Role of histone deacetylase inhibitors in diabetic cardiomyopathy in experimental models (Review)

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Received June 17, 2022; Accepted August 2, 2022

DOI: 10.3892/mi.2022.51

Abstract. In diabetes, metabolic dysregulation, caused by hyperglycemia, leads to both structural and functional changes in cardiomyocytes and subsequently leads to the development of cardiomyopathy. Histone deacetylases (HDAC) are enzymes that regulate gene transcription. Their actions have been examined in the development of multiple disorders, such as cardiovascular diseases and diabetes. The use of HDAC inhibitors (HDACIs), as potential therapeutic agents against disease progression has yielded promising results. The present review article reports preclinical trials identified in which HDACIs were administered to mice suffering from diabetic cardiomyopathy (DCM), and discusses the role and mechanisms of action of HDAC and HDACIs in DCM. A review of the literature was performed using the PubMed database, aiming to identify publications in the English language concerning the role of HDACIs in DCM. More specifically, key words, separately and in various combinations, such as HDACIs, HDAC, diabetes, cardiomyopathy, heart failure and ischemia/reperfusion injury, were used. Furthermore, the references from all the articles were cross-checked in order to include any other eligible studies. The full-text articles assessed for eligibility were eight, covering the period from 2015 to 2019; finally, all of them were included. The use of HDACIs exhibited encouraging results against DCM progression through various mechanisms, including the reduction of reactive oxygen species generation, inflammatory cytokine production and fibrosis, and an increase in autophagy and angiogenesis.

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Key words: histone deacetylase, histone deacetylase inhibitors, cardiomyopathy, diabetes, heart failure

Contents

1. Introduction

To date, studies have indicated that there is a strong association between diabetes and heart failure. Diabetes mellitus (DM) is one of the most common risk factors for the development of non-ischemic heart failure, and its identification results in the initiation of cardioprotective therapy (1). Therefore, cardiovascular complications constitute the main cause of morbidity and mortality in diabetic patients. In total, 80% of related deaths occur due to cardiovascular diseases in these patients (2). These complications include atherosclerosis, coronary artery disease, and myocardial infarction (3). Diabetic cardiomyopathy (DCM), is another cardiac disorder caused by diabetes (4).

DCM is defined as a heart disorder of a diabetic patient in which abnormal myocardial structures, such as coronary lesions, valvular heart disease and hypertension are absent. This disorder is characterized by diastolic or systolic dysfunction, combined with structural changes, such as fibrosis and hypertrophy (5). The pathophysiology of DCM is complex and involves various mechanisms, such as inflammation, mitochondrial dysfunction, apoptosis, oxidative stress, lipotoxicity, fibrosis and disruptions in insulin signaling (6). Even though extensive research has been conducted concerning diabetic cardiovascular disorders, the efficacy of treatment remains a challenge (7,8).

Multiple contributing mechanisms are associated with diabetic heart disease. It is well established that hyperglycemia plays a critical role in diabetes-related heart failure (9,10). Following a protein modification mechanism and the induction of epigenetic alterations, as well as mitochondrial damage, hyperglycemia results in myocardial dysfunction. Oxidative stress is also associated with both non-cardiac and cardiac diabetes-related complications. Oxidative stress usually provokes impaired cardiomyocyte calcium handling and leads to reduced cardiac contractility and relaxation. Inflammation is another mechanism that leads to the progression of diabetes. Increased inflammatory signaling often results in macrophage infiltration and thus, in cardiac DM-related complications (9).

Moreover, autonomic dysfunction has an impact on myocardial performance, and systemic and coronary vascular function (11). Autonomic dysfunction is a significant complication of DM that is firmly linked to a roughly five-fold increased risk of cardiovascular mortality. Its presentation ranges from resting tachycardia and a fixed heart rate to the development of silent myocardial infarction (12).

Consequently, myocardial hypertrophy, fibrosis and myocardial dysfunction lead to the progression of heart failure. Cardiac complications, such as disrupted insulin signaling, the renin-angiotensin-aldosterone system, and small and large-vessel disease lead to alterations in myocardial energetics, cardiac remodeling and impaired perfusion (11). Myocardial energy depletion in individuals suffering from DM is multifactorial and is associated with limitations in the uptake and utilization of substrates, mitochondrial dysfunction and affected energy transfer from mitochondria to myofibrils. These metabolic alterations combined with affected myocardial perfusion, may result in the reduced ability of the heart to cope with acute increases in workload (13).

As a result, myocardial dysfunction, cardiac stiffness and myocardial fibrosis occur. Finally, cytosolic calcium trafficking and gene expression cause excitation-contraction decoupling, and lead to cardiomyocyte contraction and relaxation (11).

Histone deacetylases (HDACs) are enzymes that exert their activities through the alteration of chromatin regulation. The balance between HDACs and histone acetyltransferases (HATs) controls that regulation. As their name suggests, they remove acetyl-groups from histones. They actually regulate the interaction between the negatively charged DNA and positively charged histones. Thus, they serve as a repressor of transcription (14) (Fig. 1). The 18 HDACs are divided into four classes as follows: The class I Rpd3-like proteins (HDAC1, HDAC2, HDAC3 and HDAC8); the class II Hda1-like proteins (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10); the class III Sir2-like proteins [sirtuin (SIRT)1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6 and SIRT7]; and the class IV protein (HDAC11) (15).

The HDACs of classes I, II and IV exhibit a zinc-dependent activity. On the contrary, class III HDACs or SIRTs (SIRT1-7) require nicotinamide adenine dinucleotide (NAD) for catalysis (Table I) (14). Their crucial roles in epigenetics and gene expression have rendered them potential targets in various diseases, including both metabolic and cardiovascular entities (16).

HDAC inhibitors (HDACIs) are already used as anticancer agents. Of note, four of them have already been approved by the US Food and Drug Administration (FDA) against hematological malignancies (14). Additionally, their anticancer activity has been reported extensively in the literature, including colorectal, hepatocellular, pancreatic, breast, thyroid, lung, endometrial, and other cancers such as uveal and cutaneous melanoma (17-27). Furthermore, their role appear to be crucial in fighting other diseases, including viral infections and both inflammatory and neurological disorders (28,29). Hyperglycemia is a crucial factor that contributes to the development of oxidative stress, mitochondrial injury, reactive oxygen species (ROS) and myocardial inflammation (30,31). Thus, HDACIs appear to be promising therapeutic agents against cardiovascular diseases, including DCM.

The present review article reports pre-clinical trials identified in which HDACIs were tested in animal models of DCM. The roles and mechanisms of action of HDACIs in metabolic and cardiovascular diseases were also discussed.

2. Role of HDACIs in experimental models of DCM

In 2015, Chen *et al* (31) examined the role of sodium butyrate, which is a specific HDACI, in preventing myocardial dysfunction in diabetic mice. They established a model of diabetes using mice by injecting the mice intraperitoneally with streptozocin. The next step was the administration of sodium butyrate to certain subgroups of these mice. The echocardiography findings revealed that cardiac dysfunction was attenuated in he diabetic mice receiving sodium butyrate. Additionally, the attenuation of cardiac remodeling and interstitial fibrosis were noted. These findings were associated with an increase in cardiac angiogenesis, and a decrease in both apoptosis and active caspase 3. Glucose metabolism was improved through the upregulation of glucose transporter

Table I. HDAC classification.

Class I	Class II	Class III	Class IV
Zn^+-dependent		NAD-dependent	Zn^+-dependent
HDAC1	IIA	SIRT1	HDAC11
HDAC2	HDAC4	SIRT2	
HDAC3	HDAC5	SIRT3	
HDAC8	HDAC7	SIRT4	
	HDAC9	SIRT5	
		SIRT6	
		SIRT7	
	IIB		
	HDAC6		
	HDAC10		

HDAC, histone deacetylase; SIRT, sirtuin; NAD, nicotinamide adenine dinucleotide.

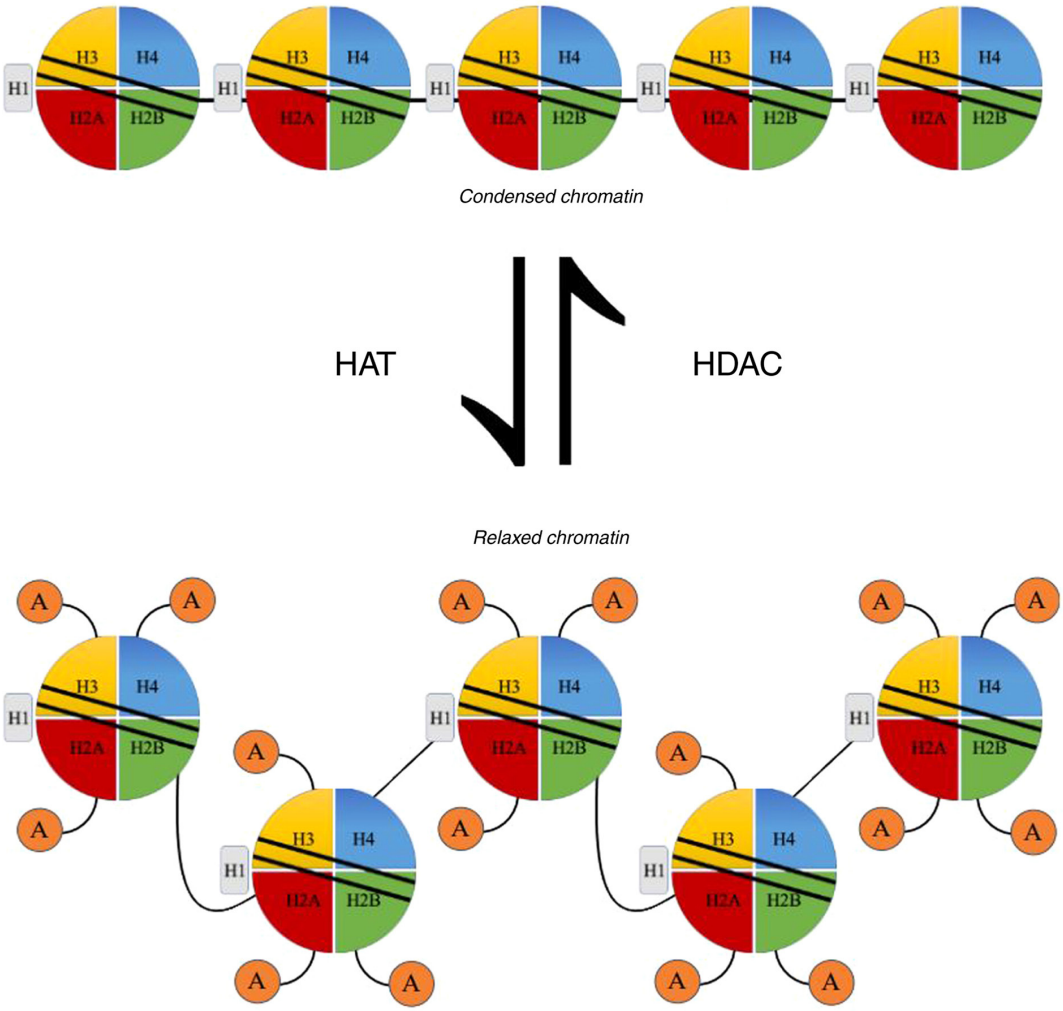

Figure 1. HDAC function. H, histone; HAT, histone acetyltransferase; HDAC, histone deacetylase; A, acetyl-group.

(GLUT)-1 and -4. Finally, sodium butyrate exerted an anti-oxidant effect on the myocardium by elevating superoxide dismutase levels (31).

Lee *et al* (32,33) conducted research on diabetic rats who received low doses of streptozocin. MPT0E014, which is a pan-HDACI, was administered to a subgroup of diabetic rats.

Table II. Preclinical studies of histone deacetylase inhibitors in diabetic cardiomyopathy.

Authors, year	Specimen	HDACI	Outcome	(Refs.)
Chen *et al*, 2015	• Control mice • Control receiving sodium butyrate mice • Mice with streptozocin-induced diabetes • Mice with streptozocin-induced diabetes receiving sodium butyrate	Sodium butyrate (inhibitor of HDAC class I and IIA)	Reduction of apoptosis, oxidative stress, cardiac remodeling, fibrosis. Upregulation of GLUT-1 and -4, and angiogenesis.	(31)
Zhang *et al*, 2017	• Mice fed a high-fat diet • Mice fed a high-fat diet and treated with sodium butyrate • Mice fed a standard chow diet • Mice fed a standard chow diet and treated with sodium butyrate	Sodium butyrate	Reduction of obesity, hypercholesterolemia, hyperglycemia, apoptosis, oxidative stress, left ventricular wall thickness and internal diameter. Increase in angiogenesis.	(7)
Wu *et al*, 2017	• Control rats • Control rats subjected to myocardial ischemia/reperfusion injury • Diabetic rats • Diabetic rats subjected to myocardial ischemia/reperfusion injury	Trichostatin A	Protected against myocardial ischemia/reperfusion injury and hypoxia/reoxygenation injury under diabetic. conditions	(34)
Xu *et al*, 2017	• Mice with type 1 diabetes • Mice with type 1 diabetes treated with VPA • Mice with type 1 diabetes treated with RGFP966 • Control • Control and VPA • Control and RGFP966	RGFP966 (Selective HDAC-3 inhibitor), VPA (pan-HDACI)	Reduction of cardiac hypertrophy, cardiomyocyte size, fibrosis, insulin resistance, inflammation and oxidative stress. Increase in levels of DUSP5.	(37)
Lee *et al*, 2016 and 2018	• Control • Rats fed a high-fat diet with streptozocin-induced T2D and treated with MPT0E014 • Rats fed a high-fat diet with streptozocin-induced T2D	MPT0E014 (pan-HDACI)	Reduction of glucose, triglycerides, inflammatory cytokines and apoptosis. Up-regulation of autophagy, GLUT-4 and homeostasis.	(32,33)
Leng *et al*, 2018	• Control rats • Control rats with ischemia/reperfusion injury • Diabetic rats • Diabetic rats with ischemia/reperfusion injury	Tubastatin A	Protected against myocardial ischemia/reperfusion injury under diabetic conditions	(36)
Bocchi *et al*, 2019	• Control • Mice with streptozocin-induced type 2 diabetes • Mice with streptozocin-induced type 2 diabetes and treated with SAHA	SAHA (pan-HDACI)	Increase in contractility and calcium dynamics. Reduction in intracellular oxidative stress.	(38)

DCM, diabetic cardiomyopathy; HDACI, histone deacetylase inhibitor; HDAC, histone deacetylase; GLUT, glucose transporter; T2D, type 2 diabetes; VPA, valproic acid; DUSP5, dual specificity phosphatase 5; SAHA, suberoylanilide hydroxamic acid.

The left-ventricular end-diastolic diameter was smaller in the diabetic rats receiving the HDACI compared to the diabetic rats not receiving the treatment. The reduction in blood sugar and triglyceride levels revealed the anti-hyperglycemic and hypolipidemic effects of MPT0E014. At the cellular level, GLUT-4 expression was augmented through HDACI administration via an insulin-independent pathway. The cleavage of poly(ADP-ribose) polymerase 1 (PARP-1) was decreased, inhibiting apoptosis. The levels of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α) or interleukin

Table III. Preventive mechanisms of action of HDACIs against DCM.

Reduction	Increase
ROS	Autophagy
Inflammatory cytokines (IL-1, IL-6, TNF-α, IFN-γ)	GLUT-1 and -4
Apoptosis (caspase-3)	Angiogenesis
Fibrosis	Contractility
Left ventricular thickness and internal diameter	Calcium dynamics
Insulin resistance	

DCM, diabetic cardiomyopathy; ROS, reactive oxygen species; GLUT, glucose transporters.

(IL)-6 were reduced following treatment with MPT0E014 (32). Finally, the procedure of autophagy, which is necessary for the development and homeostasis of cells, was accelerated following the administration of this HDACI (33).

Wu *et al* (34) investigated whether the suppression of HDACs in diabetic rat hearts could protect the rats from myocardial ischemia/reperfusion (MI/R) injury mediated via the PI3K/Akt pathway (34). This pathway results in the activation of anti-apoptotic proteins that inhibit mitochondrial dysfunction during MI/R injury (34,35). In their experiment, diabetic rats underwent 45 min of ischemia followed by 3 h of reperfusion. They used trichostatin A (TSA), a selective I and II HDACI, both *in vitro* and *in vivo* experiments. Their study was the first to demonstrate that MI/R injury and diabetes increased HDAC activity in rat hearts. However, TSA protected the function and integrity of mitochondria both *in vivo* and *in vitro* through the expression of p-Akt via the increased phosphorylation of p-Foxo3a and Foxo3a in the cytoplasm of myocardial cells (34).

Leng *et al* (36) used the same methods and experimental model as those in the study by Wu *et al* (34); however, they concentrated on the inhibition of HDAC6 activity using tubastatin A (Tub A), a highly selective HDAC6 inhibitor. Their research demonstrated that both *in vivo* and *in vitro,* Tub A exhibited its cardioprotective actions in diabetic rat hearts by modulating peroxiredoxin 1 (Prdx1) acetylation and attenuating ROS generation and subsequent cellular injury (36).

Another group of researchers examined the association between the inhibition of HDAC3 and DCM. RGFP966, a selective HDAC3 inhibitor, and valproic acid were administered to mice with type 1 diabetes (37). Treatment with RGFP966 prevented cardiac hypertrophy through various mechanisms. Firstly, a reduction in heart hypertrophy and fibrosis markers was noted. Histologically, cardiomyocyte size, fibrosis and the accumulation of collagen were suppressed. Insulin resistance, oxidative stress and inflammatory processes were all diminished. TNF-α, plasminogen activator inhibitor-1 and ROS production were downregulated, whereas the expression of GLUT-4 was upregulated. The dual specificity phosphatase 5 (DUSP5), which is an extracellular signal-regulated kinase 1 and 2 (ERK1/2) nuclear phosphatase, inhibits phosphorylated extracellular signal-regulated kinases ERK1/2, which accelerates cardiac hypertrophy (37). The administration of RGFP966 exerted its cardioprotective effects through an increase in the levels of DUSP5. Last but not least, they demonstrated that these effects lasted for a period of time, since the protective activity of RGFP966 remained for 3 months after the end of its administration (37).

Zhang *et al* (7) performed a study in which they administered sodium butyrate to mice with type 2 diabetes. Treatment with sodium butyrate reduced obesity, hypercholesterolemia, and glucose intolerance. In addition, the wall thickness and the internal dimension of the left ventricle were smaller in the diabetic group treated with sodium butyrate, compared with the untreated diabetic group. Both the size of the cardiomyocytes and collagen presence were limited in the mice receiving the HDACI. The production of superoxide and active caspase-3, which is an apoptotic agent, were significantly reduced. Angiogenesis and capillary formation were enhanced using sodium butyrate. Finally, sodium butyrate can activate signaling pathways, such as mitogen-activated protein kinase 3 (MKK3)/p38/regulated-activated kinase (PRAK) and Akt-1, in order to regulate proper cardiac function (7).

Bocchi *et al* (38) reported the action of suberoylanilide hydroxamic acid (SAHA), a pan-HDACI, in the cardiomyocytes of diabetic rats. Ventricular cardiomyocytes were extracted in order to measure their contractility and calcium dynamics. These cells were either treated with SAHA for 90 min or left untreated. The group treated with SAHA exhibited higher contractility and calcium dynamics. This was a result of the upregulation in ryanodine receptors and a decrease in intracellular ROS levels (38).

Table II summarizes the findings of all the aforementioned studies reporting the potential role of HDACIs against DCM in experimental models (5,31-34,36-38).

3. Mechanisms of prevention of cardiac hypertrophy via the inhibition of HDACs

HDACIs are divided according to their actions on HDACs. They are divided into hydroxamic acids, short-chain fatty acids, cyclic peptides and benzamides. They are mostly studied and used against malignancies (8). However, extensive research into the possible therapeutic effects of HDACIs on DCM has been performed (5,31-34,36-38). HDAsC contribute to the development of DCM through various metabolic and hypertrophic pathways (39).

The inhibition of HDACs prevents cardiac hypertrophy a number of mechanisms. As described above, active caspase-3 is a protein which triggers apoptosis. The anti-apoptotic effects of HDACIs are demonstrated through the reduction of apoptosis (31). The inflammatory process is reduced through the downregulation of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6 and IFN-γ (40). Angiogenesis is accomplished through the increased production of vascular endothelial growth factor (VEGF) (41). The reduction of ROS generation diminishes oxidative stress (37) and can be accomplished by the modulation of acetylation of Prdx1 (36). Autophagy is an adaptive mechanism, whose absence induces intracellular death (42). As Lee *et al* (32,33) demonstrated,

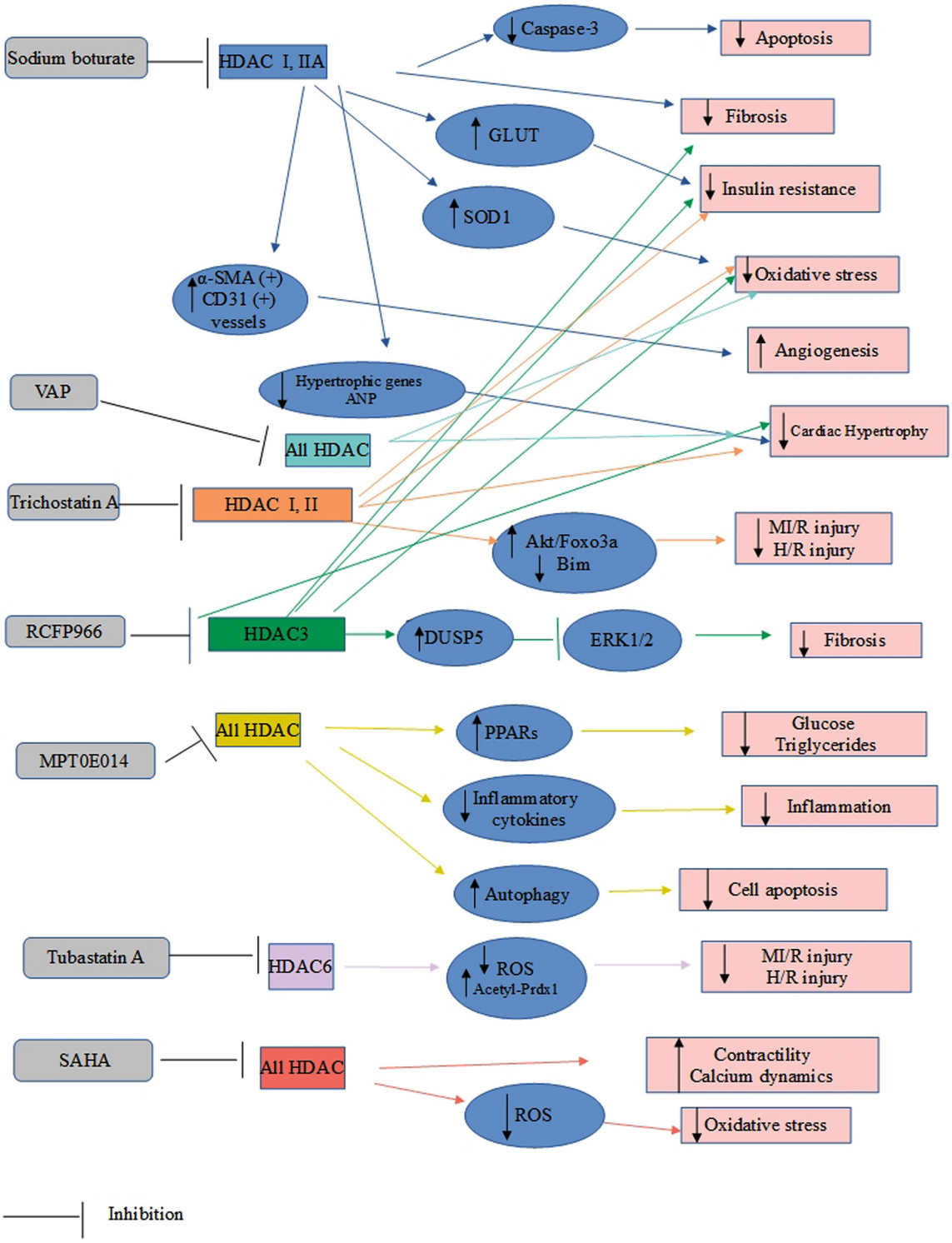

Figure 2. Mechanisms of action of HDAC inhibitors against diabetic cardiomyopathy. ANP, atrial natriuretic peptide; α-SMA, α smooth muscle actin; DUSP5, dual specificity phosphatase 5; GLUT, glucose transporter; HDAC, histone deacetylase; H/R, hypoxia/reoxygenation; MI/R, myocardial ischemia/reperfusion; PPARs, peroxisome proliferator activated receptors; PRDX1, peroxiredoxin 1; ROS, reactive oxygen species; SAHA, suberoylanilide hydroxamic acid; SOD1, superoxide dismutase 1; T2D, type 2 diabetes; VPA, valproic acid.

HDACIs can increase autophagy and protect the myocardium. Wu *et al* (34) demonstrated that the protection of the function of mitochondria via the regulation of P13K/Akt expression decreased cell apoptosis and protected the diabetic heart. The transcription of GLUT-4 is regulated by class II HDAC in skeletal muscles (43,44). The upregulation of GLUT by HDACIs leads to the entrance of glucose into cells and to a reduction in both insulin resistance and hyperglycemia (32,45). Fibrosis is reduced by inhibiting TGF-β and the angiotensin type 2 receptor (46). The mechanisms of action of HDACIσ against DCM are reported in Table III and are illustrated in Fig. 2.

4. Conclusion and future perspectives

Conventionally, HDACIs are considered as anticancer drugs. However, they appear to be useful in the treatment of other non-malignant diseases. The present review article reported numerous preclinical trials, which examined the association between HDACs, HDACIs and DCM. The use of HDACIs has yielded encouraging results against disease progression. Research has markedly enhance current knowledge on HDACs and their roles in metabolic and cardiovascular dysfunction. Additionally, HDACs are considered as possible therapeutic targets against heart failure in general. Due to the novelty of this approach, further research into the mechanisms of action and biochemical pathways of HDACs and their inhibitors is warranted prior to any clinical applications. Extending current knowledge regarding the therapeutic potential of HDACIs against these diseases will pave the way for the discovery of novel targeted epigenetic drugs. Thus, millions of individuals will be beneficially affected worldwide in the future.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AG, CD, NG and VVK conceptualized the study. VEG, DAS, PP, ED, AP, AS, KT, GM, Gky, GKo and DD analyzed the data from the literature to be included in the review, and wrote and prepared the draft of the manuscript. GKo and DD provided critical revisions. ED, AS and AP prepared the figure and the tables. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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