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The etiological changes of acetylation in peripheral nerve injury–induced neuropathic hypersensitivity

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Abstract

Neuropathic pain is a common chronic pain condition with mechanisms far clearly been elucidated. Mounting preclinical and clinical studies have shown neuropathic pain is highly associated with histone acetylation modification, which follows expression regulation of various pain-related molecules such as mGluR1/5, glutamate aspartate transporter, glutamate transporter-1, GAD65, $Na_v1.8$, Kv4.3, μ-opioid receptor, brain-derived neurotrophic factor, and certain chemokines. As two types of pivotal enzymes involved in histone acetylation, histone deacetylases induce histone deacetylation to silence gene expression; in contrast, histone acetyl transferases facilitate histone acetylation to potentiate gene transcription. Accordingly, upregulation or blockade of acetylation may be a promising intervention direction for neuropathic pain treatment. In fact, numerous animal studies have suggested various histone deacetylase inhibitors, Sirt (class III histone deacetylases) activators, and histone acetyl transferases inhibitors are effective in neuropathic pain treatment via targeting specific epigenetic sites. In this review, we summarize the characteristics of the molecules and mechanisms of neuropathy-related acetylation, as well as the acetylation upregulation and blockade for neuropathic pain therapy. Finally, we will discuss the current drug advances focusing on neuropathy-related acetylation along with the underlying treatment mechanisms.

Keywords

Nerve injury, neuropathic pain, etiology, acetylation, outcomes

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Introduction

Neuropathic pain is a complex chronic pain condition that results from direct injury or disease affecting the somatosensory system, thereby reducing the life quality of millions of people worldwide.[1] Despite recent advances, the pathophysiological mechanisms of neuropathic pain remain incompletely clarified, and current available therapies remain unsatisfactory.

Various insults including nerve injury, chemotherapeutics, and diabetes can induce and promote chronic pain development through epigenetic modulation of DNA or DNA-packaging histones with no presence of DNA sequence change. Further, mounting evidence shows histones-related acetylation regulation is highly associated with neuropathic pain, leading to

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chromosome structural changes followed with transcription regulation of various receptors, transporters, enzymes, nociceptors, structural proteins, cytokines, chemokines, and chemokine receptors in dorsal root ganglion (DRG), in the spinal cord, and in other supraspinal regions.

Histone acetylation depends on two types of pivotal enzymes: histone deacetylases (HDACs) and histone acetyl transferases (HATs).[2] In most studies, HDACs upregulate in response to nerve insults, resulting in histone deacetylation and promoting chronic pain development. Certain studies also indicate that HATs upregulate, which promote histone acetylation and pain induction. HDACs and HATs activity, as well as histone acetylation levels are dynamic, serving as promising intervention targets for neuropathic pain treatment. We therefore review the current knowledge and advances surrounding this disorder with regards to acetylation in neuropathic pain and its involved molecules, mechanisms, and intervention targets.

Acetylation and gene expression

Chromatin structure consists of certain pairs of genomic DNA packaged around a conservative histone octamer with two of each of the histones including H2A, H2B, H3, and H4. Histone tails, in addition to *N*-terminal domains of such histone octamers, extend from the nucleosomal disk and are highly susceptible to post-translational regulation forms such as methylation, phosphorylation, ubiquitination, and acetylation. Compared to methylation, histone acetylation is a more labile and transient posttranslational modification that rapidly orchestrates gene expression in response to external stimuli.[2]

As two pivotal enzymes involved in histone acetylation, HDACs usually remove the acetyl groups and increase the affinity for DNA binding, causing relatively compact chromatin followed with gene expression inhibition. In contrast, HATs counteract the electrostatic structure between histones and DNA, predisposing the chromosome structure to be more relaxed and promote gene transcription.[3] Until now, there have been 18 different HDACs categorized into four groups: class I (encompassing HDAC 1–3, 8), II (HDAC 4–7, 9, 10), III (also termed sirutins, including sirutins 1–7), and IV (HDAC 11).[4] Class II is further categorized into IIa (HDAC 4, 5, 7, 9) and IIb (HDAC 6 and 10). HDACs class I, II, and IV are zinc-dependent, whereas class III HDACs are nicotinamide (NAD^+)-dependent.[5] Nearly all HDACs are expressed in the nucleus, and specifically in pain-related regions including DRG, the spinal cord, and in supraspinal regions; class II HDACs can traffic between the nucleus and the cytoplasm.[6] Besides, HATs include three groups: p300/CREB binding protein HATs, Gcn5-related HATs, and MYST-related HATs.[7] Both HDACs and HATs are keystones in dynamically modulating acetylation, as well as subsequent gene transcription and pain regulation.[8]

Acetylation: A fundamental factor in epigenetic mechanism for neuropathic pain

Numerous preclinical and clinical studies have indicated the participation of HDACs and HATs in distinctive neuropathic pain conditions (see Table 1 for a summary). Understanding the molecules and mechanism of neuropathy related acetylation regulation is of great medical significance. The following discussion is a brief overview of these subjects.

Molecules affected by acetylation in neuropathic pain

Various receptors, transporters, and enzymes involved in glutamatergic and γ-aminobutyric acid (GABA)ergic synaptic transmission are affected by acetylation in neuropathic pain. For example, in Zhou et al.'s study,[15] increased histone H3 acetylation in *mGrm1/5* (encoding mGluR1/5) promoter regions upregulated mGluR1/5 expression in rats with diabetic neuropathy. Indeed, experts have observed decreased glutamate aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1) expression in the spinal dorsal horn after spinal nerve ligation (SNL), which HDAC inhibitor (HDACI) valproate could restore, followed with pain behaviors improvement.[16] Besides, as glutamic acid decarboxylase 65 (GAD65) encoding gene, *Gad2* gene expression significantly decreased in neuropathic pain rats in nucleus raphe magnus (NRM) via HDAC-mediated histones H3 and H4 hypo-acetylation; this contributed significantly to impaired GABAergic inhibition and central sensitization.[17]

Furthermore, studies have reported the acetylation expression at the promoters of certain pain associated genes, like $Na_v1.8$, Kv4.3, μ-opioid receptor (MOR), and brain-derived neurotrophic factor (BDNF) to change following nerve injury. Nerve injury induces histone H3 and H4 deacetylation at $Na_v1.8$, Kv4.3, and MOR promoter regions to silence their expression.[18,19] Nerve injury upregulates histone H3 and H4 acetylation at BDNF promoter region in DRG, as well as histone H4 acetylation at the Cdk5 promoter region in the spinal cord, and works to increase BDNF and Cdk5 expression, respectively.[20,21] In nerve injury–induced demyelination, myelin-associated molecules such as Sox10, myelin protein zero, and maltose binding protein expression, downregulate partly through Rho kinase, p300 activation, and NF-κB acetylation.[22]

Furthermore, acetylation regulation affected the expression of some molecules in the

Table 1. Expression of histone acetylation under various neuropathic pain conditions.

Pain models	Enzymes	Histones acetylation	Observational time points	Detected cell/tissue	References
PSL	HDAC1↑	H3K9 Ac↓	NA	Microglia in the superficial dorsal horn	9
SNI	HDAC2↑	NA	7 days post nerve injury	Superficial dorsal horn astrocytes but not neurons	10
SCI	HDAC3↑	NA	NA	PBMCs	11
SNL	HDAC4↑	NA	3, 7, 14, and 21 days after surgery	Spinal dorsal horn neurons but not astrocytes or microglia	12
CCI	Sirt1↓	H4K16 Ac ↑	1, 3, 7, 14, and 21 days after surgery	The spinal cord	13
PIPN	Sirt1↓	H4K16 Ac ↑	NA	The spinal cord	14
DNP	Sirt1↓	H3 Ac↓	14 and 21 days after STZ injection	Spinal dorsal horn neurons but not astrocytes or microglia	15

PSL: partial sciatic nerve ligation; SNI: spared nerve injury; SCI: spinal cord injury; SNL: spinal nerve ligation; CCI: chronic constriction injury; PIPN: paclitaxel-induced neuropathic pain; DNP: diabetic neuropathic pain; PBMCs: peripheral blood mononuclear cells; STZ: streptozotocin; ↑: upregulation; ↓: downregulation; NA, not available.

chemokines–chemokine (CC) receptor system. For example, partial sciatic nerve ligation (PSL) upregulated C–X–C ligand type 2 (also called macrophage inflammatory protein 2 (MIP-2)), and C–X–C receptor type 2 (CXCR2) expression via increasing histone H3 acetylation (H3K9Ac) in the MIP-2 and CXCR2 promoter regions.[23] CCL2, CCL3, and C–X–C receptor type 2 (CXCR2) expression increase after PSL due to enhanced acetylation in the promoters of their encoding genes.[24] Consistently, in pacilitaxel- or vincristine-induced neuropathic pain, CXCL12 protein and messenger RNA expression increased by increasing the binding of signal transducer and activator of transcription 3 (STAT3) to CXCL12 promoter and upregulating H4 acetylation in its promoter; underlying antitubulin chemotherapeutics-induced persistent pain.[25] Pacilitaxel also increased H4 acetylation in the Cx3cl1 promoter region in an NF-κB dependent manner, thereby contributing to paclitaxel-induced mechanical allodynia.[26]

Mechanisms of neuropathy-related acetylation

Protein kinase activation. Certain protein kinases activation is highly associated with neuropathy-related acetylation, and typically underlays neuropathic pain pathogenesis. SGK1 is one subfamily of genes responsible for encoding serine/threonine protein kinase; it was activated following SNL, leading to HDAC4 phosphorylation, enhanced coupling with 14–3-3β, and increased cytoplasm retention within the spinal dorsal horn neurons. Either SGK1 inhibition with GSK650394 or HDAC4 blockade by LMK235 prevented allodynia, while HDAC4 blockade has no effect on SGK1 phosphorylation or 14–3-3β expression. These results indicate HDAC4 may act as a downstream regulator of SGK1. Formation and cytoplasmic retention of 14–3-3β–HDAC4 complex is therefore one critical mechanism for neuropathic pain development.[12]

Besides, spared nerve injury (SNI) consistently increases HDAC1 protein and acetylation levels, forming a heterodimeric complex with c-Jun in astrocytes expressing c-Jun *N*-terminal kinase (JNK) in the spinal dorsal horn, accompanying nociceptive phenotype without expression changes of HDAC3, H3Ac, DNMT3a, and MeCP2. HDAC1 inhibitor LG325 prominently ameliorates pain behaviors by suppressing the JNK–c-Jun signaling pathway.[27] Furthermore, brachial plexus avulsion induces neuropathy pain possibly via increasing protein kinase B (Akt) phosphorylation and its targeted mammalian target of rapamycin (mTOR) expression. HDACI trichostatin A (TSA) significantly improves mechanical hyperalgesia via suppressing Akt phosphorylation, inhibiting TPRV1, TRPM8 overexpression, and alleviating neuroinflammation.[28]

Abnormal glutamatergic and GABAergic synaptic transmission. Neuropathy-related acetylation disturbs glutamatergic and GABAergic synaptic transmission. For example, metabotropic glutamate receptors type 2 (mGluR2), expressed at primary afferent synapses in the spinal dorsal horn, suppress synaptic transmission. Chiechio et al.[29] supposed that HDACs inhibitors upregulate the expression of mGluR2 receptor to attenuate pain via NF-κB pathway activation secondary to increased NF-κB p65 subunit acetylation. In diabetic neuropathic pain rats, studies have observed H3 acetylation, increased in *mGrm1/5* (mGluR1/5 encoding gene) promoter regions and upregulated mGluR1/5 expression, which play an essential role in central sensitization. Sirt1 activator SRT1720 and Sirt1 shRNA could reverse or induce spinal neuronal activation and pain phenotype, respectively.[15] Other than glutamatergic receptors, a downregulation or knockdown of GLAST and GLT-1 in the spinal dorsal horn potentiates the spontaneous

nociceptive phenotype and contributes to the neuropathic pain development.[30]

Besides, impaired GABAergic synaptic inhibition results from *Gad2* gene expression inhibition via HDAC-mediated histones H3 and H4 hypo-acetylation in NRM. This is highly related to sustained pain sensitization in rats. HDACIs significantly increase GAD65 activity, recover GABAergic synaptic inhibition, and relieve pain hypersensitivity.[17] Collectively, abnormal mGluR2, GLAST, GLT-1, GAD65 expression, and HDACs regulation may serve as mechanisms for neuropathic pain development.

Transcription factor–mediated epigenetic mechanism. Neuron-restrictive silencer factor (NRSF), a transcriptional inhibitory factor, is responsible for transcriptional inhibiting of NRSF containing genes, including $Na_v1.8$, $K_V4.3$, and MOR by means of recruiting HDACs via its corepressors—mSin3 and CoREST.[31] Following nerve injury, extensive deacetylation of histone H3 and H4 combined with the $Na_v1.8$ gene around an NRSF binding site (the neuron-restrictive silencing elements (NRSE) region), leading to $Na_v1.8$ transcriptional inhibition. An HDACs blockade leads to restoration of such downregulated $Na_v1.8$ gene expression and recovered C-fibers sensitivity.[18] Similarly, histone H4, but not H3 acetylation, at Kv4.3-NRSE prominently downregulates post nerve injury, restorable via NRSF knockdown.[19] HDACs inhibitor blocks nerve injury–induced MOR downregulation and recovers the morphine antinociceptive action through an HDAC-mediated mechanism.[32] Collectively, studies indicate that nerve injury induces an epigenetic silencing of pain-related genes, including $Na_v1.8$, Kv4.3, and MOR via transcriptional suppressing NRSF in the DRG.

Cytokines and chemokines–chemokine receptors system upregulation. Upregulation of the inflammatory molecules, including cytokines, chemokines, and chemokine receptors is an important mechanism in neuropathic pain development. Cytokines such as TNF-a, which are primarily released by macrophages or other immune cells, are significant in central sensitization and neuropathic pain. Orally administrated HDACI sodium butyrate weakens CCI-induced increases in TNF-α level, and such anti-inflammatory action underlies its anti-nociceptive effect.[33] Similarly, paclitaxel dose dependently induced painful neuropathy is concomitant with NF-κB p65 subunit activation and spinal cord cytokines (TNF-α, IL-1β, IL-6) upregulation. Icariin, a Sirt1 activator, dosage-dependently reverses paclitaxel-induced spinal neuroinflammation, Sirt1 downregulation, and histone H4 acetylation, subsequently also improving pain behaviors.[14] Other than cytokines, chemokines, and chemokine receptors such as MIP-2, CXCR2, CCL2, CCL3, and CXCL12 also play an essential role in augmenting neuropathic pain. PSL upregulated MIP-2 and CXCR2 expression are mainly localized on neutrophils and macrophages, and accumulate in the injury sciatic nerve by increasing histone H3 acetylation (H3K9Ac) in the MIP-2 and CXCR2 promoter region. Administration of HAT inhibitor suppresses such upregulation of MIP, CXCR2, at the same time ameliorating PSL-induced neuropathic pain.[23] PSL similarly increased CCL2, CCL3, and their relevant receptors CCR2, CCR1/5 expression in the injured sciatic nerve possibly via increasing H3K9Ac and H3K9me3 in the CCL2 and CCL3 genes promoter regions; this increase can be blocked by the HDACI (anacardic acid).[24] CXCL12 expression consistently increases microtubule-targeted chemotherapeutics, inducing neuropathic pain. Paclitaxel and vincristine could increase the combination of STAT3 to CXCL12 gene promoter and contribute to CXCL12 transcription enhancement by upregulating the histone H4 acetylation in its gene promoter.[25] Collectively, studies suggest that nerve injury may induce histone hypo-acetylation or acetylation, followed with neuroinflammation via upregulating the level of cytokines and the CC receptors system, which is another alternative neuropathic pain mechanism.

Acetylation: A promising target for treating neuropathic pain

Acetylation upregulation

Uchida et al. are the first to explore the role of histone hypoacetylation in the context of neuropathic pain. They have found that nerve injury induces broad histone hypo-acetylation at NRSE sequences within MOR and $Na_v1.8$ genes. Moreover, in their investigation, NRSF knockdown remarkably blocked nerve injury–induced transcriptional inhibition of MOR, $Na_v1.8$, TRPA1, and TRPM8 expression in the DRG, and it recovered C-fiber sensitivity and peripheral morphine analgesia.[18,19,32]

Several studies also suggest that HDAC regulation has an antinociceptive effect following neuropathic pain. Intrathecal injection of HDAC I inhibitor MS-275 improves hypersensitivity in traumatic nerve injury or antiretroviral drug–induced peripheral neuropathy, the effects of which may relate to H3K9Ac upregulation in the spinal cord.[34] Consistently, in animal studies, PSL and SNL have increased histone HDAC1 overexpression and histone H3 deacetylation in the spinal dorsal horn, while HDAC inhibition and followed restoration of histone acetylation have an antinociceptive effect.[9,35] In addition, studies have observed that enhanced histone H3 acetylation contributes to the protective effect of d-beta-hydroxybutyrate (DBHB), which is an

endogenous inhibitor of HDAC I and IIa, in SCI-induced motor impairment and pain hypersensitivity.[36]

Acetylation blockade

In contrast to histone hypoacetylation, histone acetylation also increases in response to nerve injury and corresponding histone acetylation blockade is effective. For example, intrathecal inhibition of STAT3 by Cre-encoding virus or inhibitor S3I-201 may ameliorate paclitaxel- or vincristine-induced mechanical allodynia through suppressing a CXCL12 upsurge in dorsal horn neurons by decreasing H4 acetylation.[25] Besides, after PSL, H3K9 acetylation upregulates in the injured sciatic nerve on the promoter regions of MIP, CXCR2, CCL2, and CCL3, HAT inhibitor anacardic acid blocked the increase of such molecules and exerted the antinociceptive effect.[23,24] In another study, curcumin dose dependently exerts a protective role in neuropathic pain via reducing p300/CBP recruitment and histone H3/H4 acetylation to the promoter of genes BDNF and Cox-2.[37] Furthermore, activation of Sirt1 blocks a neuropathy-induced increase of spinal histone H3/H4 acetylation.[14,15,38] Similarly, Sirt2 overexpression inhibits NF-κB p65 subunit acetylation both in vivo and in vitro, followed by the inhibition of NF-κB signaling pathway and neuroinflammation, thereby finally attenuating nerve injury–induced nociceptive behaviors.[39,40] Taken together, either upregulation or blockade of acetylation may serve as promising therapeutic targets in treating neuropathic pain.

Drug discovery focusing on neuropathy-related acetylation

HDAC regulation. As mentioned above, HDAC regulation has great potential for neuropathic pain therapy. Normally, HDACIs include both zinc-dependent HDACIs and NAD^+ dependent inhibitors (Sirt inhibitors), with the former further categorized into four subclasses based on distinctive chemical structures: hydroxamates, benzamides, short-chain fatty acids (SCFAs), and cyclic tetrapeptide.[41] Sirt inhibitors, on the other hand, differ greatly in their structures.[42] Clinical trials validate the safety and efficacy of many HDACIs, and some inhibitors have received approval from the US Food and Drug Administration (FDA) for cancer treatment.[43]

Most hydroxamates act as pan-HDACIs and present characteristics of a weak selectivity and a relative short half-life, but they have a long-lasting effect.[44] Two commonly used such inhibitors are suberoylanilide hydroxamic acid (SAHA) and TSA. In 2006, FDA has approved SAHA for treating patients with advanced primary cutaneous T-cell lymphoma[45]; SAHA may be the most widely used HDACI in pain research. In our previous study, SNI prominently increases spinal glutamate/GAD65 ratio, which is partially restored by subcutaneous (20 μg) or intrathecal injection (40 μg) of SAHA at day 14 post nerve injury.[46] In addition, SAHA intraperitoneal injection at a dose of 5 mg/kg once daily from day 3 to 9 post nerve injury significantly ameliorates PSL-induced pain hypersensitivity and C-fiber sensitivity via recovering the decreased Nav1.8, TRPV1, and TRPM8 expression, but not NRSF and CGRP expression.[47] And another hydroxamates HDACI, TSA increases the *Gad2* gene promoter acetylation, enhancing its transcription,[17] while promoting the trafficking of δ-opioid receptors to pain-modulating neuronal synapses, potentiating δ-opioid analgesia post CCI.[48] However, few use TSA for clinical pain research due to its relatively high toxicity, though it remains widely used as a template drug for novel HDACIs development.[41]

One of the most commonly used benzamides is *N*-(2-aminophenyl)-4-benzamide derivative (MS-275), which represents a promising drug of HDACIs due to high selectivity, strong specificity, and low toxicity; this makes it an exciting HDACI for pain research, and especially for research in neuropathic pain.[49] Denk et al.[34] found intrathecal injection of MS-275 at a dose of 30 nmol/d and 60 nmol/d through an osmotic pump prominently attenuated mechanical and thermal pain to an extent of 40% to 50% in PSL and stavudine-induced peripheral neuropathy; the effect may be associated with the global increase of H3K9Ac in the spinal cord. Selectively targeting HDAC1 is a promising path for neuropathic pain treatment.

SCFAs inhibit HDACs classes I and IIa with the largest efficacy, but the weakest potency, of which three commonly studied are valproate, butyrate, and phenylbutyrate. Valproate is widely used as an anticonvulsant in several kinds of epilepsy,[50] while neuropathic pain and epilepsy share similar pathological mechanisms such as membrane hyperexcitability. With these factors considered, a study evaluated the effect of valproate under neuropathic pain. Repeated oral administration of sodium valproate may restore the expression of GLAST and GLT-1 in the dorsal horn and enhance analgesia of the glutamate transporter activator riluzole, synergistically ameliorating nociceptive behaviors.[16,51] However, teratogenicity and hepatic cytotoxicity, two rare lethal side effects of valproate, limited clinical application.[52] Sodium butyrate similarly inhibits HDACs, including classes I and IIa, dose dependently (200–400 mg/kg, oral for 14 days) ameliorates mechanical and cold allodynia, as well as thermal hyperalgesia.[33] However, using butyrate in neuropathic pain treatment may be limited by its weak potency. DBHB acts as an endogenous inhibitor of HDACs classes I and IIa. It is structurally highly related to butyrate and is reported by

Table 2. Antinociceptive effects of HDAC and HAT inhibitors in various neuropathic pain models.

		Pain models						
HDACIs	Targets	SNI	PSL	SNL	ADIPN	CCI	PIPN	SCI
SAHA	HDAC I and II	s.c., i.t., ↓mechanical pain[46]	ip. ↓mechanical and thermal pain[47]	i.t., ↓mechanical and thermal pain[53]	NA	NA	NA	NA
TSA	HDAC I and II	NA	NA	NRM infusion ↓thermal pain[17]	NA	NRM infusion ↓mechanical pain[48]	NA	NA
MS-275	HDAC1	NA	i.t., ↓mechanical and thermal pain[34]	NA	i.t., ↓mechanical pain[34]	NA	NA	NA
Valproate	HDAC I and IIa	NA	NA	oral ↓mechanical and thermal pain[16,51]	NA	NA	NA	NA
Butyrate	HDAC I and IIa	NA	NA	NA	NA	Oral ↓cold allodynia, mechanical, and thermal pain[33]	NA	NA
DBHB	HDAC I and IIa	NA	NA	NA	NA	NA	NA	s.c., ↓mechanical and thermal pain[36]
Baicalin	HDAC I	NA	NA	i.t., ↓mechanical and thermal pain[35]	NA	NA	NA	NA
Sirt activators								
Resveratrol	Sirt1	NA	NA	NA	NA	i.t., ↓mechanical and thermal pain[13,38]	NA	NA
Icariin	Sirt1	NA	NA	NA	NA	NA	Oral ↓mechanical pain[14]	NA
HAT inhibitors								
Anacardic acid	HAT	NA	pn., ip., ↓tactile allodynia and thermal pain[23]	NA	NA	NA	NA	NA
Curcumin	HAT	NA	NA	NA	NA	ip., ↓mechanical pain and thermal pain[37]	NA	NA

HDACI: HDAC inhibitor; SAHA: suberoylanilide hydroxamic acid; TSA: trichostatin A; DBHB, d-beta-hydroxybutyrate; SNI: spared nerve injury; PSL: partial sciatic nerve ligation; SNL: spinal nerve ligation; ADIPN: antiretroviral drug–induced peripheral neuropathy; CCI: chronic constriction injury; PIPN: paclitaxel-induced neuropathic pain; SCI: spinal cord injury; NRM: nucleus raphe magnus; s.c.: subcutaneous; i.t.: intrathecal; ip: intraperitoneal; pn, perineural; ↓: down regulation; NA: not available.

Qian et al.[36] to prevent SCI-induced motor impairment and pain hypersensitivity, partly by means of promoting histone H3 acetylation in the spinal cord and upregulating the transcription factor FOXO3a, catalase, and SOD2 expression in the injured region of SCI mice in one study. Of note, the short half-life and relative long treatment duration (continuous oral consumption for several months) of DBHB worked to question the feasibility of such a treatment paradigm in humans.

Until now, the effect of cyclic tetrapeptide has received no investigation in the neuropathic pain literature and needs further investigation. Other than artificial drugs, some medicinal herbs such as baicalin, an antiinflammatory flavonoid, has been shown to significantly decrease HDAC1 expression, upregulate the spinal histone H3 acetylation, and improve pain sensitivity.[35] These qualities render it a valuable analgesic adjuvant in clinical pain management.

On the other hand, some drugs, owing to the Sirt1 agonist property, have been used to alleviate neuropathic pain in animal studies. For example, intrathecal injection of resveratrol before CCI may produce an obvious improvement effect on nociceptive behaviors.[13,38] In addition, icariin intragastric administrated at 100 mg/kg rather than 50 mg/kg for 7 days can reverse paclitaxel-related Sirt1 downregulation and H4 acetylation, alleviating neuropathic mechanical allodynia.[14]

HAT inhibitors. Other than HDACIs, some have suggested that HAT inhibitors are effective at improving pain phenotypes in neuropathic pain. After PSL, administering HAT inhibitor anacardic acid inhibits the acetylation of histone H3 in MIP and CXCR2 promoter regions.[23] It also increases H3K9Ac and H3K9me3 in the *CCL2* and *CCL3* genes promoter regions to upregulate CCL2, CCL3, and their relevant receptors CCR2, CCR1/5 expression in the injured sciatic nerve.[24] Furthermore, curcumin, a medicinal herb with HAT inhibitory activity, prominently improves neuropathic pain behavior by inhibiting *bdnf* and *cox-2* gene expression at a dose of 40 mg/kg or 60 mg/kg over a duration of 7 days.[37]

Although these drugs are valid for alleviating neuropathic pain symptoms, there exist limitations. First, most currently available HDACIs act both centrally and peripherally, especially not a specific lysine site, which has raised worries about drug toxicity.[49] Second, many of these compounds need a long-term, large-dose treatment paradigm owing to a weak potency, inevitably decreasing patients' compliance and increasing side effects. When applying these compounds in neuropathic pain research, it is prudent to take these factors into account.

Conclusion

The role of histone acetylation and histone deacetylation in neuropathic pain has increasingly attracted attention in recent years. Studies have shown that various HDACIs, Sirt activators, and HATs inhibitors are effective in neuropathic pain treatment in animal models via targeting specific epigenetic sites (see Table 2). Although the exact mechanisms of histone acetylation change in the context of neuropathic pain remain murky, targeting unbalanced histone acetylation may provide an exciting and effective treatment alternative. It is conceivable that, with the advent of a more specific and potent inhibitor or activator, these compounds will play an essential role in pain therapy in the coming years.

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