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Review

Is there any therapeutic value for the use of histone deacetylase inhibitors for chronic pain?

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ABSTRACT

Chronic pain is a complex clinical condition that reduces the quality of life for billions of people. In recent years, the role of epigenetic modulation in the control of long-term neuronal plasticity has attracted the attention of pain researchers. The epigenetic mechanisms include covalent modifications of DNA and/or histone proteins. Mounting evidence suggests that the activity of histone deacetylases (HDACs) and levels of histone acetylation are dynamic and that these enzymes modulate pain-related synaptic plasticity. Therefore, HDACs play essential roles in chronic pain development and maintenance. In this mini review, we will discuss the role of HDACs in the pathogenesis of chronic pain and will consider the therapeutic value of HDAC inhibitors in treating chronic pain.

Contents

Abbreviations: BDNF, brain derived neurotropic factor; CCI, chronic constriction injury; CFA, complete Freund's adjuvant; CNS, central nervous system; GAD, glutamic acid decarboxylase; GLT-1, glutamate transporter-1; HDACs, histone deacetylases; HDACI, histone deacetylase inhibitor; HATs, histone acetyltransferases; LPS, lipopolysaccharide; MORs, μ-opioid receptors; NRM, nucleus raphe magnus; NRSE, neuron-restrictive silencer element; PSL, partial sciatic nerve ligation; SAHA, suberoylanilide hydroxamic acid; SCFAs, short chain fatty acids; SNI, spared nerve injury; SNL, spinal nerve ligation; TSA, trichostatin A.

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1. Introduction

Chronic pain is a complex clinical condition that reduces the quality of life for billions of people (van Hecke et al., 2013). Treatment for chronic pain is far from satisfactory, in part due to the poor understanding of the underlying mechanisms of this condition (Kissin, 2010). It is well accepted that following various insults, nociceptors in the peripheral nervous system and neurons and glia in the central nervous system (CNS) become sensitized (Basbaum et al., 2009). This increased sensitivity is accompanied by functional and structural changes, namely, synaptic plasticity (Campbell and Meyer, 2006). Chronic pain-related plasticity is dependent on persistent cellular and molecular changes, which are caused by potentially self-perpetuating mechanisms involving alterations in the regulation of gene expression and subsequent protein synthesis (Descalzi et al., 2015). In recent years, the role of epigenetic mechanisms in regulating gene expression in long-term neuronal plasticity has attracted extensive attention in the field of pain research (Borrelli et al., 2008; Denk and McMahon, 2012; Buchheit et al., 2012).

2. Epigenetic modulation: an overview

Environmental insults, including tissue damage, inflammation, and infection, can induce and sustain pain via epigenetic mechanisms, which can occur independently of DNA sequence-level changes (Sweatt, 2013). Epigenetic changes covalently modify DNA, DNA-packaging histones, and noncoding RNAs (ncRNAs). The major type of DNA modification is the methylation of cytosine residues. DNA methylation typically occurs on carbon 5 of the pyrimidine ring of cytosine residues followed by guanine residues, which are sequences known as CpG sites. DNA methyltransferases (DNMTs, including DNMT1, DNMT3a, and DNMT3b) catalyze this reaction (Geranton and Tochiki, 2015). Methylated CpGs are thought to recruit several nuclear proteins known as methylated CpG–binding proteins (MBDs), but repel other transcription factors. The binding of these proteins may recruit inhibitory transcription factors and down-regulate or silence gene transcription (Borrelli et al., 2008). Recent studies have shown that targeting DNA methylation by antagonizing DNMTs could inhibit mechanical and thermal hypersensitivity in neuropathic and inflammatory pain models (Wang et al., 2011; Pan et al., 2014). However further data regarding the therapeutic potential of the modulation of DNA methylation is limited.

The primary types of epigenetic histone modifications include lysine acetylation, lysine and arginine methylation, and serine and threonine phosphorylation. In general, acetylation and phosphorylation promote active transcription, resulting in the greater availability of DNA to interact with transcriptional machinery (Geranton and Tochiki, 2015). Histone methylation, however, can have both activating and silencing effects on gene expression depending on the specific histone residue modified. For example, a recent study by Hui-Lin Pan's group showed that nerve injury increased histone 3 lysine 9 (H3K9) dimethylation in the promoters of genes encoding K^+ channels, but did not affect the levels of DNA methylation on these genes in DRGs (Laumet et al., 2015). Moreover, the activity of euchromatic histone-lysine N-methyltransferase-2 (G9a) contributes to epigenetic silencing of K^+ channels in the development of neuropathic pain (Laumet et al., 2015). These data support the essential role of histone methylation in chronic pain. However, relatively more is known about the roles of histone acetylation and deacetylation in the development and maintenance of chronic pain.

Acetylation and deacetylation of histone proteins are catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively (Berger, 2007). The interactions between HATs and HDACs determine the net balance of histone acetylation (Binder et al., 2013). Mounting evidence suggests that during pain-related synaptic plasticity, the expression and activities of HDACs are dynamic (Geranton and Tochiki, 2015; Cherng et al., 2014; Matsushita et al., 2013; Kiguchi et al., 2013; Denk et al., 2013). Therefore, in the present review, we focus on mechanisms of histone acetylation and the role of HDACs in chronic pain and discuss recent attempts to treat chronic pain with HDAC inhibitors (HDACIs).

3. Mechanisms of histone acetylation and deacetylation

The chromatin structure consists of repeating units of 147 base pairs of genomic DNA wrapped around a highly conserved histone octamer that is formed by two of each of the four histone proteins: H2A, H2B, H3, and H4 (Strahl and Allis, 2000). The N-terminal domains of histones within this octameric complex, known as histone tails, can either remain relatively mobile or adopt a variety of different structures. Histone tails extend from the nucleosomal disk, which facilitates their interaction with post-translational modifying enzymes. Several amino-acid residues, including serine (S), threonine (T), and tyrosine (Y), in histone tails can undergo phosphorylation, while lysine (K) and arginine (R) can be methylated and acetylated (Ruthenburg et al., 2007).

These histone modifications are known as "marks" and provide specific docking sites for many enzymes and proteins. Histone marks can be conferred by HATs, histone methyltransferases, and histone kinases and can be reversed by "eraser" proteins, such as HDACs and phosphatases (Strahl and Allis, 2000). Histone acetylation is thought to be more labile than histone methylation and therefore to represent a more transient cellular modification that quickly promotes gene expression in response to environmental stimuli (Berger, 2007). A tightly controlled equilibrium exists between HATs and HDACs, which plays an essential role in the dynamic control of acetylation and, consequently, transcription (Berger, 2007; Sweatt, 2013; Morrison et al., 2007).

With acetyl-coenzyme A as an acetyl group donor, HATs can acetylate the lysine residues on N-terminal histone tails. The addition of acetyl groups neutralizes the positive charge of the lysine residue and reduces the electrostatic interaction between this amino acid and the phosphate group on DNA. In turn, this weakened interaction induces chromatin relaxation, thus enhancing gene expression (Pazin and Kadonaga, 1997). In contrast, HDAC-mediated deacetylation causes the removal of lysine acetyl groups and results in chromatin condensation, thus repressing gene transcription (Annunziato and Hansen, 2000).

4. Classification of HATs and histone deacetylases (HDACs)

HATs are categorized into three families: Gcn5-related acetyltransferases (GNATs); MOZ, Ybf2/Sas3, Sas2 and Tip60 (MYST)-related HATs; and p300/CREB binding protein (CBP) HATs (Lee and Workman, 2007). HDACs are divided into 4 classes based on their function and structural homology to yeast HDACs (de Ruijter et al., 2003). Class I HDACs include HDAC1, 2, 3 and 8, which are related to the yeast enzyme, Rpd3. Class II HDACs includes HDAC4, 5, 6, 7, 9 and 10, which are related to the yeast protein, HDA1. Furthermore, based on structural differences, Class II HDACs can be further divided into two subclasses: IIa (HDAC4, 5, 7 and 9) and IIb (HDAC6 and 10) (Xu et al., 2007). Class III HDACs include SIRT1–SIRT7. HDACs in this class are referred to as "sirtuins" due to their homology to the yeast HDAC, Sir2 (Saunders and Verdin, 2007). HDAC11 is the most recently identified isoform and has been placed in an independent class (IV) due to its unique molecular structure. Class