Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/59/20241366

Antidepressant drugs targeting on the histone deacetylase (HDAC) research progress

Yi Ding

China Medical University Shenyang, 110000, China

40351745@ads.qub.ac.uk

Abstract. Depression is a high incidence, low clinical cure rate, and high recurrence rates of mental disorders. Antidepressant drug development has been going on for several years, and is widely used in the market of monoamine oxidase inhibitors, for example, tricyclic antidepressants. There has been a lot of progress, but they still can't take effect immediately, and may cause adverse reactions or other defects in the patients' nervous system and urinary system. At present, with the rapid development of global society, people are facing increasing mental stress, and the high incidence of depression is becoming increasingly severe. The development of antidepressant drugs is of urgency and importance. This article from the perspective of epigenetics, is based on the modification of histone acetylation, analysis of depression causes the histones to acetylate enzyme (HDAC), and targeted at HDAC drugs, mainly HDAC inhibitors (HDACi). This article reviews the therapeutic effects and therapeutic mechanisms of histone deacetylase (HDAC)-targeted drugs on depression, so as to provide a reference for exploring new treatment methods for depression.

Keywords: depression, epigenetics, histone acetylation and histone go acetylation enzyme (HDAC), histone acetylation enzyme inhibitors (HDACi).

1. Introduction

Depression is a common clinicallt persistent and serious mental illness, caused by various reasons, with low mood and loss of interest as the core symptoms of the disease, which can be accompanied by thinking retardation, sleep disorders, executive dysfunction, social dysfunction, and more serious suicide ideation [1]. At present, depression is mainly treated by psychotherapy, physical therapy and drug treatment [2]. At present, the common drugs for the treatment of depression are new types of antidepressants, including but not limited to selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepi-nephrine reuptake inhibitors (NOS) Inhibitors, SNRIs), norepinephrine and serotonin can antidepressants (noradrenergic and specificserotonergic anti-depressants (NASSAs), 5-HT2A receptor antagonists, 5-HT reuptake inhibitors, etc. Except for 5-HT2C receptor antagonist properties of melatonin receptor agonists (argonaut beauty pull), all other drugs mainly regulate function and can monoamine neurotransmitters [3] in patients with depression, although the disease will be eased after treatment, as a result of these drug targets being widely distributed in the body, different degrees of adverse reactions will appear. The adverse reactions of patients are mainly reflected in neurological dysfunction, cardiovascular dysfunction, urinary dysfunction, digestive dysfunction, blood circulation

DOI: 10.54254/2753-8818/59/20241366

dysfunction, muscle dysfunction, skin damage, etc. The specific number and proportion of patients are shown in Table 1.

Table 1. Analysis of adverse effects of antidepressants [n(%)]

Types of adverse reactions	Number of cases (84 cases)	Proportion
Neurological abnormalities	42	42/84 (50.00)
Abnormal cardiovascular function	6	6/84 (7.14)
Urinary dysfunction	4	4/84 (4.76)
Digestive abnormalities	18	18/84 (21.42)
Abnormal blood circulation function	19	19/84 (22.51)
Abnormal muscle function	22	22/84 (26.19)
Skin lesions	12	12/84 (14.28)

This review focuses on the limitations of current antidepressants and explores the pathological link between histone acetylation (HDAC) and the pathogenesis of depression from the perspective of epigenetics. In this paper, the mechanisms and efficacy tests of currently designed drugs targeting different HDacs are reviewed, and the limitations of current drug design are discussed so as to provide new ideas for the development of depression drugs.

2. Introduction To Epigenetics

Recent studies have shown that epigenetics is related to the occurrence and development of depression [4]. Epigenetics is a science that studies the biological phenomenon that genes produce heritable phenotypes and reversible molecular information through mitosis without changing the DNA sequence. Epigenetics plays a key role in transcription, chromosome organization, genome stability and imprinting [5]. The regulation of gene expression involves a series of processes, such as DNA methylation, histone modification, and non-coding RNA regulation. At present, the research on histone acetylation is the most extensive.

3. Hdac and the pathology of depression

The common histones H2A, H2B, H3 and H4 form dimers to form histone octamers to maintain genome stability and regulate DNA expression. Histone acetylation in acetyl transferase (histone acetyltransferase, HAT), under the catalysis of transferring acetyl groups, and adding more in the main protein lysine residues or protein N process on the side. HAT activates gene transcription and histone deacetylase (HDAC) inhibits gene transcription.

3.1. HDAC and astrocytes

HDAC can promote the differentiation of neural stem cells and NPCS into neurons or glia [6]. Inhibition of HDAC reduces GFAP expression in primary astrocytes (AS) and astrocytoma cells in the human brain [7]. Studies have shown that histone acetylation can reduce inflammation, thus protecting the AS nerve [8]. When the histone deacetylase (HDAC) plays a role, it will lead to a reduced histone acetylation level, so that inflammation levels of astrocytes (AS), Studies have shown that AS inflammation may lead to the central nervous system (CNS), including depression, multiple diseases. Studies have found that inflammatory factors of disorders may be one of the important mechanisms of depression. In the serum and cerebrospinal fluid of patients with depression, the expression of proinflammatory factors increased significantly, while patients with inflammatory body disease are more likely to suffer depression [9].

DOI: 10.54254/2753-8818/59/20241366

3.2. The relationship between different types of HDacs and depression

HDACs were originally found in saccharomyces cerevisiae. It has found that human HDACs have 18 kinds, respectively named HDAC1, HDAC11, SIRT1, and SIRT7. Histone acetylation is jointly regulated by the HATs and HDACs, under normal circumstances to histone acetylation, and the level is in a state of dynamic balance [10], which regulates many cellular processes [11, 12].

Studies have shown that HDAC-mediated changes in histone acetylation affect stress responses, depression-like behaviors, and antidepressant effects [13-16].

3.2.1. Class I HDacs

Class I HDAC (HDAC I: HDAC1, 2, 3, and 8) and histone acetylation enzyme 1 (histone deacetylase 1, HDA1) gene homology. HDAC I expression in the body is widespread, mainly located in the nucleus, and the enzymatic activity of substrates is higher [17].

It has been shown that mice exposed to chronic social failure stimuli have a sustained increase in histone acetylation levels (H3K14ac), which is associated with reduced histone deacetylase 2 (HDAC2) levels in the NAC [18]. Injected with the NAC HDAC inhibitor (MS-275), it can improve depression behaviors. Another study showed that animals overexpressing HDAC2 in the NAC region exhibited more depressive-like behaviors [19].

3.2.2. Class II HDAC

Class II HDacs (HDAC IIa:HDAC4, 5, 7, and 9; HDACIIb:HDAC6 and 10) are located in the nucleus, generally in a non-phosphorylated state, and are phosphorylated in response to specific signals. They interact with transcription factors and are recruited to target genes to inhibit their transcription [20]. At present the study of class II HDAC is mainly concentrated on HDAC4 and HDAC5.

Sarkar et al's study found that HDAC4 expression in the hippocampus can lead to depression in adult rats [21].

Studies have found that chronic administration of prothiazide (a trichyclic antidepressant) to depressive-like mice is associated with selective down-regulation of HDAC5 in the mouse hippocampus, and after SD, it is found that the whole brain H3K14ac and H4K12ac levels are up-regulated [33] and the acetylation levels of several other lysine sites of histone H4 such as 5, 8 and 16 are changed [22]. Among them, the hippocampus H3 acetylation levels are rising short, then continue to reduce [23]. At the same time the hippocampus is closely related to the depression mechanism of brain derived neurotrophic factor (BDNF) mRNA levels. The antidepressants imipramine can increase BDNF promoter of histone acetylation and reverse the decline [24], virus mediated HDAC5 Expression of blocking the antidepressant effect of c thiazine [25]. It has a negative effect on depression treatment in mice. HDAC5 in the hippocampus may promote the development of depression, and targeted inhibition of HDAC5 activity in the hippocampus provides a new strategy for the design of novel antidepressant drugs.

3.2.3. Class III HDAC

Class III HDAC (HDAC III) also called sirtuins including SIRT1-7 (SIRT), is a kind of dependence on NAD + silence regulatory proteins [26]. Sirts exist in the nucleus, cytoplasm, and mitochondria and perform physiological functions such as regulating cell survival, metabolism, and apoptosis [27]. Studies found that class III HDAC is similar to the hippocampus neural plasticity and depression (SIRT) behavior [28-30].

Studies have shown that SIRT activation in the hippocampus plays an antidepressant role, and blocking its function will enhance depressive-like behaviors [28]. Targeted activation of the SIRT pathway in the hippocampus may be a new method for the treatment of depression.

DOI: 10.54254/2753-8818/59/20241366

4. Targeting Role In The Drug Design Of Hdac And Efficacy Test

4.1. HDAC Inhibitors (HDACi)

At present, most of the commonly used drugs targeting HDAC are HDAC inhibitors (HDACi). Studies have shown that HDACi has the potential to treat neurodegenerative diseases, epilepsy, schizophrenia and other mental diseases [31-34]. In addition, the antidepressant drugs to some extent, also influence the acetylation status and improve brain synaptic plasticity, thus playing a role of antidepressant [35], targeted work on HDAC has a huge potential of antidepressant drugs.

4.2. The classification of HDACi

Currently, according to the structure HDACi can be divided into four categories: short chain fatty acid, hydroxy ox-ime acids, cyclic peptide, benzamide [36]. The different targeted drugs for the treatment of depression mechanisms of HDAC are shown in Table 2.

Table 2. The different targeted drugs for the treatment of depression mechanisms of HDAC

Target	Drug	Species	Molecular mechanisms of action
Class I HDAC inhibitors	MS-275	Mice	↑ H3 acetylation in the mPFC, exerting antidepressant-like effects. ↑Rac1 in the NAc, synapse structural plasticity normalization ↑H3 acetylation in the hippocampus and the NAC, exerting antidepressant-like effect
Class I and II HDAC inhibitor	Sodium butyrate	Mice	HDAC5 downregulation, ↑H3 acetylation in BDNF gene promoter, ↓ depression-like behavior
			↓ Depression-like behavior, ↑HDAC2, ↑ pCREB, ↑H3 acetylation, ↑BNDF in the hippocampus
		Rats	↓ Depression-like behavior, ↑transthyretin (Ttr)expression, ↓serotonin 2A receptor,↑H4 acetylation at Ttr gene promoter
	SAHA	Mice	↑H3 acetylation in the hippocampus and the NAc, exerting antidepressant-like effects
			↑GDNF in the Nac, HDAC2 inhibiton
			↓ Depression-like behavior,↑BDNF in the PFC
	Valproic Acid	Rats	↓ Depression-like behavior, ↓ corticosterone plasma level
HDAC1/2 inhibitor	Cpd60	Mice	↑Histone acetylation at the promoter regions of upregulated transcripts.
HDAC4/5 inhibitor	LMK-235	Mice	↓ Depression-like behavior
HDAC6 inhibitor	ACY-738	Mice	Relieve the inhibitory effect on 5-HT mediated signaling

5. Current research on the mechanism of hdaci

5.1. SAHA

Methylenehydroxamic acid (SAHA/Vorinostat) is a potent inhibitor of histone deacetylases (HDACs) and is known to have antidepressant properties. As shown in Table 2, SAHA can alleviate depression-like behaviors through three main action pathways, including (1) increasing H3 acetylation levels in the mouse hippocampus and NAC by inhibiting HDAC activity; (2) upregulating the expression of GDNF in NAC; and (3) increasing BDNF in PFC.

DOI: 10.54254/2753-8818/59/20241366

Studies have shown that SAHA has an effect on the expression of GluN2A, GluN2B (NMDA receptor subunit), (p-) AMPK and ΔFos proteins, which are integral parts of the brain signal transduction pathway, are also involved in the pathophysiology of depression and the mechanism of antidepressant effects [37]. It has also been reported in the literature that SAHA administration in the NAc of mice suffering from SD showed an antidepressant effect, and peripheral administration of SAHA could also reverse depressive-like behavior after CUMS stress [38]. This effect may improve depression by up-regulating the expression of glial-derived neurotrophic factor (GDNF). Studies have also shown a close relationship between depression and inflammation: patients with depression have higher levels of proinflammatory cytokines, C-reactive protein, chemokines, and cell adhesion molecules [39], and the incidence of depression is as high as 50% after treatment with interferon-α [40]. Therefore, SAHA may treat depression by reducing inflammatory damage.

5.2. MS-275

MS-275 is a class I HDAC inhibitor. As shown in Table 2, MS-275 mainly through three ways play a role of antidepressant. It has been shown that after the injection, H3 acetylation levels in the mPFC of mice are increased, and depression-like behaviors are alleviated. These results suggest that MS-275 exerts antidepressant effects by promoting H3 acetylation in the mPFC [41].

Another study found increased Rac1 levels in the mouse NAc after MS-275 injection, normalizing synaptic structural plasticity and reducing depressive-like behavior [42]. Another study tested H3 acetylation levels in the hippocampus and NAC of mice after administration of MS-275 and found that H3 acetylation levels increased, suggesting that MS-275 exerted antidepressant effects [43, 44].

5.3. Cpd60

Cpd60 is an HDAC1/2 inhibitor. As shown in Table 2, Cpd60 is found to attenuate depression-like behaviors in mice by upregulating histone acetylation in the promoter region of the transcripts [45].

5.4. LMK-235

LMK-235 is a kind of HDAC4/5 inhibitor, and studies have found that after the injection of LMK - 235 symptoms of depression in mice [46]. These results indicate that LMK-235 can improve the level of histone acetylation in mice by inhibiting the activity of HDAC4 and HDAC5, thus achieving the effect of treatment of depression.

5.5. Valproic Acid

Valproic Acid (VPA), a class I and II HDAC inhibitor, was found to reduce plasma levels of corticosterone and alleviate depression-like behaviors in mice after injection of VPA [47].

5.6. ACY-738

ACY-738 is an HDAC6 inhibitor, and it was found that peripheral administration of ACY-738 in depressed mice significantly reduced immobility time in water and alleviated depression-like behavior, which achieved antidepressant effects by deregulating signaling on 5-HT-mediated signaling [48].

6. Conclusion

Now, with the development and progress of society, depression has become a major threat to human mental health. In terms of the treatment of depression, there are a lot of ways, including drug therapy for the treatment as the main way. The design of the depression drugs has become the main problem faced by the treatment of depression. According to the pathogenesis of depression, many hypothesis have been proposed. At present, most depression drugs are designed based on the monoamine hypothesis. However, there are many problems with the antidepressant drugs on the market, such as fluoxetine and triserin, which can cause nausea, vomiting, diarrhea and other side effects, and can not take effect immediately. Because the pathogenesis of depression is still unknown. The introduction of epigenetics provides a new direction for the development of drugs for depression and provides a new mechanism

DOI: 10.54254/2753-8818/59/20241366

by which the environment affects the disease. At present, histone modification is the most widely studied, and histone acetylation is one of the important processes, in which histone deacetylase (HDAC) has become an important drug target. The current designed drugs' category mainly is for HDAC inhibitor, HDACi mainly plays a role in the following ways: (1) raise glial cell derived neurotrophic factor (glial-derived neurotrophic factor, GDNF) expression to improve depression; (2) reduce inflammatory injury to alleviate depression; (3) The depression-like behavior was alleviated by upregulating histone acetylation in the promoter region of the transcripts. (4) modulating the glutamate-5-HT system to improve glutamate transmission. Studies have shown that currently designed HDAC drugs such as a class of HDAC inhibitors MS-275 and HDAC5 inhibitors ACY-738 can enhance the efficacy of classical antidepressant drugs such as fluoxetine [49]. But as a result of HDAC in the human body contains many targets, low specificity, so increased the complexity of the drug design, at present there are certain difficulties in the development of drugs, drug experiments for animal experiment, has not been applied to clinical, need more understand the mechanism of action of known HDAC experiment, Improving the specificity of drug action and solving how drugs cross the blood-brain barrier (BBB) are the core problems today.

References

[1] Weifeng Guo, Xiaolan Cao, Lei Sheng, et al. Expert consensus on diagnosis and treatment of depression with integrated traditional Chinese and Western medicine [J]. Chinese Journal of Integrated Traditional and Western Medicine, 40(2): 141-148 (2020).

[2] Berton O., Nestler E.J. New approaches to antidepressant drug discovery: beyond monoamines [J]. Nat Rev Neurosci, 7:137-151 (2006).

[3] Machado-vieira R., Henter I.D., Zarate C. A. J. New targets for rapid antidepressant action [J]. Progress in neurobiology, 152: 21-37 (2017).

[4] Lawrence M., Daujat S., Schneider R. Lateral thinking: how histone modifications regulate gene expression. Trends Genet, 32: 42-56 (2016).

[5] Ladd-Acosta C., Fallin M.D. The role of epigenetics in genetic and environmental epidemicology. Epigenetics, pp.1-283 (2016).

[6] Yang J., Tang Y., Liu H., et al. Suppression of histone deacetylation promotes the differentiation of human pluripotent stem cells towards neural progenitor cells [J]. BMC Biol, 12: 95 (2014).

[7] Kanski R., Sneeboer M. A., Van Bodegraven E. J., et al. Histone acetylation in astrocytes suppresses GFAP and stimulates a reorganization of the intermediate filament network [J]. J Cell Sci, 127(Pt 20): 4368-4380 (2014).

[8] Suh H. S., Choi S., Khattar P., et al. Histone deacetylase inhibitors suppress the expression of inflammatory and innate immune response genes in human microglia and astrocytes [J]. Neuroimmune Pharmacol, 5(4): 521-532 (2010).

[9] Liddelow S.A., Guttenplan K.A., Clarke LE, Neurotoxic reactive astrocytes are induced by activatedmicroglia [J]. Nature, 541(7638):481-487 (2017).

[10] Chen X., Guan X.J., Peng X.H., et al. Acetylation of lysine 9on histone H3 is associated with increased pro-inflammatory cytokine release in a cigarette smoke-induced rat modelthrough HDAC1 depression.Inflamm Res, 64, 513-526 (2015).

[11] Whittle, J. R., et al. Sirtuins, nuclear hormone receptor acetylation and transcriptional regulation. Trend. Endocrinol. Metab. 18, 356–364 (2007).

[12] Bao, J. & Sack, M. N. Protein deacetylation by sirtuins: delineating a post-translational regulatory program responsive to nutrient and redox stressors. Cell. Mol. Life Sci. 67, 3073-3087 (2010).

[13] Uchida, S., et al. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 69, 359–372 (2011).

[14] Covington, H. E., et al. Hippocampal-dependent antidepressant-like activity of histone deacetylase inhibition. Neurosci. Lett. 493, 122-126 (2011).

[15] Schroeder, F. A., Lin, C. L., Crusio, W. E. & Akbarian, S. Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. Biol. Psychiatry 62, 55–64 (2007).
[16] Yamawaki, Y. et al. Antidepressant-like effect of sodium butyrate (HDAC inhibitor) and its molecular mechanism of action in the rat hippocampus. World J. Biol. Psychiatry 13, 458–467 (2012).
[17] Yang X.J., Seto E. The Rpd3/Hda1 family of lysine deacetylases:from bacteria and yeast to mice and men [J]. Nat Rev Mol CellBiol, 9:206-218 (2008).
[18] Covington, H. E., et al. Antidepressant actions of histone deacetylase inhibitors. J. Neurosci. 29, 11451–11460 (2009).
[19] Uchida, S., et al. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 69, 359–372 (2011).
[20] Renthal W., Maze I., Krishnan V., et al. Histone deacetylase 5epigenetically controls behavioral adaptations to chronic emo-tional stimuli [J]. Neuron, 56:517-529 (2007).
[21] Sarkar, A., et al. Hippocampal HDAC4 contributes to postnatal fluoxetine-evoked depression-like behavior. Neuropsychopharmacology 39, 2221-2232 (2014).
[22] Kenworthy C.A., Sengupta A., Luz S.M., et al. Social defeat induces changes in histone acetylation and expression of histone modifying enzymes in the ventral hippocampus,prefrontal cartex, and dorsal raphe nucleus [J].Neuroscience, 264:88-98 (2014).
[23] Covington H.E., Vialou V.F., LaPlant Q., et al. Hippocampal-dependent antidepressant-like activity of histone deacetylaseinhibition [J]. Neurosci Lett, 493:122-126 (2011).
[24] Tsankova N.M., Berton O., Renthal W., et al. Sustained hippocampalchromatin regulation in a mouse model of depression and antidepressant action [J]. Nat Neurosci, 9:519-525 (2006).
[25] Tsankova, N. M., et al. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat. Neurosci. 9, 519–525 (2006).
[26] Seto E., Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes [J]. Cold Spring Harb Perspect Biol, 6:a018713 (2014).
[27] Schwer B., Verdin E. On served metabolic regulatory functions of sirtuins [J]. Cell Metab, 2008,7:104-112.
[28] Abe-Higuchi, N. et al. Hippocampal sirtuin 1 signaling mediates depression-like behavior. Biol. Psychiatry 80, 815-826 (2016).
[29] Gao, J., et al. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 466, 1105–1109 (2010).
[30] Michan, S., et al. SIRT1 is essential for normal cognitive function and synaptic plasticity. J Neurosci 30, (in Chinese) 9695–9707 (2010).
[31] Kelly D.L., Conley R.R., Feldman S., et al. Adjunct divalproex orlithium to clozapine in treatment-resistant schizophrenia. Psychiatr Q, 77:81-95 (2006).
[32] Fischer A., Sananbenesi F., Mungenast A., et al. Targeting the correct HDAC(s)to treat cognitive disorders [J]. Trends Pharmacol Sci, 2010, 31:605-617.
[33] Suo H., Wang P., Tong J., et al. NRSF is an essential mediator for the neuroprotection of trichostatin A in the MPTP mouse model of Parkinson's disease [J]. Neuropharmacology, 99:67-78 (2015).
[34] Citraro R., Leo A., De Caro C., et al. Effects of histone deacetylase inhibitors on the development of epilepsy and psychiatric comorbidity in WAG/Rij rats [J]. Mol Neurobiol, 57:408-421 (2020).
[35] Erburu M., Munoz-Cobo I., Dominguez-Andres J., et al. Chronicstress and antidepressant induced changes in HDAC5 and SIRT2 affect synaptic plasticity [J]. Eur Neuropsychopharmacol, 25:2036-2048 (2015).
[36] Ververis K., Hiong A., Karagiannis T.C., et al. Histone deacetylase inhibitors (HDACIs): multi-targeted anticancer agents [J]. Bio-logics, 7:47-60 (2013).

[37] Misztak, P., Sowa-Kućma, M., Szewczyk, B., et al. Vorinostat (SAHA) May Exert Its Antidepressant-Like Effects Through the Modulation of Oxidative Stress Pathways. Neurotox Res 39, 170-181 (2021).
[38] Uchida S., Hara K., Kobayashi A., et al. Epigenetic status ofGDNF in the ventral striatum determines susceptibility andadaptation to daily stressful [J]. Neuron, 69:359-372 (2011).
[39] Leighton S.P., Nerurkar L., Krishnadas R., et al. Chemokines in depression in health and in inflammatory illness:a systematic review and meta-analysis [J]. Mol Psychiatry, 23:48-58 (2018).
[40] Raison C.L., Capuron L., Miller A.H. Cytokines sing the blues: inflammation and the pathogenesis of depression [J]. TrendsImmunol, 27:24 to 31 (2006).
[41] Covington, H. E., Maze, I., Vialou, V. & Nestler, E. J. Antidepressant action of HDAC inhibition in the prefrontal cortex. Neuroscience 298, 329–335 (2015).
[42] Golden, S. A., et al. Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. Nat. Med. 19, 337-344 (2013).
[43] Covington, H. E., et al. Hippocampal-dependent antidepressant-like activity of histone deacetylase inhibition. Neurosci. Lett. 493, 122–126 (2011).
[44] Covington, H. E., et al. Antidepressant actions of histone deacetylase inhibitors. J. Neurosci. 29, 11451-11460 (2009).
[45] Schroeder, F. A., et al. A selective HDAC 1/2 inhibitor modulates chromatin and gene expression in brain and alters mouse behavior in two mood-related tests. PLoS ONE 8, e71323 (2013).
[46] Higuchi, F., et al. Hippocampal microRNA-124 enhances chronic stress resilience in mice. J. Neurosci. 36, Neurosci. 36, 7253-7267 (2016).
[47] Goudarzi, M., et al. Valproic acid administration exerts protective effects against stress-related anhedonia in rats. J. Chem. Neuroanat. 105, 101768 (2020).
[48] Fukada M., Hanai A., Nakayama A., et al. Loss of deacetylation activity of HDAC6 affects emotional behavior in mice [J]. PLoS One, 7: e30924 (2012).
[49] Ghosh B., Zhao W.N., Reis S.A., et al. Dissecting structure-activity- relationships of crebinostat: brain penetrant HDAC inhibitors for neuroepigenetic regulation [J]. Bioorg Med Chem Lett, 26:1265-1271 (2016).