HDAC Inhibition Modifies Cardiac PPARs and Fatty Acid Metabolism in Diabetic Cardiomyopathy

Manisha Oza*

SVKM's Dr Bhanuben Nanavati College of Pharmacy, Vile Parle (W), Mumbai 400056, India

Corresponding Author*

Manisha Oza,

SVKM's Dr Bhanuben Nanavati College of Pharmacy, Vile Parle (W), Mumbai 400056, India,

Phone: 917518453931

E-mail: oza.manisha@gmail.com

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Abstract

Peroxisome proliferator-activated receptors (PPARs) control the homeostasis of lipids and glucose in the heart. Inhibitors of the enzyme histone deacetylase (HDAC) have anti-inflammatory properties that may be crucial in controlling PPARs and fatty acid metabolism. This study sought to determine whether the HDAC inhibitor MPT0E014 could influence myocardial PPARs, inflammation, and fatty acid metabolism in DM cardiomyopathy. In order to assess the electrophysiological activity, heart structure, fatty acid metabolism, inflammation, and PPAR isoform expressions in control and streptozotocin-nicotinamide-induced DM rats with or without MPT0E014, electrocardiography, echocardiography, and western blotting were used. DM and MPT0E014-treated DM rats showed decreased body weights and higher blood glucose levels compared to control rats. DM rats had larger left ventricular end-diastolic diameter and longer QT intervals than control and MPT0E014-treated rats did. The cardiac PPAR- and PPAR-protein expressions were higher in the control and MPT0E014-treated DM rats, but the cardiac PPAR- was lower than in the DM rats. The levels of the proteins 5' adenosine monophosphate-activated protein kinase 2, PPAR-coactivator 1, phosphorylated acetyl CoA carboxylase, cluster of differentiation 36, diacylglycerol acyltransferase 1 (DGAT1), DGAT2, tumour necrosis factor-, and interleukin-6 were also lower in control and MPT0E014-treated DM rats than in By modifying cardiac PPARS, fatty acid metabolism, and proinflammatory cytokines, HDAC inhibition greatly reduced DM cardiomyopathy.

Keywords: Retinoid X receptors; Cardiovascular diseases; RXRα ligand; Diabetes; Wound healing; Electrocardiography.

Introduction

An absolute or relative absence of insulin is a complex, chronic condition known as diabetes mellitus (DM). In 2010, 285 million adults worldwide were affected by DM; by 2030, this figure is anticipated to rise to 439 million. The main factor contributing to DM-related morbidity and mortality is cardiovascular problems. DM cardiomyopathy, which is caused by increased oxidative stress, inflammation, fibrosis, metabolic abnormalities, and vascular disorders, has a negative impact on the outcomes of DM. Studies on humans and animals have demonstrated that hyperglycemia alters the metabolism of DM cardiomyocyte. Myocardial dysfunction in DM is brought on by intramyocellular free fatty acid (FFA) accumulation brought on by fixed myocardial substrate utilization. However important blood glucose management is in the management of DM cardiomyopathy, it is still insufficient [1].

Histone deacetylase (HDAC) inhibition has been extensively researched as a cancer treatment strategy. HDAC inhibition may also affect the renin-angiotensin system, metabolism, inflammation, oxidative stress, and cardiovascular disorders. Heart enlargement and metabolic abnormalities, such as up regulation of genes involved in fatty acid uptake and oxidation as well as retardation of glucose uptake, are caused by cardiac HDAC3 deletion. Increased inflammation and oxidative stress are linked to DM, and these factors may contribute to heart metabolism being out of whack. According to studies, DM heart performance may suffer from increased FFA oxidation and poor glucose utilisation [2]. In a hyperglycemic state, HDAC inhibition significantly reduces oxidative stress and inflammation. Cardiomyopathy has an increase in HDAC activity. HDAC inhibition's metabolic functions in the DM hearts have not yet been fully understood. It is yet unknown whether reducing the abnormalities in fatty acid metabolism helps to control DM cardiomyopathy. Peroxisome proliferator-activated receptors (PPARs),, and also control the use and storage of energy by forming heterodimers with the retinoid X receptor (RXR), RXR and PPARs work together to control inflammation and atherosclerosis. In a prior investigation, we discovered that DM can alter PPARs in cardiomyocyte [3]. Furthermore, a multicomponent corepressor complex with HDAC activity is connected to the unleaded PPAR- heterodimeric complex. The coactivator complex with histone acetylase activity is brought in to replace the corepressor complex after it binds to the PPAR-ligand. . This causes chromatin to reorganise, which makes active transcription possible. Through binding to the PPAR response element, its associated repressor complex, and HDAC, PPAR- also inhibits the transcriptional activity of PPAR- and PPAR. It is yet unknown, though, how the HDAC inhibitor regulates the production of the cardiac PPAR isoform in DM cardiomyocyte. Therefore, the aim of this investigation was to examine if PPARs, fatty acid metabolism, and inflammation in DM hearts can be modulated by the HDAC inhibitor MPT0E014 [4].

Materials and Methods

Preparations involving Animals, Blood Samples, and Tissue

This study received approval from Taipei Medical University's Institutional Animal Care and Use Committee and adhered to both the university's guidelines and the US National Institutes of Health's (NIH Publication number 85-23, revised 1996) guide for the care and use of laboratory animals (LAC-2014-0237). Rats were kept in regular housing environments and fed commercial rat food and unlimited amounts of tap water. Male Wistar 10-week-old rats (335 g 4.5) were given nicotinamide (150 mg/kg, Sigma-Aldrich, St. Louis, MO, USA) intraperitoneally 15 min before receiving streptozotocin (65 mg/kg STZ, Sigma) intraperitoneally once after a 10-hour overnight fast to cause diabetes mellitus (DM DM was identified as having excessive fasting plasma glucose (15 mmol/L), as determined by a glucometer (Ascensia Elite, Bayer Health Care, and Mishawaka, IN, USA) [5]. Rats were divided into control, DM, and DM that had received MPT0E014 treatment at the age of 12 weeks. In the experimental rats, MPT0E014 (a pan-HDAC inhibitor, 50 mg/kg in 50% polyethylene glycol 400 and 0.25% carboxymethyl cellulose) or vehicle was administered orally once daily for seven days. At 13 weeks old, sodium pentobarbital (100 mg/kg) was administered intraperitoneally to the rats to induce anaesthesia before they were slaughtered. Before euthanasia, body weights were recorded and blood was drawn for analysis. For protein isolation, transverse tissue fragments were snap-frozen in liquid nitrogen from the ventricles. Using SPOTCHEM II Inorganic Phosphorus reagent strips, the SPOTCHEM analyzer (Minami-Ku, Kyoto, Japan) measured the fasting serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol. Rat ELISA kit (Sigma) was used to measure serum FFA and a Mercodia Ultrasensitive Rat Insulin ELISA was used to measure serum fasting insulin [6].

Measurements of the electrocardiogram and the echocardiogram

At 10 and 13 weeks of age, transthoracic echocardiography was done on the control and DM rats with and without MPT0E014 administration using the Vivid I ultrasonography cardiovascular system (GE Healthcare, Haifa, Israel) under isoflurane anaesthesia (5% for induction and 2% for maintenance). The left ventricle's (LV) end-diastolic diameter (LVEDd), end-systolic diameter (LVESd), interventricular septal thickness in diastole (IVSd), end-diastolic volume (EDV), end-systolic volume (ESV), fractional shortening (FS), and ejection % were all measured using M-Mode tracing (EF).

At 10 and 13 weeks of age, electrocardiograms (ECGs) were taken from standard lead II limb leads using a bio amplifier (AD Instruments, Castle Hill, Australia). Results for the control group of rats as well as the DM rats treated with and without MPT0E014 were continuously shown throughout the trial [7].

Western Blot Analysis

SDS-PAGE (sodium dodecylsulfate polyacrylamide gel electrophoresis) was used to separate equal amounts of proteins (40 g), and then the proteins were electrophoretically transferred to nitrocellulose membranes. Tumor necrosis factor- (TNF-) (AbDSerotec, MorphoSys UK, Oxford, UK), interleukin- (IL-) 6 (Bender Med Systems, Vienna, Austria), PPAR- coactivator- (PGC-) 1 (Abcam, Cambridge, UK), 5' adenosine monophosphate-activated protein kinase 2 (AMPK2; Cell Signaling, Beverly, MA, USA), and (Millipore, St. Louis, MO, USA), diacylglycerol acyltransferase 1 (DGAT1), DGAT2 (Abcam), cluster of differentiation 36 (CD36) (Abcam), phosphorylated AMPK2 (pAMPK2; Millipore), Akt; phosphorylated Akt; and secondary antibodies coupled with horseradish peroxidase (pAkt; Cell Signaling) (HRP; Leinco Technology, St. Louis, MO, USA). AlphaEaseFC software was used to examine the results after bound antibodies were found using a Millipore enhanced chemiluminescence detection equipment (Alpha Innotech, San Leandro, CA, USA). To ensure equivalent protein loading, the targeted bands were standardised to cardiac glyceraldehyde 3-phosphate dehydrogenase (GAPDH; Sigma-Aldrich) [8].

Discussion

Pro-inflammatory state and higher tissue cytokine concentrations are linked to DM. Recent research has shown that HDAC inhibitors have positive anti-inflammatory effects. Therefore, through their anti-inflammatory effects, HDAC inhibitors may have a cardio protective potential in DM cardiomyopathy. Improved insulin signalling has been linked to HDAC inhibition. According to this study, plasma insulin levels in DM rats with and without HDAC inhibition were comparable. The treatment for MPT0E014 did, however, halt the DM hearts' declining pAKT levels. According to these results, inhibiting HDAC may enhance insulin signalling, which would therefore enhance cardiac health and metabolic equilibrium in DM hearts. Additionally, we showed that the increased blood glucose levels in the DM group were correlated with greater protein expressions of the inflammatory cytokines TNF- and IL-6 in the myocardium. The considerable decreases in cardiac TNF- and IL-6 proteins in MPT0E014-treated DM rats imply that the HDAC inhibitor, MPT0E014, may at least in part act as an anti-inflammatory therapy for DM cardiomyopathy as it only slightly lowers blood glucose levels. Therefore, improved insulin sensitivity, which was linked to a reduction in inflammation, may be the underlying reason for MPT0E014's ability to lower blood sugar levels in people with DM cardiomyopathy [9].

Additionally, DM and myocardial lipid build-up are linked. Increased lipid uptake in the cardiomyocyte may have contributed to cardiac lipotoxicity, which could have had detrimental effects on the myocardial function. This study discovered that DM rats have aberrant cardiac fatty acid metabolic signals, which is consistent with earlier studies. The myocardium's glucose metabolism is significantly mediated by AMPK, and it is crucial for controlling the exchange of energy metabolism when cells are under stress [10]. The activation of AMPK2 in the DM hearts also most likely boosted fatty acid oxidation through phosphorylation and inhibition of ACC because AMPK also facilitates fatty acid consumption through its regulation of ACC. Additionally, through AMPK activation, PGC-1's expression is stimulated and its activity is directly increased. Fatty acid -oxidation and excessive myocardial lipid build-up, which could affect cardiac lipid and glucose consumption and the energy balance, are controlled in part by PGC-1. PGC-1 activity is necessary for AMPK to regulate the expression of several essential roles in mitochondrial and glucose metabolism. As a result, PGC-1 is essential to AMPK's ability to respond to energy in stressful circumstances [11].

Increased levels of AMPK2 and pACC proteins suggest that fatty acid transporter protein CD36 may help to increase intracellular fatty acid absorption in DM hearts. Through its control of the fatty acid transporter CD36, AMPK was also linked to the supply of fatty acids to cardiomyocyte. Although Montgomery et al. claimed that cardiac HDAC3 deletion had no discernible effect on CD36 in healthy hearts; we discovered that HDAC inhibition greatly reduced the increase of CD36 caused by DM. Our results indicate that HDAC inhibitors may play a significant role in regulating fatty acid substrates in the myocardium because AMPK2 and pACC protein levels were reversed in the DM rats after treatment with the HDAC inhibitor, MPT0E014 [12]. The mechanism of lipotoxicity in DM cardiomyopathy results from increased availability of lipid intermediates such diacylglycerol as well as accumulation of triacylglycerol per se. The penultimate step in the production of triglycerides is catalysed by DGAT, which has two isoforms known as DGAT1 and DGAT2. The kinetic rate of triglyceride absorption from the gastrointestinal tract and energy expenditure are both influenced by DGAT1. When it comes to regulating in vivo triglyceride homeostasis, DGAT2 appears to be dominating. In our DM hearts, it was discovered that DGAT1 and DGAT2 levels were raised. The overabundance of fatty acids in DM hearts may have led to reactive oxidative stress, which may have also seriously harmed the myocardium in DM cardiomyopathy [13].

In DM hearts, as in other studies, we discovered a considerably dilated LV chamber with a reduced EF and a shorter FS. Additionally, the DM hearts were linked to longer QT and QTc intervals as well as a larger heart-to-body-weight ratio. Previous studies demonstrated that improving cardiac contractility in DM hearts by restoring normal fatty acid metabolism. Intriguingly, we discovered significant improvements in myocardial systolic and diastolic functions with shortening of the QT and QTc intervals and a decreased heart-size-to-body-weight ratio in MPT0E014-treated DM rats in addition to the reversal in the ratio of pAMPK2 to total AMPK2 and other myocardial fatty acid regulators. These results imply that adequate energy following HDAC inhibition is related to the improvement in cardiac function. MPT0E014 is an HDAC inhibitor that may be able to treat DM cardiomyopathy [14].

Similar to our earlier research, our DM hearts showed significant declines in both PPAR- and PPAR-protein levels as well as an increase in myocardial PPAR-protein levels despite an increase in fatty acid oxidation. This finding suggests a compensatory response in maintaining the contractile function induced by proinflammatory cytokines during hyperglycemia. We discovered that cardiac PPAR- protein levels were down regulated after 3 weeks of DM, which is consistent with other research that concentrated on the early phases of DM. Additionally, patients with type 1 DM had enhanced myocardial fatty acid metabolism, which is consistent with the results of our research. But according to a number of other studies, DM animal models have an increase in cardiac PPAR-. The discrepancies between these researches could be the result of several experimental circumstances, such as a different animal species, genetic background, or DM severity or duration.

We proved for the first time that the HDAC inhibitor MPT0E014 restored the effects of hyperglycemia on cardiac PPARs in DM hearts. The effect of MPT0E014 on cardiac PPARs may have resulted from its anti-inflammatory effects as inflammation can control PPAR isoform expression. Additionally, MPT0E014 may alter cardiac metabolism by influencing PPARs and inflammatory cytokines to lessen the build-up of fatty acids in the hearts of people with diabetes [15].

Conclusions

Because of its effects on cardiac PPARs, fatty acid regulation, and proinflammatory cytokines, MPT0E014 ameliorates the cardiovascular abnormalities in a DM rat model.

Conflict of Interest

None

Acknowledgement

None

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