1,2, 4, 7 and ↓ HDAC9 expression in non-stressed mice after chronic imipramine treatment; ↓ HDAC5 expression in stressed mice after imipramine treatment
				Viral-mediated overexpression of HDAC4 and 5; Social interaction test	overexpression of HDAC5 (but not HDAC4) blocked the antidepressant efficacy of imipramine in defeated mice
Ferland & Schrader [17]	Wistar rats	Chronic variable stress (14 days)	Hippocampus (CA1,CA3, DG)	Western blot	↓ acetylation of H4 (Lys12) and phospho-acetyl H3 (Lys9/Ser10) in CA3 and DG of stressed rats
				SIRT1 activity assay; Western blot	↑ SIRT1 activity (but not protein expression) in CA3 and DG
Choi et al. [64]	Sprague-Dawley rats	Chronic unpredictable stress (35 days) + ketamine	Hippocampus	Western blot	↑ phosphorylation of HDAC5 (Ser259, Ser498) and acetylation of H3 i H4 after ketamine treatment in hippocampal neurons (*in vitro* study)
				Viral-mediated knockdown of HDAC5; Novelty suppressed feeding test; Forced swim test	hippocampal knockdown of HDAC5 blocked the antidepressant effects of ketamine both in unstressed and stressed rats
Han et al. [21]	ICR mice	Chronic restraint stress (CRS; 14 days)	Hippocampus	qPCR; Western blot	↓ HDAC2 and 5 mRNA as well as ↓HDAC2 and acH3 protein in stressed mice
Sarkar et al. [31]	Male Sprague–Dawley rats	Postnatal fluoxetine (PNFlx; 10 mg/kg; from 2 to 21 postnatal day)	Hippocampus	Chromatin immuoprecipitation; microarray; qPCR; Western blot	↑ HDAC4 expression and their recruitment to *mTOR* and *Gnai1* promoters in 2-month-old PNflx rats accompanied by significant increases in H3 and H4 acetylation at the *Hdac4* promoter
Covington et al. [30]	C57BL/6J mice	Chronic social defeat stress (10 days) + fluoxetine (20 mg/kg/day; 10 days)	Nuceleus Accumbens	Immunohistochemistry; qPCR; Western blot	↓ acetylation of H3 (Lys14) 1 h and ↑acH3K14 level 24 h, 10 and 15 days after social defeat stress; ↓ HDAC2 protein and mRNA 15 days after last social episode ↔ HDAC2 protein level after fluoxetine
Covington et al. [29]	C57BL/6J mice	Chronic social defeat stress (10 days) + fluoxetine (20 mg/kg/day; 10 days)	Hippocampus	Immunohistochemistry; qPCR; Western blot	↑ acH3 (Lys 14) level 24 h after social defeat stress normalized by fluoxetine treatment
			Amygdala		↓ acH3 (Lys 14) level 1 and 24 h after stress
Ookubo et al. [61]	C57BL/6	Lithium chloride (Li; 200 mg/kg), carbamazepine (CBZ; 40 mg/kg), olanzapine (OLZ; 15 mg/kg), clomipramine (CLM; 50 mg/kg), escitalopram oxalate (ECM; 30 mg/kg), duloxetine hydrochloride (DLX; 5 mg/kg) and mirtazapine (MIR; 20 mg/kg)	Nucleus Accumbens	Western blot	↑ acetylation of H3 after Li, OLZ, CLM, ECM and DLX; ↑ HDAC1 after Li, CBZ, CLM and MIR; ↑ HDAC2 and 3after CBZ, OLZ and MIR
			Cingulate Cortex		↑ acetylation of H3 after Li, OLZ and CLM; ↑ HDAC3 after CBZ, OLZ, CLM and MIR; ↑ HDAC5 after CBZ and OLZ, but ↓ after Li, ECM and DLX; ↑ HDAC8 after CBZ, CBM and OLZ, but ↓ after Li
			Amygdala		↑ acetylation of H3 after Li, CLM, ECM, DLX and MIR; ↑ HDAC3,5 and 10 after CBZ, OLZ, ECM, ECM, DLX and MIR and ↓ after Li
			Striatum		↑ HDAC2, 3 and 5 after CBZ, OLZ, CLM, ECM and MIR and ↓ HDAC3 and 5 after Li
			Hippocampus		↓ HDAC4 after Li, CLZ and MIR; ↓ HDAC5 after Li; ↓ HDAC7 after Li and CLZ

Table 2 (*Continued*)

Authors' names	Species/ Strain	Model/Treatment	Brain region	Methods	Findings
Uchida et al. [63]	BALB/c	Chronic ultra-mild stress (6 weeks) + imipramine 25 mg/kg (6 injections)	Ventral Striatum	Chromatin imunoprecipitation; qPCR; Western blot	↓ acetylation of H3 and ↑ HDAC2 protein and mRNA level in stressed mice normalized after imipramine treatment; ↑ HDAC4 and 5 mRNA, and ↓ HDAC6,7 and 10 mRNA level after imipramine both in non- and stressed mice
Renthal et al. [62]	CD-1 mouse	Social defeat stress (1 or 10 days) + imipramine (20 mg/kg; 1 or 28 days)	Nucleus Accumbens	qPCR	↓ HDAC5 mRNA level after chronic (but not acute) social defeat stress ↑ HDAC5 mRNA after chronic (but not acute) imipramine treatment in non-stressed mice
				Viral-mediated knockdown (KO) of HDAC5; Social interaction test; Sucrose preference test	↑ social aversion and anhedonia in defeated HDAC5 KO mice than in defeated wilde-type controls

BDNF, brain-derived neurotrophic factor; Gani1, G Protein Subunit Alpha I1; H3/4, histone H3/4; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; ↑ increase; ↓ decrease; ↔ no changes.

Another HDAC (HDAC5) that has been implicated or strongly associated with depression belongs to the II class family. Tsankova et al. [22] demonstrated a down-regulation of HDAC5 followed by an increase in histone acetylation after chronic (4 weeks), but not acute, imipramine injection in chronic social defeat stress. Viral-mediated HDAC5 overexpression in HP blocked imipramine's ability to reverse depression-like behavior. On the other hand, another study found a reduced HDAC5 mRNA level in NAc in chronic social defeat stress [62], and its increase after imipramine treatment both in stressed and non-stressed animals [62,63]. Furthermore, a knockdown of HDAC5 in the nucleus acumbens resulted in an increase in social aversion and anhedonia in defeated mice compared to defeated wild-type controls [62]. On the contrary, some studies have indicated a significant upregulation of HDAC5 protein in the CA1 (but not CA3 and DG) area of HP after chronic variable stress (CVS) in mice [17].

It appears that nuclear export of HDAC5 regulates ketamine-induced MEF-2 (*myocyte enhancer factor-2)* transcriptional activation. Ketamine has been shown to down-regulate HDAC5 expression in chronic unpredictable stress (CUS) in rats. A proposed mechanism of antidepressant activity of ketamine involves Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)- and protein kinase D (PKD)-dependent phosphorylation of HDAC5 on two specific sites (S259 and S498) critical for the antidepressant activity of ketamine [64]. Additionally, it seems that hippocampal HDAC4 overexpression is typical and characteristic of the depression-like behavior observed in the forced swim test (FST) in animals with a history of postnatal fluoxetine (PNFlx) treatment. HDAC4 expression was significantly increased in all three age (21 postnatal day, 2 months, 18 months) groups examined. Chromatin Immunoprecipitation (ChIP) showed that increased HDAC4 recruitment is accompanied by decreased activation of histone

Table 3
Characteristic of histone deacetylase inhibitors (HDACi) with potential antidepressant-activity (based on [26,105]).

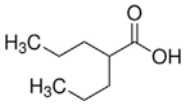
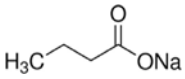
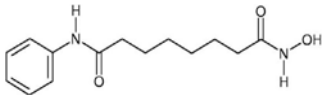
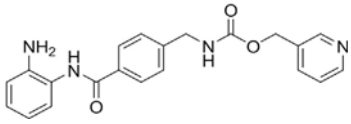
Compound/Inhibitor	Chemical structure	Structure	Molecular formula	Molecular weight	HDAC Target	*In Vitro* Potency
Valproic acid (divalproex sodium; VPA)	Carboxylate		$C_8H_{16}O_2$	144.21	HDAC1 HDAC2 HDAC3	mM
Sodium butyrate (SB)			$C_4H_7NaO_2$	110.09	HDAC1 HDAC2 HDAC3 HDAC8	mM
Vorinostat (suberanilohydroxamic acid; SAHA)	Hydroxamate		$C_{14}H_{20}N_2O_3$	264.32	HDAC1 HDAC2 HDAC3 HDAC8 HDAC9	μM
Entinostat (SNDX-275 or MS-275)	Benzamide		$C_{21}H_{20}N_4O_3$	376.408	HDAC1 HDAC2 HDAC3 HDAC9	μM

Table 4
Summary of preclinical study on the antidepressant-like activity of the HDAC inhibitors.

Authors' names	Species/Strain	Model/Treatment	Methods	Findings
Covington et al. [30]	C57BL/6J mice	Chronic social defeat stress (10 days) + microincjections of SAHA (100 uM) or MS-275 (100 uM) into Nucleus Accumbens	Social interaction test; Sucrose preference test; Forced swim test Immunohistochemistry; Western blot	Chronic stress-induced social aversion and increase of immobility time were reversed after MS-275 and SAHA treatment ↑ acH3 (Lys 14) and normalization of patterns of gene expression after MS-275 administration in NAc
Covington et al. [29]	C57BL/6J mice	Social defeat stress (20 days) + microinjection of MS-275 (100 uM) into Dorsal Hippocampus or Amygdala	Social interaction test; Sucrose preference test; Forced swim test; Immunohistochemistry	↔ social interaction and immobility time and ↓ anhedonia after intrahippocampal infusion of MS-275 in defeated mice; ↑ social interaction, ↔ anhedonia and immobility time after intra-amygdala infusion of MS-275 in stressed mice ↑ acH3 after MS-275 in HP
Liu et al. [11]	Sprague-Dawley rats	Chronic unpredictable stress (CUS; 28 days) + Valproate acid (VPA; 300 mg/kg; 28 days intragastric)	Forced swim est; Open-field test Western blot Sodium dismutase (SOD) activity and malondialdehyde (MDA) assay kit	Chronic-induced increase of immobility time and decrease of ambulation were reversed after VPA administration; no changes in rearing score after VPA in stressed rats ↓ protein level acH3 (Lys 9)/H3 and acH4 (Lys 12)/H4; ↑ HDAC5 and no changes in acH3 (Lys 14)/H3 in HP of CUS-treated rats; normalization of acH4 (Lys 12)/H4 and HDAC5 level in HP after VPA administration in CUS rats CUS-induced ↓ SOD activity and ↑ MDA content were normalized in HP by VPA treatment
Han et al. [21]	ICR mice	Chronic restraint stress (CRS; 14 days) + Sodium butyrate (SB; 0.3 g/kg or 0.6 g/kg)	Tail suspension test; Forced swim test; Sucrose preference test; Light-dark exploration Immunohistochemistry; Western blot	↓ anhedonia, time spent in dark and immobility time after SB0.6 administration in CRS-treated mice SB0.6 reverses CRS-induced decrease in acH3 level in HP
Gundersen & Blendy [28]	F1 hybrid offspring crosses of 129SvEv and C57Bl/6 mice	Sodium butyrate (SB; 100 mg/kg or 1.2 g/kg, 1 or 21 days)	Forced swim test; Novelty-induced hypophagia Western blot	↑ immobility time and ↑ latency to consume peanut butter chips in the novel environment after acute (but not chronic) treatment with SB100 ↑ acH4/H3 and acH3/H3 protein in HP after acute SB100 and/or 1.2 treatment, respectively; ↓ acH4/H3 (no changes in acH3/H3) in HP after chronic SB100 administration
Sarkar et al. [31]	Sprague–Dawley rats	Pups from postnatal day P2 to P21 were treated orally with fluoxetine 10 mg/kg (PNFlx); 2-months old PNFlx rats + Fluoxetine 10 mg/kg or/and Sodium Butyrate 300 mg/kg for 21 days *ip* (AFlx)	Social interaction test; Forced swim test; Open-field test Microarray Chromatin Immunoprecipitation Assay; qPCR Western blot	↓ time spent in social grooming and frequency of pouncing and ↑ immobility time and immobility events in PNFlx rats; ↑ latency to approach center and ↓ time spent in the center and path length in the center in PNFlx animals; postnatal treatment with SB and adult fluoxetine (AFlx) treatment prevented the PNFlx-evoked behavioral changes ↑ *Hdac4, Ppp2r2b, Gal, Dcx, Kcnh2, Grm8, ElkI* and ↓ *mTOR, Gnai1, Prkcc, HcnI, Notch3 and Avpr2* mRNA levels in HP of PNFlx rats; co-administration of SB prevented the PNFlx-evoked dysregulation of *Hdac4* and *mTOR*, but not *Gnai1, Prkcc* and *HcnI* in HP; AFlx administration did no alter hippocampal expression of *Hdac4, mTOR, Gnai1, HcnI* and *Prkcc* ↑ acetylation of H3 and H4 at the *Hdac4* promoter and ↑ HDAC4 enrichment *in Gnai1* and *mTOR* promoter in HP of PNFlx rats and normalization after adult fluoxetine treatment ↓ mTOR protein level in HP of PNFlx rats and no changes after AFlx treatment
Yamawaki et al. [32]	Sprague–Dawley rats	Sodium butyrate (SB; 1.2 g/kg *ip*, 1 or 7 days)	Forced swim test; Tail suspension test; Elevated plus-maze Open-field test DNA microarray Chromatin immunoprecipitation Western blot	↓ immobility time in rats after repeated (but not acute) SB administration No changes ↑ *Ttr* and ↓*Slc8a3*, *Casr, Htr2a, Tcf12* and no changes in *Sin3a, Gnrhr, Crhr2, Bdnf, Slc8a2* gene expression in HP after repeated SB treatment ↑ levels of acH4-associated DNA at the Ttr promotor region in HP of rats repeated treated with SB ↑ Ttr and no changes in acH3/H3, acH4/H4 protein level in HP after repeated SB administration

Table 4 (*Continued*)

Authors' names	Species/Strain	Model/Treatment	Methods	Findings
Lin et al. [33]	Sprague–Dawley rats	MS-275 (10; 50 and 100 uM; 7 days; bilaterally infusion to the Ventrolateral Orbital Cortex –VLO)	Forced swim test	↓ immobility time after infusion MS-275 100 uM and ↑ climbing time after MS-275 50 and 100 uM
			Tail suspension test	↓ immobility time after infusion MS-275 at a doses of 50 uM and 100 uM vs DMSO
			Open-field test	No changes
			Western blot	Dose-dependent ↑ CREB, acH3, BDNF protein level in VLO after MS-275 treatment
			qPCR	↑ CREB gene expression after MS-275 50 and 100 uM; ↑ BDNF gene expression after MS-275 10; 50 and 100 uM

acH3/4, acetylated histone H3/4; Avpr2, Arginine Vasopressin Receptor2; Bdnf, brain-derived neurotrophic factor; Casr, calcium-sensing receptor; Crhr2, corticotropin releasing hormone receptor 2; Dcx, dublecortin; Elk1, ETS domain-containing protein Elk-1; Gal, galanin; Gnai1, G Protein Subunit Alpha I1; Gnrhr, gonadotropin releasing hormone receptor; Grm8, glutamate metabotropic receptor 8; H3/4, histone 3/4; HcnI, hyperpolarization-activated cyclic nucleotide-gated channel 1; Hdac4/5, histone deacetylase 4/5; HP, Hippocampus; Htr2a, 5-hydroxytryptamine receptor 2A; Kcnh2, potassium voltage-gated channel subfamily H member 2; mTOR, mammalian target of rapamycin; NAc, Nucleus Accumbens; Notch3, Neurogenic locus notch homolog protein 3; Ppp2r2b, protein phosphatase 2 regulatory subunit Bbeta; Prkcc, protein kinase C gamma; Sin3a, SIN3 Transcription Regulator Family Member A; Slc8a2/3, solute carrier family 8 member A2/3; Tcf12, Transcription factor 7-like 2; Ttr, transthyretin; ↑ increase; ↓ decrease; ↔ no changes

acetylation at the mammalian target of rapamycin *(mTOR*) and G Protein Subunit Alpha I1 (*Gnai1)* promoters. Interestingly, treatment of PNFlx animals with SB protected against the dysregulation of *HDAC4* and *mTOR*, and consequently the development of depression- and anxiety-like behavior. Similarly, re-administration of fluoxetine in PNFlx adult mice normalized the expression of *HDAC4*, which prevented its displacement to the *mTOR* and *Gnai1* promoters and attenuated depression-like behavior; whereas, the viral-mediated hippocampal overexpression of HDAC4 was associated with depressive symptoms [31]. Other authors also suggest the importance of remaining HDACs in the pathophysiology and treatment of depression (for review, see Table 2).

Available data alludes to the involvement of HDACs and related mechanisms in the development of depressive disorders and the molecular mechanisms of antidepressant drug action. It is thus safe to assume that compounds modulating the activities of HDACs may point to a promising direction in the search for new and more effective antidepressant therapies.

HDACi family: four groups, different activities

HDAC inhibitors are powerful tools for manipulating histone deacetylases. To date, a large number of HDACi have either been purified from natural sources or have been synthesized. Generally, the HDACi family is structurally grouped into four classes: hydroxamic acids (e.g. SAHA or Trichostatin A), cyclic tetrapeptides (e.g. trapoxin B or romidepsin), benzamides (e.g. entinostat or CI-994) and aliphatic/short-chain fatty acids (e.g. valproic acid; VPA or SB) [65]. Each of these HDACi compounds blocks the activity of one or more of the 18 HDACs, resulting in an increase in the accumulation of hyperacetylated nucleosome core histones in most regions of chromatin, but affecting the expression of only a small subset of genes and thus leading to the transcriptional activation of some genes, but the repression of an equal or larger number of other genes [66].

Interest in HDACi began almost 30 years ago and currently they are emerging as a new class of potential anticancer agents and have been shown to induce differentiation, cell-cycle arrest, and apoptosis and to inhibit migration, invasion, and angiogenesis in many cancer cell lines. In addition, these compounds inhibit tumor growth in animal models and show antitumor activity in patients [67]. Furthermore, HDACi have a long history of use in psychiatry and neurology mainly as mood stabilizers and anti-epileptics [68,69]. They were used in the treatment of neurological diseases, even before the molecular targets of these drugs were described. More recently, HDACi have been extensively investigated as possible treatments for neurodegenerative diseases (e.g. Alzheimer's, Parkinson's and Huntington's disease) [70–72] and other diseases, such as depressive disorders [32,73–76].

Antidepressant-like efficacy of the HDACi: effect on animal behavior and gene expression

In the last decade, various HDACi have been studied in connection with the regulation of mood and behavior. The most promising HDACi with high antidepressant potential are listed and briefly characterized in Table 3. While detailed summary of the preclinical research evaluating their efficacy and potential usefulness in the treatment of depression using animal behavioral tests and models of the disease is presented in Table 4.

One of the most widely studied HDACi is belonging to the short-chain fatty acid sodium butyrate (the sodium salt of butyric acid). SB acts as a HDAC inhibitor for HDAC1 (IC_{50} 0.3 mM), HDAC2 (IC_{50} 0.4 mM) and HDAC7 (IC_{50} 0.3 mM) in mice [77], and in humans is physiologically produced by the colonic microflora (microbiota) during fermentation of digestible fiber such as cereal flour, inulin, and psyllium [78]. As indicated by forced swim test (FST) and tail suspension test (TST), administration of SB induced antidepressant-like effects in rodents (observed as a significant decrease in immobility scores), and was associated with an increase in histone H4 acetylation of the *TTR* (transthyretin) gene [28,32]. It was also demonstrated that SB (600 mg/kg) exhibited antidepressant efficacy (assessed by sucrose preference, light/dark, TST and FST) and simultaneously affected the level of phospho-cAMP response element binding protein (CREB), AcH3, HDAC2 and brain-derived neurotrophic factor (BDNF) levels in HP of the ICR (Imprinting Control Region) of mice subjected to CRS [21]. Similarly, treatment with SB significantly attenuated behavioral deficits in mice exposed to chronic unpredictable mild stress (CUMS) which was accompanied by an increase in 5-HT concentration and BDNF expression in the frontal cortex (FC) [79]. Moreover, in Sprague-Dawley rats after 1.2 g/kg (*ip*) and 300 mg/kg of SB administered orally, changes in animal behavior and elevated expression of a large number of depression-related genes in HP were found [31,32]. It is also highly likely that the mechanism of antidepressant action of SB may also be associated with its inhibitory effect on immune-inflammatory and oxidative stress pathways resulting in lower expression of pro-inflammatory cytokines (interferon-γ, Intereukin-6, Interleukin-1β) and nitric oxide [80,81]. In microglial cells, butyrate down-regulated lipopolysaccharide (LPS)-induced NFκB signaling as well as expression of Toll-like receptor 4 (TLR4) and further inhibited proteasome activity and thus inhibits

cytosolic NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation [82]. Clinical research have shown that the antioxidant activity of SB reduces reactive oxygen species and increases the amount of reduced glutathione [83].

Commonly used in the pharmacotherapy of affective disorders VPA is another analogue of short-chain fatty acid HDAC inhibitors. It was demonstrated that VPA microinjected into the ventrolateral orbital cortex (VLO) regulated memory processes and induced antidepressant effect in Sprague-Dawley rats in the FST [84]. Also, intragastric administration of VPA (300 mg/kg; 28 days) in a CUS model resulted in a reduction of anxiety and depression-like symptoms, a decrease in corticosterone secretion, and expression of tyrosine hydroxylase (TH; both at the protein and mRNA levels) as well as elevated levels of BDNF mRNA in HP [11,85]. A possible mechanism of VPA action also involves region-specific changes in the level of??-aminobutyric acid (GABA) [86]. Several studies have shown an increase in GABA concentration in the brain after VPA administration, thus potentiating GABAergic transmission in specific brain regions [87]. So far, it is not clear, whether this effect is due to the activation of glutamic acid decarboxylase (GAD; enzyme responsible for GABA synthesis), or inhibition of the catabolic enzymes succinic semialdehyde dehydrogenase (SSAD) and GABA transaminase (GABA-T) [88,89]. Besides, VPA may have a direct effect on K^+ channels in the neuronal membrane and also attenuate N-methyl-D-aspartate (NMDA)-mediated neuronal excitation as well as block Ca^{2+} and Na^+ or voltage-gated K^+ channels [90].

The increasing number of studies suggest that also newer (so-called second generation) HDACi exhibit antidepressant activity. Covington et al. [30] showed that continuous infusion of two-second generation HDACi – suberoylanilide hydroxamic acid (SAHA; vorinostat) and entinostat (MS-275) into NAc (both compounds at a dose of 100 μM) of mice subjected to chronic social defeat stress, reversed the stress-induced social avoidance in defeated mice and restored the amount of time the animals spent interacting socially. Furthermore, the antidepressant-like activity of HDACi was also observed in other behavioral assays, such as the FST (for both SAHA and MS-275) or sucrose preference test (only MS-275). It was also demonstrated that both compounds have no effect on locomotor activity but increase AcH3K14 levels contrary to fluoxetine. Besides that, gene expression array showed that MS-275 regulates about 12 genes important in depression (e.g. *slc17a, nrn1, rab3b, TNFRSF1A,* and *sin3b)* similar to fluoxetine [30]. Antidepressant-like effect (observed as a reversal of stress-induced social avoidance and increased acH3) of MS-275 (100 μM) were also noticed following intrahippocampal and intraamygdalar infusion in male C57Bl/6J mice [29]. Also in a study by Lin et al. [33] bilateral administration of MS-275 in the VLO (at a dose of 10, 50 or 100 μM; 0.5 μl per side) reduced immobility time in the FST and TST (especially at a dose of 100 μM for 7 days) compared to saline-treated controls. The results were similar to the effects of systematically administered fluoxetine. The behavioral effects of MS-275 were associated with an increase in histone H3 acetylation and elevated CREB and BDNF levels in the VLO [33]. The antidepressant potential of another compound, a benzamide-based and slow-binding inhibitor of HDAC1/2 has been equally shown. A 1-week systemic treatment with Compound 60 (Cpd-60; 45 mg/kg; *ip*) contributed to reducing immobility in the FST and locomotor activity following acute amphetamine challenge in C57BL/6 mice, which is consistent with established effects of clinical antidepressants and mood stabilizers [91]. Molecular study of the prefrontal cortex (PFC), HP and NAc after Cpd-60 treatment revealed some alterations in gene expression (similar to that observed after lithium administration) and an increase in histone acetylation levels. On the contrary, injection of vorinostat (fast-binding) at a dose of 25 mg/kg (*ip*) was sufficient to increase histone acetylation in the brain (especially in PFC), but did not change mood-related behaviors and had dissimilar transcriptional regulatory effects when compared to Cpd-60 [91].

Recently, a unique potentially fast-acting antidepressant l-acetylcarnitine (LAC) has been described. It is marketed for the treatment of neuropathic pain, which causes analgesia by increasing metabotropic glutamate receptor 2 (mGluR2) expression via an epigenetic mechanism shared by HDACi [92]. LAC (100 mg/kg) exhibited rapid and long-lasting antidepressant effect within 2–3 days following intraperitoneal administration both in Flinders Sensitive Line rats and in mice exposed to CUS. The activity of the drug in behavioral tests was comparable to the effects seen with 2–3 wk treatment with clopmipramine. Nasca et al. [92] suggest that LAC promotes rapid antidepressant responses by histone acetylation by controlling the transcription of *BDNF* and *mGluR2* in HP and PFC.

Interestingly, the potential antidepressant activity of the class III HDAC inhibitors has been equally demonstrated in some preclinical studies. Ferland et al. [93], showed that infusion of sirtinol (SIRT1 inhibitor; 50 μM/L) into DG prevented the chronic variable stress-mediated decrease in histone acetylation as well as ERK1/2 and Bcl-2 protein levels in DG of rats. These results corresponded to enhanced performance on the novel object location memory task, as well as reduced anhedonic behavior [93]. On the contrary, another study indicated that increased hippocampal SIRT1 activity blocks depression-like behavior in mice caused by chronic ultra-mild stress, resulting in a state of stress resilience. Conversely, the infusion of the SIRT1 inhibitor, sirtinol (100 μM/L) into HP induced pro-depressive behavior [94]. In line with this observation, a recently published report showed the inhibition of SIRT2 by tenovin-D3 resulted in depression-like behaviors and impaired hippocampal neurogenesis in rats. The overexpression of SIRT2 by the intra-hippocampal infusion of a recombinant adenovirus vector expressing mouse SIRT2 reversed the CUS-induced depressive-like behaviors and promoted neurogenesis [95].

Many authors have also suggested a potentiating role of HDACi in combination with classical antidepressant drugs, especially SSRIs. Convington et al. [29] demonstrated the enhancing effect of MS-275 (infused into the brain) on the antidepressant action of fluoxetine (20 mg/kg). Similar results were also obtained after chronic (but not acute) intraperitoneal co-administration of SB and fluoxetine at a dose of 10 mg/kg [96]. Also in a recent report, the co-administration of a behaviorally inactive dose of HDAC6i (ACY-738) and a sub-effective dose of citalopram exerted effects comparable to a 40-fold higher dose of citalopram administered alone [97]. These observations are particularly interesting because they suggest a convergence of the intracellular mechanisms of SSRIs action and HDACs inhibition and give a glimmer of hope that we are on the verge of discovering new, more effective and safer forms of therapies for depression.

Potential clinical usefulness of HDACi in the pharmacotherapy of depressive disorders: perspectives and main limitations

Histone deacetylase inhibitors because of their mechanism of action and related biological effects represent novel and promising tools for the therapy of many human diseases. To date, most of the clinical trials (~600) using HDACi (as mono- or polytherapy) have concentrated on the possibility of their use in the treatment of cancer (~550 trials) (see www.clinicaltrials.gov). Fifteen of these compounds are listed as potential drugs [98]; however, only four HDACi: vorinostat, romidepsin, belinostat, and panobinostat have been approved by the U.S. FDA for clinical use (treatment of T-cell lymphoma and multiple myelomas

respectively) [99]. The main argument for their use as anticancer agents is the fact that, in contrast to many other cytostatics, HADCi are active against proliferating and non-proliferating tumor cells and have a relatively low toxicity to normal body cells [100]. Despite the fact that numerous studies have been carried out on other HDACi (e.g. MS-275 or SB), the efficacy, safety, and consequently the possibility of their use in the treatment of cancer remains debaTable So is their use in the therapy of other (non-malignant) diseases. To date, no clinical trials evaluating the suitability of HDACi in the treatment of mood disorders exist. Consequently, we can only speculate on the potential effectiveness of this class of compounds in human depression based primarily on results from preclinical studies.

As mentioned in the previous section, antidepressant-like efficacy has been demonstrated for several HDACi (the most powerful are summarized in Table 3). The results of these studies appear to be very promising for the future of antidepressant therapy; however, currently the clinical use of the majority of HDACi is rather problematic. The main risk associated with their use (especially long-term) in humans results from the lack of target specificity. HDACi (with a few exceptions) exhibit pleiotropic effects, whose global consequences (e.g. demethylation leading to the activation of inexpedient genes, including oncogenes) are difficult to predict. Low target specificity of HDACi is also reflected in the number of adverse effects observed in clinical trials, among which the most frequent are diarrhea, nausea, and fatigue [99,101]. Unfortunately, in most animal studies on depression, HDACi had to be administered repeatedly to produce an antidepressant-like effect [11,21,29,32,33]. These observations suggest that long-term administration of HDACi may also be required in the clinical treatment of depression which makes them similar to currently used antidepressants. This in addition to the numerous side effects that they elicit in humans casts doubts on their potential use in the treatment of mood disorders. For the same reason, vorinostat, already administered as an anticancer drug, will unlikely be used as a monotherapy in the treatment of depressive disorders in humans [101]. Highly problematic is the clinical use of two broad types of HDACi, i.e. VPA (a mood stabilizer) and butyric acid as well. These compounds usually work at higher doses (millimolar amounts) due to the low target specificity and limited penetration into the brain. For this reason, they are more likely to be used by researchers to improve knowledge on the role of individual HDACs in various brain diseases and their region-specific involvement than as therapeutics. The best solution to the problem of low specificity of HDACi might be to search for or synthesize novel and highly selective compounds (or new analogues). One of such promising compounds is MS-275 which blocks the activity of solely Class I HDACs with the greatest specificity toward HDAC1 [98]. Its intracerebral infusion for few days reversed depression-like symptoms and resulting in characteristic changes in gene expression in the brain reminiscent of the action of antidepressant drugs [29,30,33]. Moreover, it is known that MS-275 crosses the blood-brain-barrier easily, thus it can be administered orally with minimum side effects. Because of these positive indicators, further studies on this compound need to be pursued vigorously. Other selective HDACi (like Cpd-60, ACY-738, ACY-775, mocetinostat, romidepsin or CI-994) appear to be promising as they are now being investigated in the context of central nervous system disorders [102]. On the other hand, there are very interesting reports showing that the reduction of HDAC activity by MS-275, SB or ACY-738 can significantly enhance the efficacy of classical antidepressants (in particular fluoxetine), even when used in low doses [29,96,97]. However, whether the antidepressant activity of fluoxetine or other antidepressants is enhanced through an HDACi activity or a non-HDAC-dependent, cell-signaling-induced hyper-acetylation of histones is so far not known [103]. Even so, preliminary results seem to be very encouraging and give new hopes for the discovery of better, more effective antidepressant therapies which may be very useful especially in treating drug-resistant patients.

Conclusions

HDACi appear to be powerful and promising tools that reinforce the effects of drug therapies, not only in cancer treatment but in psychiatric disorders as well. A large number of very recent publications suggest a crucial role for HDACi in the pathogenesis of psychiatric disorders. It seems that the role of HDACs in heterologous disorders, like depression, will continue to increase as research continues to garner momentum. HDACs may represent the missing link we have been looking for to explain the pathogenesis of disorders like MDD because they can fill the gaps that cannot be explained by genetics. Furthermore, HDACi may trigger the creation of new models of therapy in psychiatric disorders. The use of HDACi should also be considered in the adjuvant treatment of patients with depression, as they seem to potentiate the effects of antidepressants.

Disclosure

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