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Review

Histone deacetylases in hearing loss: Current perspectives for therapy

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Abstract

Hearing loss is one of the most frequent health issues in industrialized countries. The pathogenesis and molecular mechanisms of hearing loss are still unclear. Histone deacetylases (HDACs) are emerging as key enzymes in many physiological processes, including chromatin remodeling, regulation of transcription, DNA repair, metabolism, genome stability and protein secretion. Recent studies indicated that HDACs are associated with the development and progression of hearing loss. Dysfunction of HDACs could promote the oxidative stress and aging in the inner ear. In light of considering the current stagnation in the development of therapeutic options, the need for new strategies in the treatment of hearing loss has never been so pressing. In this review, we will summarize the reported literatures for HDACs in hearing loss and discuss how HDAC family members show different performances for the possibility of process of diseases development. The possibility of pharmacological intervention on hearing loss opens a novel path in the treatment of hearing loss.
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Keywords: Histone deacetylase; HDAC inhibitor; Cochlea; Inner ear; Hearing loss

Contents

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1. Introduction

Hair cells of organ of Corti are susceptible to acoustic trauma, ototoxic drugs, infections or aging, thus resulting in permanent hearing loss (Brigande and Heller, 2009; Kurabi et al., 2016; Layman et al., 2015). Unlike non-mammalian vertebrates such as birds and fish, damaged hair cells of mammals are unable to regenerate thereby resulting in permanent hearing loss (Forge et al., 1993; Warchol et al., 1993). As a consequence, it is of great importance to develop strategies to prevent hair cell impairment or promote hair cell regeneration. A possible role of histone deacetylases (HDACs) has emerged. HDACs are emerging as key enzymes in many physiological processes, including chromatin remodeling, regulation of transcription, DNA repair, metabolism, protein secretion and stem cell regulation (Haigis and Sinclair, 2010; Mohseni et al., 2013).

Most studies of HDACs have been focused on aging-relative diseases and cancer (Haigis and Sinclair, 2010; Hubbard and Sinclair, 2014; Longo and Kennedy, 2006; Park et al., 2016; Lee et al., 2016). Many HDAC inhibitors have been reported to have neuro-protection or anti-aging activities. Improved understanding of the role of HDACs and molecular mechanisms underlying their function will be beneficial to further establish the utility of HDACs as hearing impairment targets. Thus, the development of small molecules targeting HADCs as anti-hearing loss therapeutics has been a focus of recent studies. This review will focus on the functions of HADCs in hearing loss and the potential of HADC inhibitors in the treatment of hearing loss.

2. Brief overview of histone deacetylases and histone deacetylases inhibitors

2.1. Histone deacetylase family members

HDACs play essential parts in many important functions for humans, leading to condensation of the chromatin structure and repression of gene expression (Shakespear et al., 2011; Mohseni et al., 2013; Yang and Seto, 2008). Eighteen distinct histone deacetylases are grouped into classes I–IV based on sequence homology to the original yeast enzymes and domain organization (Nakagawa and Guarente, 2011; Witt et al., 2009). Classes I, II and IV (HDAC1–11) are viewed as "classical" HDACs and they bear homology to each other as well as orthology to the same *Saccharomyces cerevisiae* proteins (Rpd3 and Hda1) which catalyze deacetylation in a Zn^{2+}-dependent manner (de Ruijter et al., 2003; Yang and Seto, 2008) (Fig. 1). Class I contains HDAC1, HDAC2, HDAC3 and HDAC8, while classes IIa and IIb contain HDAC4, HDAC5, HDAC7 and HDAC9, and HDAC6 and HDAC10, respectively. Class IV only comprises HDAC11 whose phylogenetics differ from classes I and II (Joshi et al., 2013; Voelter-Mahlknecht et al., 2005). While Class III, Sirtuins (Silencing information regulator 2, Sir2), contains seven members (SIRT1–SIRT7) that bears homology to the *Saccharomyces cerevisiae* protein (Nakagawa and Guarente, 2011). In contrast to the classical HDACs, Sirtuins are nicotinamide–adenine–dinucleotide (NAD^+) dependent deacetylases and ADP-ribosyltransferases (Feige and Auwerx, 2008; Frye, 1999).

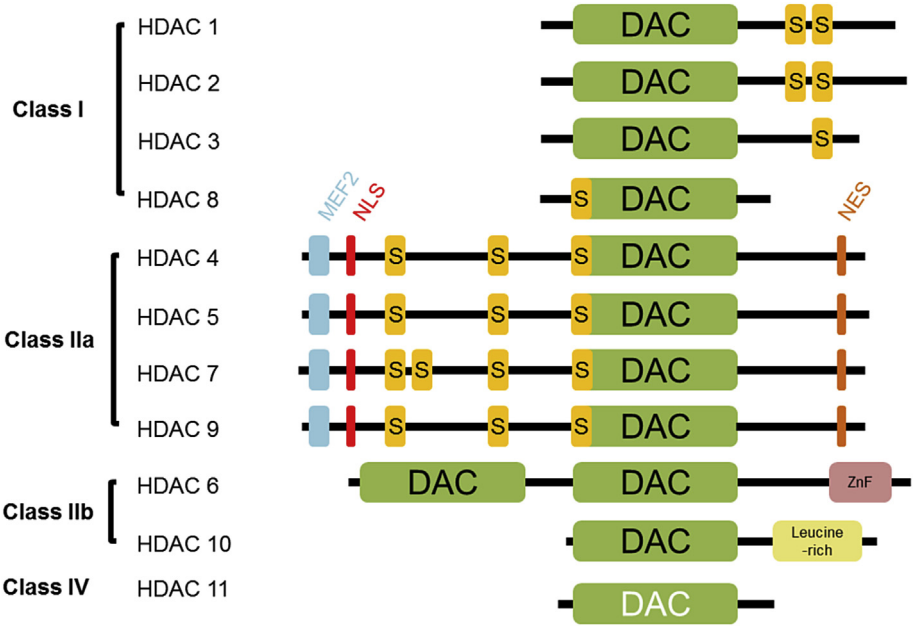

Fig. 1. Simplified depiction of the 11 human HDACs. DAC marks the conserved deacetylation domains, S are serine residues that can be phosphorylated. MEF2 denotes a binding domain for the transcription factor myocyte enhancer factor 2 and ZnF depicts a zinc finger motif. NLS and NES are nuclear localization and nuclear export sequences, respectively.
Adapted from Haberland et al. (2009) and Joshi et al. (2013).

HDACs are initially described as histone modifying enzymes, but they have been shown to interact with numerous non-histone proteins (e.g. high mobility group box protein) and be involved in critical cellular processes such as cell cycle regulation, oxidase activity, aging and cell death (He et al., 2013; Joshi et al., 2013; Lapierre et al., 2015; Prola et al., 2017; Wilting et al., 2010). The cellular localization of HDACs varies depending on the signals and the presence of certain localization domains in the HDAC protein (de Ruijter et al., 2003) (Table 1). Class I HDACs are predominantly located in the nucleus. HDAC1 and HDAC2 are both found in the neonatal organ of Corti including outer hair cells (OHCs), inner hair cell (IHC), dark cells (DCs), outer pillar cells (OPC), inner pillar cells (IPC) (Layman et al., 2013). Class II HDACs can shuttle between the nucleus and the cytoplasm due to a nuclear export sequence near their C-terminus (Joshi et al., 2013). HDAC6 presents almost exclusively in the cytoplasm since its primary function seems to be deacetylation of tubulin and binding of ubiquitinylated proteins in the cell's stress response (Hubbert et al., 2002; Kawaguchi et al., 2003). Shuttling of class IIa HDACs is mediated via phosphorylation of at least three serine residues and a variety of intracellular signals such as CamK activity in Ca^{2+} signaling or protein kinase D (PKD) activated in developmental pathways or VEGF signaling (Parra and Verdin, 2010; McKinsey, 2007). Phosphorylated class IIa HDACs are bound by 14-3-3 chaperone proteins and transported to the cytoplasm, which act as further levels of regulations of histone deacetylation and means to transport the HDACs into proximity of their cytoplasmic non-histone substrates and binding partners (Grozinger and Schreiber, 2000; Parra and Verdin, 2010). HDAC11 can be localized both in the nucleus and the cytoplasm and binds to the survival motor neuron complex (SMN) that is associated with U12-dependent spliceosome activity (Joshi et al., 2013; Meister et al., 2001).

SIRT1, SIRT6, and SIRT7 are found predominantly in the nucleus; SIRT2 is primarily cytoplasmic; SIRT3–5 are localized in mitochondria (Michan and Sinclair, 2007; North and Verdin, 2007). The intracellular localization of Sirtuins is dynamic, depending upon cell type, cellular stress, and molecular interactions (Hisahara et al., 2008; Rack et al., 2014; Scher et al., 2007). Sirtuins have been implicated in a variety of disease-related processes including inflammatory responses, cell survival, metabolic imbalance, and aging (Fu et al., 2016; Gerhart-Hines et al., 2007; Liu et al., 2015; Park et al., 2016; Rowlands et al., 2015; Xiong et al., 2015). Although the scope and detail of Sirtuins functions and molecular mechanisms are not yet fully elucidated, these enzymes are considered as potential availability for disease treatment.

Table 1
HDACs and related functions in the ear.

	HDAC family member	Intracellular localization	Functions
Class I	HDAC1	Nuclear	Cell survival; regulation of apoptosis; epigenetic regulation
	HDAC2	Nuclear	Cell survival; epigenetic regulation
	HDAC3	Cytoplasmic, nuclear	Cell survival; regulation of apoptosis
	HDAC8	Nuclear	Function not investigated
Class II a	HDAC4	Cytoplasmic, nuclear	Regulation of apoptosis
	HDAC5	Cytoplasmic, nuclear	Function not investigated
	HDAC7	Cytoplasmic, nuclear	Function not investigated
	HDAC9	Cytoplasmic, nuclear	Function not investigated
Class II b	HDAC6	Cytoplasmic	Epigenetic regulation
	HDAC10	Cytoplasmic	Function not investigated
Class III	SIRT1	Cytoplasmic, nuclear	Proliferation; activation of steroidogenesis; oxidative stress response; aging process; regulation of apoptosis
	SIRT2	Cytoplasmic, nuclear	Aging process
	SIRT3	Mitochondrial	Aging process
	SIRT4	Mitochondrial	Oxidative stress response; aging process
	SIRT5	Mitochondrial	Oxidative stress response; aging process
	SIRT6	Nuclear	Aging process
	SIRT7	Nuclear	Function not investigated
Class IV	HDAC11	Cytoplasmic	Function not investigated

2.2. Histone deacetylase inhibitors

Since HDACs are central players in epigenetic gene regulation and intracellular signaling, there have been strong efforts to develop small molecule HDAC inhibitors. The first HDAC inhibitor is trichostatin A (TSA), which inhibits HDAC1, HDAC2, HDAC3, HDAC6, HDAC10 and HDAC11 (Yoshida et al., 1990). Since then, many natural and synthetic compounds have been discovered. HDAC inhibitors can be subdivided into four groups: hydroxamic acids or hydroxamates, benzamides, cyclic peptides and aliphatic acids (Table 2) (Kim and Bae, 2011). All HDAC inhibitors have the ability to bind the conserved active site zinc ion of the classic HDACs (Maolanon et al., 2017). Since the conformation of the active site can vary substantially between different HDACs because of their ability to bind to many substrates, not all HDAC inhibitors are effective against all HDACs (Maolanon et al., 2017). To date, four compounds vorinostat (SAHA), belinostat, panobinostat, and romidepsin (FK228) are approved for clinical use by the Food and Drug Administration (Atadja, 2009; Holkova et al., 2017; Marks and Breslow, 2007; Olsen et al., 2007; Plumb et al., 2003).

Table 2
A selection of HDAC*i* of the four classes hydroxamates, bezamides, cyclic peptides and aliphatic acids (put together from Benedetti et al., 2014; Kim and Bae, 2011).

Hydroxamate	Benzamide	Cyclic peptide	Aliphatic acid
Trichostatin A	Mocetinostat	Apicidin	Valproic acid
Suberoylanilide hydroxamic acid (SAHA, Vorinostat)	Entinostat (MS-275)	Romidepsin	Sodium phenylbutyrate

SAHA is reported to effectively inhibit HDAC1, HDAC2 and HDAC3 of the class I HDACs and HDAC4, HDAC6, HDAC7 and HDAC9 of the class II HDACs at concentrations below 10 μM (Witt et al., 2009; Bantscheff et al., 2011). More class-specific HDAC inhibitors such as MS-275 (Entinostat) are also being investigated in clinical trials (Kummar et al., 2007). However, there are no long-term results therapies, yet, concerning advantages of class- or isoform-specific HDAC inhibitors (New et al., 2012). Since Sirtuins are dependent on nicotinamide adenosine dinucleotide (NAD^+) as cosubstrate, not Zn^{2+} ion, they are virtually unaffected by classical HDAC inhibitors (Imai et al., 2000; Landry et al., 2000). Most of sirtuin inhibitors available today target SIRT1 and SIRT2. For example, Carbinol, Sirtinol and Salermide can inhibit the activity of SIRT1 and SIRT2, with efficient anti-tumor activity and anti-inflammatory activity (Lugrin et al., 2013; Peck et al., 2010). EX-527 and CHIC-35 are selective small molecular inhibitors against SIRT1; AGK2 and AK-7 are selective inhibitors of SIRT2 (Peck et al., 2010; Wang et al., 2017; Westerberg et al., 2015). Currently, the promising HDAC inhibitors for potential therapeutic use have been developed to this effect in the preclinical and clinical test phase. Sirtinol has been investigated in human breast cancer MCF7 cells and lung cancer H1299 cells (Ota et al., 2006). EX-527 has been investigated in Phase II clinical trials for Huntington's disease (Westerberg et al., 2015).

Activators of Sirtuins also have been developed. Existing evidence shows that Sirtuin activators such as resveratrol, SRT1460, SRT1720 and SRT2183, which are mainly developed for SIRT1, can delay age-related diseases including diabetes, inflammation, cancer and others (Chini et al., 2016; Moussa et al., 2017; Pacholec et al., 2010; Xiong et al., 2015). However, the biochemical mechanism is still under debate.

3. Expression and function of HDACs in hearing loss

3.1. HDACs in sudden sensorineural hearing loss

Sudden sensorineural hearing loss (SSNHL) is defined as a syndrome that develops rapidly with hearing loss progressing within 72 h (Stew et al., 2012). In a recent study of SSNHL, HDAC2 protein expression was significantly reduced in refractory SSNHL patients compared to normal subjects (Hou et al., 2016). After intratympanic methylprednisolone perfusion (IMP) which is widely used to treat SSNHL, the levels of HDAC2 mRNA and protein were both upregulated in the IMP-sensitive SSNHL patients (Hou et al., 2016).

3.2. HDACs in noise induced hearing loss

Noise-induced hearing loss (NIHL) is characterized by hair cells loss in the auditory end organ caused by prolonged exposure to high levels of noise (Goodyear et al., 2012; Kurabi et al., 2016). The molecular mechanisms (such as reactive oxygen species and stress pathway signaling) that underlie noise induced hair cell damage remain unclear. In a first study of NIHL in CBA/J mice, HDAC1 and HDAC4 expressions increased after exposure to noise compared with control group, whereas histone H3 lysine 9 acetylation (H3K9ac) significantly decreased (Wen et al., 2015). This observation was confirmed in their recent study (Chen et al., 2016). In that study, HDAC1, HDAC2 and HDAC3 expressions were increased in the nuclei of cochlear cells of NIHL mice. siRNA mediated HDAC1, HDAC2, or HDAC3 knockdown reduced HDAC expressions in outer hair cells (OHCs), but did not attenuate the noise-induced permanent threshold shifts (PTS). This means that a change in the histone acetylation system could lead to a change in the pathogenesis of NIHL. Brown et al. (2014) found genetic stabilization of NAD^+ levels in cochlear protected mice from NIHL and the mice were resistant to transient and permanent hearing loss. And this effect is also observed in the SIRT3-overexpressing mice. SIRT3 is known as a NAD^+ dependent mitochondrial deacetylase. In SIRT3-overexpressing mice, there is no significant threshold shift on day 14. However, NAD^+ overexpressing mice with SIRT3 gene knockout are sensitive to noise exposure, revealing SIRT3 contribute to the protective effects of NAD^+ against NIHL (Brown et al., 2014).

Abbreviations used

ARHL	Age-related hearing loss
DC	Dark cell
HDAC	Histone deacetylases
H3K9ac	Histone H3 lysine 9 acetylation
IHC	Inner hair cell
IMP	Intratympanic methylprednisolone perfusion
IPC	Inner pillar cell
MEF2	Myocyte enhancer factor 2
NAD^+	Nicotinamide adenosine dinucleotide
Nf-κB	Nuclear factor-κB
NIHL	Noise-induced hearing loss
OHC	Outer hair cell
OPC	Outer pillar cell
PKD	Protein kinase D
PTS	Permanent threshold shifts
ROS	Reactive oxygen species
Sir2	Silencing information regulator 2
SSNHL	Sudden sensorineural hearing loss
SMN	Survival motor neuron complex

3.3. HDACs in ototoxic drug induced hearing loss

Ototoxic deafness is severe and permanent hearing loss and/or vestibular dysfunction caused by ototoxic drugs, such as aminoglycoside antibiotics, loop diuretics, antimalarials and platinum chemotherapy (Layman et al., 2015; Landier, 2016; Lin et al., 2015). Accumulating evidence have suggested that the aminoglycoside antibiotics-induced ototoxicity is associated with the generation of reactive oxygen species (ROS) and nuclear factor-κB (Nf-κB) misregulation in outer hair cells (Jiang et al., 2016; Kamogashira et al., 2015; Layman et al., 2015). Ototoxic functional impairment and cellular degeneration are involved in activated non-classic apoptotic and necrotic pathways (Fernández-Cervilla et al.,

2017; Jiang et al., 2006). There is growing interest and data in HDACs on their pathogenic roles in various otoxocity and hair cells regeneration. Chen et al. (2009) found that gentamicin upregulated the protein levels of HDAC1, HDAC3 and HDAC4 in organotypic cultures of the mouse corti *in vitro*, resulting in hair cell death. In another study of guinea pigs with gentamicin treatment, there is significant increased HDAC1 expression in outer hair cells and reduced hair cell number (Wang et al., 2015). Kanamycin ototoxicity increases deacetylated RelA/p65 K310 expression which is mediated by HDAC3 directly or by HDAC1 and HDAC2 indirectly, mis-regulating the Nf-κB pathway (Chen et al., 2001, 2002; Layman et al., 2015). Besides, SIRT3 was found to associate with otoprotective effects via inhibiting gentamicin-induced ROS production and apoptosis in hair cells (Quan et al., 2015).

3.4. HDAC in age-related hearing loss

Age-related hearing loss (ARHL), one of the most prevalent chronic degenerative conditions, is characterized by a decline in auditory function in the elderly (Halonen et al., 2016). The pathology linked to ARHL includes the hair cells loss, stria vascularis atrophy, and spiral ganglion neurons loss. It has been reported that mitochondrial dysfunction and oxidative stress play a major role in molecular mechanism of ARHL (Tan et al., 2017). To date, HDACs may also play an important role in the development of ARHL (Xiong et al., 2014, 2015; Takumida et al., 2016). SIRT1, SIRT3, and SIRT5 mRNA and protein are found in the inner ear including hair cells, strial marginal cells, strial intermediate cells, type I and type IV fibrocytes of the spiral ligament and spiral ganglion neurons (Xiong et al., 2014; Takumida et al., 2016). However, the levels of SIRT1, SIRT3, and SIRT5 mRNA and protein were decreased in the degeneration of the organ of Corti and spiral ganglion cell in the elderly mice with elevated hearing thresholds and hair cells loss (Xiong et al., 2014; Takumida et al., 2016). In addition, elevated expression of SIRT1, SIRT4, or SIRT5 may protect vestibular tissue against accumulation of ROS and aging potential. Moreover, it is found that miR-34a/ SIRT1/p53 signaling is correlated with ARHL (Xiong et al., 2015). In the elderly C57BL/6 mice, the levels of Sirt1 decreased in the cochlea (Xiong et al., 2014, 2015). However, p53 acetylation and apoptosis diminished following SIRT1 upregulation after miR-34a knockdown suggests a potential target for ARHL treatment. (Xiong et al., 2015).

4. Histone deacetylase inhibitors as therapy options for hearing loss

Histone deacetylase (HDAC) inhibitors are not only used as anticancer agents, but also used as anti-inflammatory, anti-oxidative stress or neuroprotection agents (Foti et al., 2013; Fischer et al., 2007; Grabarska et al., 2017; Kim et al., 2009; Ungerstedt et al., 2005; Ryu et al., 2003; Sinn et al., 2007). HDAC inhibitors can block the activity of HDACs, increase histone acetylation and then transcriptionally regulate target genes like Fas-L, NF-κB, iNOS, TNF-α, COX-2, and MMP-9, thereby diminishing counteraction of the previously described inflammation and ototoxic cell death.

HDAC inhibitor SAHA is reported to improve the memory and cognition in patients with Alzheimer's disease (AD) through increasing the neuroprotective factors and inhibiting neurotoxic proteins (Cenik et al., 2011). HDAC inhibitor phenylbutyrate could ameliorate the progressive neuro-degeneration involved in spinal muscular atrophy (SMA) (Andreassi et al., 2004; Brahe et al., 2005). Moreover, an orally active HDAC inhibitor givinostat/ITF2357 has been demonstrated to reduce the pain, arthritic component and the neutrophilia in patients with rheumatoid arthritis or systemic juvenile idiopathic arthritis (Mauro et al., 2017; Vojinovia and Damjanov, 2011). HDAC inhibitors trichostatin-A and SAHA both show protective effect on gentamicin-induced hair cell loss. Most of the outer hair cells remained the normal morphology and inner hair cell loss attenuated after 200 nM TSA treatment (Chen et al., 2009). SAHA is proved to be able to cross the mouse blood-labyrinth barrier, induce changes in histone acetylation levels, and does not negatively impact hearing function. Pre-treatment with SAHA markedly reduced noise-induced OHC loss and threshold shifts in NIHL mice (Wen et al., 2015; Chen et al., 2016). Similarly, SAHA could protect guinea pigs against cisplatin ototoxicity (Drottar et al., 2006). Another HDAC inhibitor sodium butyrate also showed oto-protective effect (Wang et al., 2015). In guinea pigs with gentamicin exposure, sodium butyrate significantly inhibited gentamicin-induced HDAC1 in expression in outer hair cells. Furthermore, sodium butyrate reduced hair cell loss and auditory brainstem response threshold shifts (Wang et al., 2015). Additionally, resveratrol, an activator of SIRT1, significantly reduced hearing threshold shifts and hair cell loss induced by miR-34a overexpression in C57BL/6 mice after a 2-month administration (Xiong et al., 2015).

Although the exact mechanisms of HDAC inhibitors' oto-protection and neuro-protection remained elusive, the good correlation with *in vivo* treatment clinical outcomes in hearing loss strongly supported its effect in treatment of hearing loss. These studies suggest that a modulated intervention in the balancing act between histone acetylation and histone deacetylation in hearing loss could represent a future treatment option.

5. Summary and future

Recent studies have demonstrated HDACs are undoubtedly key enzymes and play an important role in many pathological setting from hearing loss including sudden sensorineural hearing loss, noise induced hearing loss, ototoxic drug induced hearing loss and age related hearing loss. HDAC functions are implicated in hair cells death characterized by ROS production and apoptosis. Based on recent findings, it seems clear that histone or nonhistone targets will play key roles. Treatment with HDAC inhibitors inhibit hair cell loss and spiral ganglion neurons loss and improve permanent threshold shifts in vivo and in vitro models. These suggest that HDAC activity is involved in the development and progression of hearing loss.

Despite this key role, there are many questions about specific molecular mechanisms of HDACs and development of small molecule inhibitors remain to be addressed. The further generation of animal models lacking individual HDAC genes will reveal unexpected functions of individual HDAC and give rise to the identification of such inhibitors in s in different types of hearing loss. Thus, in the future, the discovery that these HDAC inhibitors protect hair cells and spiral ganglion neurons in the face of stress or cytotoxicity condition may ultimately impact the treatment of hearing loss.

Conflict of interest

No conflict of interest declared.

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