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Histone acetylation and histone deacetylation in neuropathic pain: An unresolved puzzle?

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ABSTRACT

Chronic pain is broadly classified into somatic, visceral or neuropathic pain depending upon the location and extent of pain perception. Evidences from different animal studies suggest that inflammatory or neuropathic pain is associated with altered acetylation and deacetylation of histone proteins, which result in abnormal transcription of nociceptive processing genes. There have been a number of studies indicating that nerve injury up-regulates histone deacetylase enzymes, which leads to increased histone deacetylation and induce chronic pain. Treatment with histone deacetylase inhibitors relieves pain by normalizing nerve injury-induced down regulation of metabotropic glutamate receptors, glutamate transporters, glutamic acid decarboxylase 65, Neuron restrictive silencer factor and Serum and glucocorticoid inducible kinase 1. On the other hand, a few studies refer to increased expression of histone acetylase enzymes in response to nerve injury that promotes histone acetylation leading to pain induction. Treatment with histone acetyl transferase inhibitors have been reported to relieve chronic pain by blocking the up-regulation of chemokines and cyclooxygenase-2, the critical factors associated with histone acetylation-induced pain. The present review describes the dual role of histone acetylation/deacetylation in development or attenuation of neuropathic pain along with the underlying mechanisms.

1. Introduction

Histone deacetylase enzymes, along with acetylpolyamine, amindohydrolases and the acetoin utilization proteins form a super family of histone deacetylase proteins (Leipe et al., 1997). There are 18 different histone deacetylases known till date and based on functions and structures, these are grouped into four classes, I, II, III and IV (Ruijter et al., 2003; Gregoretti et al., 2004). Class I includes histone deacetylase 1, 2, 3 and 8; class II includes histone deacetylase 4, 5, 6, 7, 9 and 10; class III (also termed as sirutins) includes sirutins 1–7 and class IV includes histone deacetylase 11. Class II is further classified into class IIa (includes 4,5,7 and 9) and class IIb (includes 6 and 10) (Xu et al., 2007; Wang et al., 2016). Histone deacetylases have known to play a crucial role in myriad of biological processes in the living organisms, including transcription, chromatin remodelling, cell cycle, signal transduction, and control of gene expression (Yang et al., 2007). The regulation of gene expression occurs through histone acetylation and deacetylation of transcription factors. Histone tails are positively charged due to the presence of amine groups on lysine and arginine amino acids, and are responsible for interaction between the negatively charged phosphate groups on the backbone of DNA. Histone acetylation by histone acetylase transferases, counteracts the positive charge by converting amines to amides and decreases the electrostatic interaction of histones with DNA, which renders the chromosomes more accessible for transcription (Shahbazian et al., 2007). Histone deacetylases, on the other hand, removes the acetyl groups, thereby increasing the positive charge of histone tails and increasing the affinity for binding of DNA, leading to the formation of a compacted chromatin that restraints transcription. The opposite actions of two pivotal enzymes, histone acetyl transferases and histone deacetylases maintain the balance of the dynamic process of histone acetylation and deacetylation, which on disruption leads to many neurological disorders (Fig. 1).

It has been shown that histone deacetylase enzymes are phosphoproteins (Cai et al., 2001) and their activity is influenced by phosphorylation or non-phosphorylation. It is suggested that Ser421 and Ser423 are constitutively phosphorylated and disruption of these sites reduces the enzymatic activity (Pflum et al., 2001). Studies have shown that these enzymes are critically involved in gene regulation and recent studies indicate a key role of epigenetic regulation in induction of pain which may be acute or chronic (Abel et al., 2008; Buchheit et al., 2012; Wang et al., 2016). There have been a number of experimental studies

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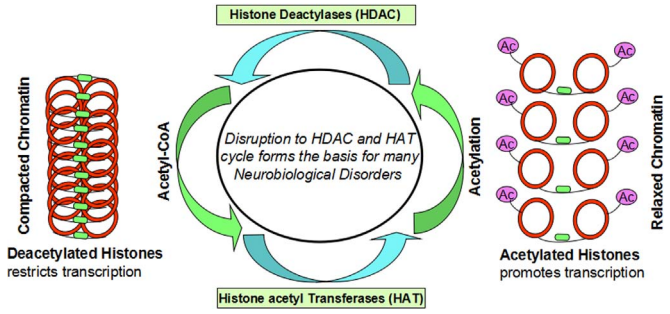

Fig. 1. Histone acetylation decreases the binding affinity of histones to DNA and relaxes the chromatin to promote transcription. Histone deacetylation increases the binding affinity of histones to DNA and compacts the chromatin to restrain transcription.

documenting that nerve injury up-regulates the levels of histone deacetylase and resulting decreased histone acetylation has been correlated with induction of pain. Accordingly, histone deacetylase inhibitors are documented to attenuate neuropathic and inflammatory pain by increasing histone acetylation (Uchida et al., 2015; Kukkar et al., 2014; Denk et al., 2013; Bai et al., 2010). On the contrary, there have been some studies suggesting that histone acetylation may promote pain and histone acetyl transferase inhibitors attenuate nerve injury-induced pain by decreasing histone acetylation (Kiguchi et al., 2012; Zhu et al., 2012). The present review describes the role of histone acetylation and deacetylation in neuropathic and inflammatory pain along with possible mechanisms.

2. Histone deacetylation promotes pain

There have been number of studies documenting that nerve injury or inflammatory conditions increase the expression of histone deacetylase enzymes and induce deacetylation of histone proteins, which may eventually result in pain induction. Accordingly, histone deacetylase inhibitors have been shown to attenuate pain in experimental models of neuropathic and inflammatory pain (Cherng et al., 2014; Zhang et al., 2011).

2.1. Evidences

Lin et al. (2015) reported an increase in expression of histone deacetylase 4 in spinal nerve ligation-induced nociceptive hypersensitivity model in rats. Moreover, there was an increase in 14-3-3β, a ubiquitous phosphor-binding protein (Gannon-Murakami and Murakami, 2002), accompanied by its coupling with histone deacetylase 4, leading to retention of deacetylase in the cytoplasm. The selective inhibition of phosphorylation of histone deacetylase 4, using LMK 235, effectively prevented nerve ligation-induced allodynia. Furthermore, knockdown of spinal 14-3-3β prevented coupling of histone deacetylase and 14-3-3β, and behavioural allodynia. However, it failed to prevent phosphorylation of deacetylase, therefore, the authors concluded that phosphorylation of histone deacetylase 4 is upstream to its coupling with 14-3-3β.

A recent experiment conducted in the spinal nerve ligation model of neuropathic pain in rats evaluated the ameliorative effect of baicalin, an anti-inflammatory flavonoid (Cherng et al., 2014). Baicalin has been shown to possess an anti-nociceptive effect in carrageenan-induced thermal hyperalgesia (Gao et al., 1999), hence, referring to its potential in treating neuropathic pain. Observations showed that nerve injury resulted in over-expression of histone deacetylase 1 and decrease in histone (H3) acetylation along with development of allodynia and hyperalgesia. Treatment with 10 μg of baicalin was found to significantly decrease deacetylase 1 expression, increase the spinal histone acetylation, reverse pain sensitivity and increase the anti-nociceptive effect of morphine (15 μg). Our own study, explored the beneficial role of histone deacetylase inhibitor in chronic constriction induced-induced neuropathic pain in rats. Sodium butyrate is a non-competitive inhibitor of histone deacetylase, which selectively inhibits class I and IIa (Khan et al., 2010) and its treatment (200 and 400 mg/kg) for 14 days ameliorated cold and mechanical allodynia, thermal hyperalgesia in a dose-dependent manner (Kukkar et al., 2014). Lu et al. (2010), demonstrated that treatment with histone deacetylase inhibitor, trichostatin A (0.5 mg/kg s.c.) for 4 weeks, suppresses the inflammatory immuno-reaction and manages the pain symptoms.

Zammataro et al. (2014), reported the role of curcumin in regulation of pain through histone acetylation. Curcumin is a naturally occurring compound that contains a p300/CREB-binding protein with histone acetyl transferase inhibitory activity (Balasubramanyam et al., 2004). In a mice model of formalin (10 μl) induced pain, systemic administration of curcumin led to down-regulation of metabotropic glutamate receptors type 2 ($mGlu_2$) in the spinal cord along with a marked hypo-acetylation of histones H3 and H4 in dorsal root ganglia. Furthermore, continuous treatment with curcumin (100 mg/kg i.p.) for 3 days suppressed the anti-nociceptive actions of glutamate agonist (LY379268 3 mg/kg s.c.). It suggests that decrease in histone acetylation may be an important mechanism in pain induction. However, pretreatment with histone deacetylase inhibitor, suberoylanilide hydroxamic acid, enhanced the analgesic activity of LY379268, again suggesting that histone acetylation may attenuate pain, while histone hypo-acetylation may potentiate pain. Hobo et al. (2011), demonstrated that administration of histone deacetylase inhibitor, valproic acid, for 3 weeks, produced anti-nociceptive effects, restored the expression of glutamate transporter-1 (*GLT-1*) and glutamate aspartate transporter (*GLAST*) in the spinal dorsal horn and enhanced the anti-nociceptive actions of riluzole in spinal nerve ligation model (Hobo et al., 2011). Previously, administration of histone deacetylase inhibitors, MS-275 and suberoylanilide hydroxamic acid is shown to reduce the nociceptive response in mice model of persistent inflammatory pain through increased expression of metabotropic glutamate receptor expression in dorsal root ganglia (Chiechio et al., 2009).

Uchida et al. (2010) demonstrated that the increase in gene expression of neuron-restrictive silencer factor in dorsal root ganglia is the major factor in dysfunction of C-fibers. It was associated with an increase in H4 acetylation at neuron-restrictive silencer factor promoter II region and marked hypo-acetylation of H3 and H4 histones at neuron restrictive silencer element sequences of μ-opioid and Na_v 1.8 genes, potential sites for neuron-restrictive silencer factor binding (Ballas et al., 2005). Furthermore, Matsushita et al. (2013), reported that treatment with histone deacetylase inhibitors restore injury-induced C-fiber sensitivity and reduce thermal and mechanical hypersensitivity, thereby, supporting the anti-nociceptive effects in response to histone acetylation (Matsushita et al., 2013). In a mice model of partial sciatic nerve ligation, histone deacetylase inhibitors restored the expression of pain controlling genes and morphine's analgesic effects (Uchida et al., 2015), suggesting that the latter may act as adjuvant to morphine in pain management. Intrathecal treatment with histone deacetylase inhibitors (MS-275 30 nmol/d and MGCD 0103 60 nmol/d), was shown to increase the histone acetylation (H3K9) in the spinal cord and reduce the mechanical and thermal hypersensitivity in partial sciatic nerve ligation and stavudine-induced neuropathy (Denk et al., 2013). Bai et al. (2010) demonstrated that histone deacetylase inhibitors specific to class II attenuate inflammatory pain in a more significant manner, as compared to class I deacetylase inhibitors. Furthermore, complete Freund's adjuvant led to selective up-regulation of histone deacetylase of class IIa (HDAC 4,5,7,9) in the spinal cord asserting that histone deacetylase inhibitors specific to class IIa may be sufficient in treating inflammatory pain.

A very recent study of Kami et al. demonstrated the increase in the number of histone deacetylase 1 positive microglia and astrocytes in the dorsal horn along with the decrease in the nuclear expression of acetylated histones (H3K9). Interestingly, the authors demonstrated