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The Role of Histone Deacetylase Inhibitors in Myocardial Infarction

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Abstract

Myocardial infarction is usually recognized as the final stage of coronary artery stenosis or occlusion in response to coronary atherosclerosis and thrombosis involving dysfunction and activation of resident vascular cells as well as the release of t-PA. As a member of family proteins for deacetylation of core histones in eukaryotic cells, Histone deacetylases are implicated in various biological processes. Accumulating evidence suggest that Histone deacetylases inhibitors regulate the release of t-PA and pro-inflammatory cytokine which can decrease myocardial infract size and preserve cardiac function ultimately. Here, we review the effect of Histone deacetylases inhibitors on the progress of myocardial infarction.

Keywords

Myocardial infarction, Histone deacetylases inhibitors, t-PA, Pro-inflammatory cytokine

Introduction

It is well known that Histone deacetylase (HDAC) and Histone acetyltransferases (HATs) are two opposing family proteins for acetylation of core histones in eukaryotic cells, Histone deacetylases inhibitors (HDACIs) can inhibit the process of histone deacetylation effectively. Based on homologous degree of yeast cells' transcription factors, HDAC can be classified into four groups: (1) Class I HDACs consist of HDAC 1, 2, 3, and 8; (2) Class II HDACs include HDAC 4, 5, 7, and 9; (3) Class III HDACs : SIRT1-7; (4) Class IV: HDAC 11. Zn^{2+} is a necessary cofactor for class I, II, IV and coenzyme is needed for class III [1]. HDACIs can hinder histone acetylation process by regulating the tightness of intertwined DNA and histones, make DNA tightly bind to histones [2]. Recently, studies have detected that HDACIs were implicated in stimulating t-PA production [3] and inhibiting pro-inflammatory cytokine generation [4]. What's more, it has been proved lately that HDACIs can inhibit lung cancer and breast cancer [5]. Here, we briefly review the effect of HDACIs on the process of MI (myocardial infarction).

Biology of HDACIs

HDACIs are generally defined as an organic compound that inhibits histone acetylation. Recent researches have showed that broad spectrum HDACIs are well-known anti-inflammatory agents which have the ability to reduce vascular inflammation [6]. On the basis of their chemical constitution, HDACIs can be divided into several categories [7]: Short chain fatty acids (butyrate, butyl benzoic acid ester and valproic acid), Hydroxamic acid (TSA and SAHA), Amino phenyl amide (FK-228) and peptide (MS-275, MGCD0103). The four kinds of HDACIs can regulate histone acetylation degree by inhibiting HDACs bind to histone. As HDACs have essential roles in both the development [8] and activation [9] of many immune cell types, including macrophage, HDACIs can inhibit the activation of macrophages effectively. HDACIs were formerly suggested to be an active target for cancer therapy, many HDACs mutations are associated with different human cancers. However, it is now obvious that many HDACIs are implicated in various biological processes, including myocardial infarction. Coronary atherosclerosis is the most common pathological process that leads to myocardial infarction. It is marked by the recruitment of macrophages and other leukocytes such as memory T cells, as well as non-leukocytes, including vascular smooth muscle cells (VSMCs) and it is now considered a chronic inflammatory disease [10]. For example, HDACI can suppress the release of IL-10 and enhance the expression of anti-inflammatory cytokines [11]. T-PA (tissue plasminogen activator) release has been found to be detective in certain conditions associated with coronary atherosclerosis [12], and it is a fact that t-PA expression can be powerfully up-graduated by HDACIs [13]. MKK3 and Akt-1 pathways both play an essential role in HDACIs–induced cardio protection for the first time and it has been proved that HDACI can improve the ventricular function and alleviate the reduction of myocardial infarct [14]. In addition, previous study demonstrated that PPARr signaling pathway is regulated by HDACIs in heart [15]. Moreover, HDACIs induce sdipogenesis and adipocyte differentiation through PPARr signaling pathway [16]. These studies suggested that HDACIs can regulate cardiac metabolism.

HDACIs and Myocardial Infraction

The progression of myocardial infarction is characterized by several steps: coronary artery occlusion, blood flow interrupted. The pathogenesis of myocardial infarction is very complex, and it is often caused by intravascular thrombus formation. The clinical outcomes can be alleviated if the thrombus is rapidly removed by the endogenous fibrinolytic system. Conversely, it will prolong the ischemic time and cause irreversible tissue damage if the thrombus persist, the extent of myocardial damage correlates directly with the extent of LV (left ventricular) remodeling [17]. There are several signaling pathways contributing to attenuating myocardial infarction by HDACIs (As it is showed in the figure 1). This multifactorial process is attributed to several important aspects, including decreased infarct size, improved

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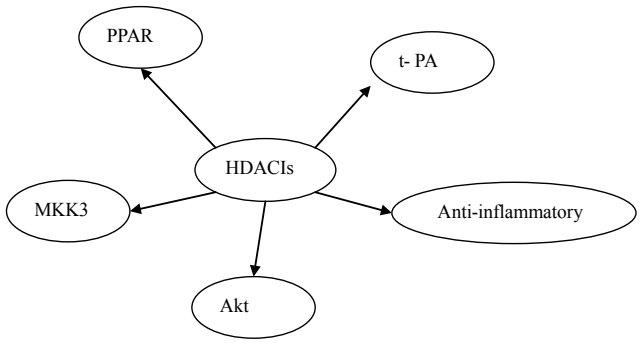

Figure 1: HDACIs can attenuate myocardial infarction through different signaling pathways. HDACIs can activate the release of t-PA, exert anti-inflammatory property, and activate Akt, MKK3, and PPAR signaling pathways.

ventricular function, prevented cardiac remodeling, improved regenerated myocardium cells and angiogenesis. A growing quantity of studies have identified that HDACIs can ameliorate myocardial infarction through different pathways, suggesting the possibility of HDACIs in influencing the progression of myocardial infarction. It has been demonstrated that inhibition of Class II HDACs can silence fatal gene activation, block cardiac hypertrophy and prevent cardiac remodeling [18]. Marten A Hoeksema, et al. found that macrophage HDAC3 deletion is beneficial in atherosclerotic mice [19]. What's more, HDACIs constitute a major cascade in controlling cardio genesis and promoting the survival of ESCs (embryonic stem cells).

Roles of HDACIs in activating the release of t-PA

Myocardial infarction is caused by intravascular clot formation, when a clotting process is initiated, the surrounding endothelium is activated and release large amounts of t-PA which can lead the clot to dissolve. t-PA enhancer- 7351C/T which is a low-secretor phenotype was found to be associated with a more than 3-fold adjusted increased risk for myocardial infarction [20]. It has been reported that t-PA release can be powerfully up-regulated by the classical HDACIs, such as butyrate and Trichostatin A (TSA), as well as to the newer HDACI MS-275 [21,22]. It suggests that t-PA gene could be sensitive to the level of histone acetylation status. t-PA is quickly released in the vicinity of the clot [23], what's more, anti-platelet drugs, novel devices (e.g. drug eluting stents), an abiding focus on time to reperfusion have also been proven critical for decreasing infract size and improving cardiac function, and HDACI has promise for fibrinolytic therapy [24].

Roles of HDACIs in exerting anti-inflammatory effect

Recent research shows that broad spectrum HDAC inhibitors are well-known anti-inflammatory agents and can reduce vascular inflammation [25]. Kazuhiro Ito, et al. have demonstrated that theophylline-a kind of HDACIs can decrease inflammatory gene expression [26], while the molecular mechanism for the anti-inflammatory action of theophylline is currently unclear. It has been proved that low concentrations of theophylline are able to inhibit the activation of NF-kB and reduce the expression of inflammatory genes. HDACIs impair the recruitment of nuclear factor NF-kB and IFN regulatory factor-1 which is a counteractive effect of HDAC-dependent IL-12p40 gene in vascular endothelial cell [27]. On the other hand, HDACIs can trigger hyper acetylation of mitogen-activated protein kinase phosphatase-1 which can inhibit LPS-induced mitogen-activated protein kinase p38 (P38MAPK) [28]. Additionally, HDACIs can inhibit the expression of IL-10 which is a counteractive effect of HDAC11 [11].

Roles of HDACIs in Akt and MKK3 signaling pathways

It has been reported that HDAC3 was associated with plaque vulnerability and strongly correlated with macrophage marker CD68, both PPARr and LXR pathways can be upregulated in HDAC3^{del} macrophages and result in less vulnerable lesions [19]. Shiojima I, et al. have demonstrated that Akt serves as a powerful survival signal to protect the heart against myocardial injury [29] and MKK3 has also been proved protective for myocytes [30]. Ting C. Zhao, et al. demonstrated that MKK3 and Akt-1 pathways both play an essential role in HDAC inhibition–induced cardioprotection for the first time and proved that HDACI can improve the ventricular function and alleviate the reduction of myocardial infarct [14]. It is known that AKT will serve as survival signal to protect the heart from myocardial infarction [31]. In addition, the activation of AKT signaling derived from mesenchymal stem cells can catalyse the prevention of cardiac remodeling, and improve the number of regenerated myocardium cells and angiogenesis and restoration of myocardial function [32].

Roles of HDACIs in PPAR signaling pathway

HDACIs can regulate adipogenesis and adipocyte differentiation through PPAR signaling pathway, which suggest the potential of HDACIs on cardiac metabolism [33]. PPAR was widely considered as an anti-inflammatory agent, and it's an important determinant of macrophage polarization, migration, differentiation. HDACIs can inhibit the recruitment of HDACs to the PPAR promoter, thus resulting in enhanced PPAR expression and activity, and suppress inflammation. PPAR-δ has the ability of anti-apoptotic and anti-inflammatory effect, it has showed that PPAR-δ activation inhibits endothelial cell apoptosis and promotes proliferation and angiogenesis after myocardial infarction [34].

Role of HDACIs in the Treatment of Myocardial Infarction

It has been proved that HDACs have a correlation with myocardial infraction in recent years. HDACIs can silence myocytes' fatal gene activation, block cardiac hypertrophy. What's more, HDACIs can protect the heart against myocardial ischemia injury and prevent remodeling. Anne Grange, et al. proved that HDACIs can reduce the size of myocardial infarction between 48.3 and 55.6% depending on different treatment protocols [35]. Ling X. Zhang demonstrated that HDACIs can promote cardio genesis, which is associated with the reduction of HDAC4 [36]. After long-term experiments conducted by different researchers, we can conclude that there are many types of HDACIs which are conducive to ameliorate myocardial infarction. Thus, they may have a therapeutic approach for treating this kind of disease.

Valproic acid (VPA)

VPA is a kind of HDACI which has been proved to increase t-PA expression either *in vivo* or *in vitro*, and can also lower plasma levels of plasminogen activator inhibitor-1 (PAI-1). Kristina Svennerholm, et al. did an explorative clinical study among male adult patients with the result showing that HDACI (especially VPA) can stimulate t-PA release, and they also found that VPA pre-treatment could increase t-PA release by a standardized acute ischemic provocation [37]. HDACIs intervention points a promising therapeutic way to improve endogenous fibrinolytic capacity, especially for the patients with high risk of thromboembolic disease. Lower dose of VPA can increase t-PA release, while high dose of VPA can cause manifold increase in it [3]. Olesen, et al. did a research with a result showing that 40% reduced risk for myocardial infarction in the treatment with VPA [38]. Both experiments proved that VPA which function as a HDACI has a positive effect in stimulating t-PA release for thromboembolic disease which can be beneficial for myocardial infarction.

Cyclic phosphatidic acid (CPA)

Cyclic phosphatidic acid (CPA) can inhibit the expression of HDAC 2, and it was isolated for the first time from myxoamoebae of a true slime mold, Physarum polycephalum, in 1992 [39], it is a naturally occurring phospholipid and can be generated by phospholipase D2 (PLD2). CPA consists of a cyclopropane-containing fatty acyl chain and a cyclic phosphate joining the sn-2 and sn-3 positions of glycerol. It has been proved that CPA can regulate peroxisome proliferator-activated receptor gamma (PPAPr) function by stabilizing the

Table 1: HDACIs and their involvements in myocardial infarction.

HDACIs	Targets	Function	Signaling pathway Reference
VPA	increase t-PA release	improve endogenous fibrinolytic capacity; reduced risk for myocardial infarction	t-PA; PAI-1 [35,37]
CPA	Inhibit HDAC2	prevent neointima formation, adipocytic differentiation, lipid accumulation	PPAR-r [38,39]
SAHA	Inhibit HDAC1,2	reduce infarct size; promote autophagy	Autophagic; [45,47] anti-inflammatory
TSA	Inhibit HDAC1,2	stimulates myogenesis and angiogenesis; reduce infarct size	Chop; p38MAPK [41,42]
Scipataid	synthetic HDACI	reduce infarct size	Reverse HDACs activity [48,49]
Mocetinostat	Inhibit HDAC 1,2 .3		IL-6/STST3 axis [35,50]

silencing mediator of retinoid and thyroid hormone receptors (SMRT)-PPARγ complex [40], and prevent neointima formation, adipocytic differentiation, lipid accumulation [41]. CPA can inhibit the development of atherosclerosis, Tamotsu Tsukahara, et al. did an experiment with a conclusion that CPA can inhibit pro-inflammatory cytokine expression after alkyl-glycerophosphate (AGP) exposed to human coronary artery endothelial cells (HCAECs) [42].

Trichostatin A (TSA)

TSA is a kind of pharmacologic HDACI which can effectively reduce blood pressure and vascular inflammation [43]. HDAC with trichostatin A (TSA) protects the heart against ischemic injury and TSA can stimulate transcription factor kB, gp91, p38 mitogen-activated protein kinase. It has been widely used as a promising anticancer agent. Treat the cultured embryonic stem cells with TSA can stimulates my genesis and angiogenesis which is associated with the restoration/preservation of myocardial function after myocardial infarction, indicating that HDACI can stimulate angiogenesis and thus decrease the size of myocardial infarction after MI [44]. Ting C. Zhao, et al. did an experiment showing that there is a significant greater reduction of myocardial infraction size in TSA treated mice as compared to the control group [24]. What's more, following the treatment of TSA, the trend of LVDP and LVEDP were improved. Ling Zhang, et al. demonstrated that TSA treatment has an amazing effect to increase the content of coronary effluent (CF), and finally concluded that TSA stimulates the self-renewal of c-kit CSCs and enhances endogenous myocardial proliferation and cytokinesis *in vivo* in MI hearts compared with the control group [34]. They also proved that TSA can improve myocardial functional recovery in the infarcted heart, stimulated endogenous myocardial regeneration, newly formed vascular structure and prevented myocardial remodeling. On the other hand, it has been indicated that TSA pretreatment could ameliorate myocardial damage by the inhibition of CHOP expression and CHOP-induced apoptosis. TSA can inhibit the apoptosis of cardiomyocytes and thus enhance cell viability [45].

Suberoylanilide hydroxamic acid (SAHA)

SAHA is a FDA-approved medicine for treatment of cutaneous T-cell lymphoma, which is a kind of HDACI with the function of anticancer [46]. Min Xie, et al. did an experiment to test the function of both TSA and SAHA in myocardial infraction, adding weight to the significant TSA-dependent protection, what's more, they found that SAHA (50 mg/kg) reduce infarct size by around 45% ($p < 0.05$), Lower dose of SAHA (30 mg/kg) manifest a trend toward reduced infarct size (§20%) [45]. All of these data established that SAHA is functionally similar to TSA in its ability to blunt I/R damage in mice and rabbit, which is of great therapeutic effects in treating with myocardial infarction [47]. They further discovered that the accumulations of auto phagosomes are observed in the infarct border zone of SAHA-treated, while, SAHA has showed to increase autophagy in cancer cells [48]. Identifying that SAHA's cardio protective effects are dependent on autophagic flux. There are many other mechanisms underlying that SAHA can be cardio protection, for example, SAHA has anti-inflammatory properties and promote the proliferation and homing of stem cells [49]. While, autophagic flux is the primary mechanism for cardio protection.

Script aid and mocetinostat

Script aid is a synthetic HDACI. Script aid resulted in a nearly identical effect when compared to Null script which is a negative control compound for script aid with a 46.8% reduction in infarct size (21.2 ± 3.3%; P = 0.035). These results strongly suggest that in murine models, HDACIs can reverse the induction of ischemia-induced HDAC activity *in vivo* and reduce myocardial infarct size by more than 50% [35]. Interestingly, pretreatment of hypoxic myocytes with scripted can repress this production to base line without significant change in RNA levers [50]. Mocetinostat is a kind of HDACIs which can inhibit HDAC1, 2, 3, Reseach has showed that the anti-fibrotic mocetinostat can modulate IL-6/STST3 axis and down-regulation of ECM production in myocardium fibroblasts in ischemic heart failure models [51,52]. But more researches should be conducted to demonstrate whether it is effective or not to applying for clinical.

Conclusions and Perspectives

HDACIs have been identified as key regulators in process of several diseases, including myocardial infarction. Numerous researches suggested that HDACIs play critical role in several aspects of myocardial infarction, such as reducing infarct size, improve t-PA level, stimulate angiogenesis, and protect myocardial function (Table 1). Several HDACIs have intensive potentials as biomarkers and therapeutic targets for diverse pathological changes involved in myocardial infarction process. While only a few of them were described to directly contribute to progress of myocardial infarction. However, the functional roles of HDACIs in myocardial infraction requiring further investigation in order to illuminate the pharmacological mechanisms and guide clinical medication in a better way.

Conflict of Interest

The authors declare no conflict of interest.

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