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Effect of Hexadecyl Azelaoyl Phosphatidylcholine on Cardiomyocyte Apoptosis in Myocardial Ischemia-Reperfusion Injury: A Hypothesis

Authors' Contribution:
Study Design A
Data Collection B
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Data Interpretation D
Manuscript Preparation E
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Reperfusion after myocardial ischemia can induce cardiomyocyte death, known as myocardial reperfusion injury. The pathophysiology of the process of reperfusion suggests the confluence multiple pathways. Recent studies have focused on the inflammatory response, which is considered to be the main mechanism during the process of myocardial ischemia-reperfusion injury and can cause cardiomyocyte apoptosis. Peroxisome proliferator-activated receptors gamma activated by endogenous ligands and exogenous ligand can decrease the inflammatory response in cardiomyocytes. Thiazolidinediones are synthetic, high-affinity, selective ligands for peroxisome proliferator-activated receptors gamma, and can inhibit the inflammatory response, decrease myocardial infarct size, and protect cardiac function. However, thiazolidinediones, including rosiglitazone and pioglitazone, can also contribute to adverse cardiovascular events such as congestive heart failure. Therefore, there are some limitations to the use of thiazolidinediones. Most endogenous ligands were of low affinity until hexadecyl azelaoyl phosphatidylcholine was identified as a high-affinity ligand and agonist for peroxisome proliferator-activated receptors gamma. Hexadecyl azelaoyl phosphatidylcholine binds recombinant peroxisome proliferator-activated receptors with an affinity (Kd(app) ≈40 nM) which is equivalent to rosiglitazone. Therefore, hexadecyl azelaoyl phosphatidylcholine is a specific peroxisome proliferator-activated receptors gamma agonist. Given these findings, we hypothesized that the use of hexadecyl azelaoyl phosphatidylcholine can activate the peroxisome proliferator-activated receptors gamma signal pathways and prevent the inflammatory response process of myocardial ischemia-reperfusion injury, with reduced cardiomyocyte apoptosis and death.

MeSH Keywords: Apoptosis • Inflammation • Myocardial Reperfusion Injury • PPAR gamma

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Background

Acute myocardial infarction (MI) remains a main public health problem worldwide, with high mortality and morbidity [1,2]. The Global Health Observatory data from the World Health Organization show that more than 7 million people each year are estimated to die due to ischemia heart disease, especially acute myocardial infarction [3].

Acute ischemia leading to infarction is associated with a rapid sequence of pathologic changes that can result in irreversible cardiomyocytes damage, apoptosis, and necrosis [4], with subsequent segmental ventricular remodeling and expansion [5]. If the pathologic changes are not prevented, AMI may cause heart failure, arrhythmias, ventricular aneurysm formation, ventricular rupture, cardiogenic shock, and cardiac arrest [6,7]. Researchers have found many cardioprotective methods to reduce cardiomyocyte apoptosis caused by AMI [8]. Immediate and prompt reperfusion therapy by percutaneous coronary intervention (PCI) or thrombolysis can reduce acute myocardial ischemia injury, decrease in-hospital mortality, and improve the long-term outlook in survivors of the acute phase. However, reperfusion following ischemia increases the infarct size and induces further cardiomyocyte death, a phenomenon known as myocardial reperfusion injury. Irreversible cell injury leading to necrosis and apoptosis may be precipitated by reperfusion [9,10].

Over the past 2 decades, researchers have found cardioprotective methods to prevent reperfusion injury by ischemia preconditioning and postconditioning, as well as remote preconditioning and postconditioning. Although the effectiveness of ischemia preconditioning and postconditioning for protecting ischemia myocardium has been demonstrated [11–13], there are at present no preconditioning and postconditioning-based therapies routinely used in clinical medicine [14].

Moreover, there is still no effective drug to prevent myocardial reperfusion injury. In this respect, myocardial reperfusion injury remains a neglected therapeutic target for cardioprotection in PCI patients. With significant research advances in the pathophysiology of myocardial ischemia-reperfusion injury (myocardial I/R injury), the possibility of pharmacological interventions against reperfusion injury have been proposed. Studies on the pathophysiology of myocardial I/R injury implicate multiple pathways, including ion channels, reactive oxygen species, inflammation, and endothelial dysfunction [15]. Many recent studies have focused on inflammatory response, which is considered to be the main mechanism during the process of myocardial ischemia/reperfusion (I/R) injury, and which can cause cardiomyocyte apoptosis [16,17].

Drug treatment options for preventing myocardial ischemia-reperfusion injury are therefore urgently needed. Our understanding of the underlying inflammatory mechanisms that can lead to cardiomyocyte apoptosis and myocardial necrosis enabled us to propose a novel therapeutic strategy that may help break the link between myocardial ischemia-reperfusion and its inflammatory response resulting in cardiomyocyte apoptosis.

The Hypothesis

We hypothesized that interfering with the inflammatory cascade, which is a process secondary to myocardial ischemia-reperfusion, will reduce cardiomyocyte apoptosis. By activating the peroxisome proliferator-activated receptors gamma (PPARγ), which play a key role in preventing the inflammatory process cascade, the use of hexadecyl azelaoyl phosphatidylcholine as the endogenous ligands of PPARγ and a specific PPARγ agonist in myocardial I/R injury will reduce cardiomyocyte apoptosis caused by reperfusion, and could prevent complications such as heart failure, arrhythmias, ventricular rupture, aneurysm formation, cardiogenic shock, and cardiac arrest.

Evaluation of Hypothesis

Inflammation is associated with myocardial ischemia-reperfusion injury

Myocardial ischemia-reperfusion can lead to cardiomyocyte apoptosis and necrosis, consequently reducing cardiac function and influencing the effects of therapeutics and prognosis. Although reperfusion injury is one of the main causes of cardiomyocytes death and heart failure, the exact pathophysiological mechanism underlying myocardial ischemia-reperfusion injury is not fully understood. The underlying pathological mechanisms are triggered when reperfusion injury occurs, and the pathophysiology mechanism is also complicated. A growing number of studies show that myocardial injury due to ischemia-reperfusion can be controlled and prevented, which has stimulated in-depth study of the mechanisms of cardioprotection. Accumulating evidence suggests that the underlying mechanisms responsible for ischemia-reperfusion injury include intracellular calcium overload [18,19], production of free oxygen radicals [20–22], oxidative stress [23,24], excessive reactive oxygen species (ROS) generation, immune cells [25,26], release of cytokines, inflammation [27], neutrophil infiltration and adhesion, and endothelial cell dysfunction [28]. All of these pathological processes finally contribute to cardiomyocyte apoptosis and death, as well as myocardial necrosis, leading to decreased cardiac contractility and cardiac function [29,30].

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Recently, a number of studies supported that the inflammatory response is one of the major mechanisms involved and plays a pivotal role in the pathogenesis of myocardial I/R injury [31,32]. It has also been demonstrated that the inhibition of targeting inflammation significantly reduced myocardial I/R injury [33,34]. It was reported that the pathologic process of myocardial I/R injury was an acute inflammatory reaction, which can then cause multiple pathological changes, including acute inflammatory cascade response, cell apoptosis, and death. The inflammatory response in the process of myocardial I/R is closely linked with neutrophil infiltration and cytokine release. When reperfusion injury occurs, the expression of pro-inflammatory factors, adhesive molecules, cytokines, and chemokines can also be up-regulated and then induce cell apoptosis. Many researches showed that neutrophil infiltration and the release of inflammatory cytokines are 2 key contributors to myocardial I/R injury [35,36]. The early reperfusion period is characterized by a burst of infiltration of larger populations of neutrophils and monocytes/macrophages [37,38]. The accumulation of neutrophils is mediated by special adhesion molecules released from the vascular endothelium. The interaction between neutrophils and adhesion molecules begins in the early period of reperfusion and it may continue for hours and days after reperfusion [32,39]. Following the accumulation of neutrophils, numerous pathological processes of inflammatory chain reaction are triggered. These activated neutrophils and monocytes/macrophages promote the release of multiple pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, IL-23 [40–42], tumor necrosis factor alpha (TNF-α) [43,44], PAF, and complement and leukotrienes in myocardial tissue [45]. These inflammatory cytokines may accelerate the inflammatory cascade by increasing the releases of other pro-inflammatory cytokines such as chemokines and adhesion molecules, recruiting neutrophils and monocytes/macrophages [46], and amplifying the inflammatory response [47–49]. The triggered inflammatory signaling after reperfusion also simultaneously activates key transcription factors such as NF-κB [50], JAK-STAT [51]. These activated transcription factors conversely enhance the overexpression of many important inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8 [52–54]. Excessive generation of inflammatory cytokines injures the myocardial tissue, not only by triggering harmful responses, but also by magnifying responses to establish a chain of injury [55]. This chain response can also result in vascular endothelial cell injury, exacerbate vascular permeability, and further activate inflammatory cells, resulting in further inflammatory response [55]. Many studies have suggested that inhibition of the inflammatory response decreases myocardial injury caused by I/R in various animal trials [56–58]. Therefore, inhibition of the inflammatory response may be a promising therapeutic strategy for attenuating myocardial I/R injury.

Inflammation is one of major causes of cardiomyocyte apoptosis

As we discussed above, inflammation is the major mechanism of myocardial I/R injury, and the release of inflammatory cytokines and the transcription factors are 2 key contributors to the inflammatory response, which could cause apoptosis in myocardial I/R injury. Apoptosis can be induced by activating death receptors, including Fas, TNF receptors (TNFR), DR3, DR4, and DR5, by their specific ligands. TNF receptors, including TNF receptor 1(TNFR1) and TNF receptor 2 (TNFR2), as a member of TNF receptor superfamily that contains a cell death domain, is one of the classic pathways which initiate a death signal. Tumor necrosis factor alpha (TNF-α) is not only an inflammatory cytokine, but also is a ligand that can bind with TNF receptors. Tumor necrosis factor alpha (TNF-α), as a death receptor ligand, characteristically triggers signaling by receptor recruitment, which conversely leads to the recruitment of specific adaptor proteins and activation of the caspase chain. TNFR1, after ligation with TNFα, induces TNF trimerization, which can activate initiator caspase-8 through the adaptor protein TRADD and initiate an apoptotic signaling cascade [59,60]. TNF-α is chiefly produced by activated macrophages. During the early myocardial reperfusion period, large populations of macrophages appear, producing large amounts of TNF-α. The release of TNF-α may accelerate the inflammatory cascade by increasing chemokines, adhesion molecules, NF-κB, and JAK-STAT, and recruiting neutrophil and monocytes/macrophages, and amplify the inflammatory response [46–49]. Many studies have shown that inhibition of the inflammatory response can reduce cardiomyocyte apoptosis in the pathological process of myocardial I/R injury.

PPARγ plays an important role in inflammatory response

Previous studies have demonstrated that the inflammatory response is one of the major mechanisms and plays a pivotal role in cardiomyocyte apoptosis in the pathogenesis of myocardial I/R injury. Therefore, the most effective treatments for myocardial ischemia-reperfusion (I/R) injury should be inhibiting of inflammatory response. With the in-depth study of the molecular mechanism of myocardial I/R injury, PPARγ has been recognized as an important regulator of the anti-inflammatory response. PPARγ is a member of the nuclear receptors superfamily and is also a ligand-activated transcription factor. Although PPARγ is highly expressed in adipose tissue, it is also detected in vascular smooth muscle cells [61,62], cardiomyocytes [63,64], endothelial cells [65], and monocytes and macrophages [66,67]. According to published studies, PPARγ has been involved in widespread pathological alterations of many diseases, including metabolic disorders, inflammation, the balance of immune cells, apoptosis and oxidative stress, and endothelial dysfunction [68–72]. Recently, based on the

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above-mentioned biological functions, PPARγ has been reported to be a promising therapeutic target against myocardial I/R injury [73].

More recent studies have demonstrated that PPARγ plays an anti-inflammatory role by inhibiting inflammatory cell recruitment and infiltration of neutrophils and monocytes/macrophages [74]. The upregulation of PPARγ gene expression could also reduce the gene expression of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-8, IL-23, TNF-α, adhesive molecules, chemokines, and leukotrienes) by negatively regulating the NF-κB, STAT, and AP-1 signaling pathways [75], inhibiting inflammatory response and cardiomyocyte apoptosis in myocardial I/R injury.

The NF-κB and JAK-STAT signaling pathways play a central role in myocardial I/R injury. There are 2 key transcription factors that can regulate expression of many genes of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8. These factors can also be activated by pro-inflammatory cytokines and inflammatory cells. This may form a vicious cycle, and the inflammatory response is endlessly amplified and further induces myocardial injury and cell death. Many studies have suggested that inhibition of the NF-κB and JAK-STAT signaling pathways in cardiomyocytes has a cardioprotective effect on myocardial ischemia-reperfusion injury [76,77]. In addition, PPARγ can negatively regulate NF-κB and JAK-STAT signaling pathways in various pathological processes [78,79].

Many studies in animal models have demonstrated that the distinct agonists of PPARγ can attenuate inflammation of myocardial I/R injure, reduce cardiomyocyte apoptosis, and then improve myocardial function [80]. A rodent model of myocardial ischemia and reperfusion injury showed that treatment with the 15-deoxy-[DELTA]12, 14-prostaglandin J2, which is an endogenous ligand of PPARγ, can reduce neutrophil infiltration, pro-inflammatory cytokine production, NF-κB activation, and myocardial injury by increasing PPARγ DNA binding [81,82]. Wayman et al. found that 15D-PGJ2 also reduces expression of adhesion molecules ICAM-1, P-selectin, chemokine macrophage chemotactic protein 1, and inducible isoform of nitric oxide synthase [83]. Another study using a mouse model of myocardial ischemia and reperfusion injury showed that quercetin via PPARγ activation reduces myocardium oxidative damage and apoptosis, and also inhibited the activation of the NF-κB pathway [84]. Rosiglitazone, as the chemical synthetic agonist of PPARγ, which is commonly used in treatment of diabetes, can reduce the accumulation of neutrophils and macrophages in myocardial I/R injury. Rosiglitazone can also markedly attenuate intercellular adhesion molecule-1 expression in myocardial I/R injury, and improve contractile dysfunction caused by ischemia/reperfusion injury in a rat model [84]. In a hypercholesteremic rabbit model of myocardial ischemia-reperfusion injury, rosiglitazone enhanced the activation of ERK1/2, decreased the activation of a pro-apoptotic MAPK, p38, restored a beneficial balance between pro- and anti-apoptotic MAPK signaling, and further reduced myocardial apoptosis [85].

Hexadecyl azelaoyl phosphatidylcholine can inhibit the inflammatory response by activating PPARγ

PPARγ belonged to the nuclear receptor family of ligand-activated transcription factors that exert important roles in various pathological processes, especially in inflammatory response in myocardial I/R injury. As we discussed above, ligand-activated PPARγ can inhibit the inflammatory response and protect cardiac function, particularly during the process of myocardial I/R injury. PPAR-γ can be activated by a variety of ligands and activators, mainly endogenous ligands and exogenous ligands. There are various potential endogenous ligands for PPARγ, including long-chain polyunsaturated fatty acids (e.g., linoleic acid, gamolenic acid, docosahexanoic acid, eicosapentaenoic acid, and arachidonic acid) [86,87], 15-deoxy D12 [88], 14-and eicosanoids (e.g., modified oxidized lipids [9-and 13-hydroxyoctadecadienoic acid (9- and -HODE) and 12- and 15-hydroxyeicosatetraenoic acid (12- and 15- HETE)]) [88]. Among all endogenous ligands, 15d-PGJ2 has received the most research attention [89]. However, none of these endogenous ligands have particularly effective agonists. Most endogenous ligands are of low affinity, and about 100 micromolar concentrations of those ligands are often required to activate PPARγ [90]. For example, as the PPARγ agonist, 15-deoxy-PGJ2 (2, 3) is unlikely to accumulate *in vivo*, and it has been reported scant 15-deoxy-PGJ2 actually exists in commercial sources of this reactive and unstable lipid [91].

In addition to natural ligands, PPARγ also has a number of synthetic high-affinity ligands that could easily be used to trigger the transcriptional activities of the PPARγ in cells. Thiazolidinediones (TZDs), or the glitazone class as the PPARγ agonists, are widely prescribed as an insulin sensitizer in the treatment of type II diabetes. The TZDs include pioglitazone, ciglitazone, rosiglitazone, and troglitazone. Troglitazone is the first drug developed for treating diabetes, followed by rosiglitazone and pioglitazone. The mechanism of action by which TZDs activate PPARγ as the high-affinity ligand was first found by Lehmann in 1995, and TZDs were also proved that the most effective of these agents (BRL49653) bound with PPAR gamma with a Kd of approximately 40 nM [92,93]. Animal experiments on the pharmacological effects of TZDs have shown that TZDs have high affinity when binding with PPARγ, and that pioglitazone can reduce the mRNA expression of monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule-1 in the ischemia region, and the number of infiltrating macrophages in the ischemia region. Pioglitazone

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can significantly inhibit the inflammatory response, decrease the myocardial infarct size by activating PPARγ, and further protect cardiac function [84,94].

Although TZDs are full agonists of PPARγ, which have antidiabetic efficacy, they have been associated with adverse effects, including weight gain [95], edema, hemodilution, bone fractures [96], plasma-volume expansion [97,98], congestive heart failure [97], and increased risk of adverse cardiovascular events. Troglitazone was withdrawn from the market due to the emergence of serious hepatotoxicity in some patients [99]. Rosiglitazone was later withdrawn in Europe and its application was limited in the United States because of an increased risk of myocardial infarction [101–103].

As we discussed above, although there are many endogenous ligands that can activate PPARγ, because of low affinity and difficulty accumulating them *in vivo*, they are not effective and specific agonists for PPARγ in myocardial ischemia reperfusion injury at the current time. TZDs are synthetic high-affinity agonists of PPARγ, and can inhibit the inflammatory response by activating PPARγ, as demonstrated in a variety of animal models; however, the use of TZDs in treating the myocardial ischemia-reperfusion injury is restricted due to the adverse effect of increasing risk of cardiovascular disease. Thus, it is urgent to find novel, high-affinity, safe, effective agonists of PPARγ to interfering with myocardial ischemia-reperfusion injury.

Researchers at the University of Utah recently identified hexadecyl azelaoyl phosphatidylcholine the small pool of alkyl phosphatidylcholines in oxLDL, which was recognized as a high-affinity ligand and agonist for PPARγ. Using the synthetic hexadecyl azelaoyl phosphatidylcholine, the researchers further studied its ability to bind with PPARγ, and found that the binding ability was dependent on concentration, with apparent affinity ≈40 nM. Hexadecyl azelaoyl phosphatidylcholine bound recombinant PPARγ with an affinity(Kd(app) ≈40 nM), which was equivalent to that of rosiglitazone. The study also verified that hexadecyl azelaoyl phosphatidylcholine efficiently accumulates in human monocytes and then exerts its effects intracellularly [104].

Studies have demonstrated that using hexadecyl azelaoyl phosphatidylcholine can reduce the cardiomyocytes apoptosis in myocardial I/R injure. Davies et al. found that hexadecyl azelaoyl phosphatidylcholine can enhance CD36 expression in CV-1 cells through endogenous receptors by nearly 3-fold [104]. Huynh et al. found that activating CD36 signaling, which can lead to activation of PPARγ, reduced infarct size by 54% and preserved hemodynamics in C57BL/6 mice subjected to 30-min coronary ligation and reperfusion [105].

Conclusions

The purpose of the study was to develop an effective therapeutic approach and a new cardioprotective drug for myocardial ischemia-reperfusion injury in order to reduce cardiomyocyte apoptosis. Hexadecyl azelaoyl phosphatidylcholine can inhibit inflammation of myocardial ischemia-reperfusion injury by activating PPARγ, reduce the cardiomyocytes apoptosis, and further improve the cardiac function. Therefore, it could be a potentially beneficial treatment drug for individuals with myocardial ischemia-reperfusion injury.

Conflict of interest statement

None.

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