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REVIEW

The Role of Short-Chain Fatty Acids in Myocardial Ischemia-Reperfusion Injury

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Abstract

Purpose of Review This study aims to review the effects of short-chain fatty acids (SCFAs) in regulating the myocardial ischemia-reperfusion injury (MIRI).

Recent Findings Coronary heart disease (CHD) is a well-known leading cause of death and disability worldwide. Cardiac substrate metabolism plays the determinant role in assessing the severity of heart injury due to the abruptly shifted energy production during the MIRI. Fatty acids are the main energy fuels for the heart, which are classified into long-, medium- and short chain fatty acids by the length of carbon chain. SCFAs are the main metabolites derived from the anaerobic bacterial fermentation of fiber-rich diets, which are shown to play a protective role in cerebrovascular disease previously. Meanwhile, accumulating evidences suggest that SCFAs can also play a crucial role in cardiac energy metabolism.

Summary Results of various studies revealed the cardioprotective effects of SCFAs by displaying anti-inflammatory and anti-ferroptotic function, connecting gut-brain neural circuit and regulating the intestinal flora.

Keywords Myocardial ischemia-reperfusion injury · Short-chain fatty acids · Cardiovascular disease · Myocardial metabolism

Introduction

Coronary heart disease (CHD) is regarded as one of the leading causes of death and disability worldwide [1] and its effects can often be attributed to the harmful effects of acute myocardial ischemia-reperfusion injury (MIRI). MIRI usually occurs in patients with acute ST-segment elevation myocardial infarction (STEMI), in whom the timely reperfusion is considered as the standard treatment for not only mitigating myocardial ischemia injury, but also limiting infarct size. However, restoration of blood flow often leads to MIRI, which may cause further tissue damage and cardiomyocyte apoptosis [2]. The thrombolytic therapy, percutaneous coronary intervention (PCI) and surgical coronary artery bypass grafting (CABG) are the most commonly used revascularisation interventions for an acute myocardial infarct. To prevent subsequent myocardial infarction attacks and adverse left ventricular remodeling, standard medical therapy including beta-blockers, ACE inhibitors, and statins is initiated after revasodilation [3]. Although existing treatments are being optimized to maintain the patency of the blocked coronary arteries and reduce mortality in the acute phase, there is still no effective treatment to prevent myocardial reperfusion injury.

As a high-energy requiring organ, the heart demands a great deal of adenosine triphosphate (ATP) to maintain physiological function. Fatty acids (FAs) and glucose serve as the main energy resources to product continuous ATP [4, 5], approximately 70% of ATP are generated from FAs [6]. According to the length of carbon chain, FAs can be classified into three types including long-chain fatty acids (LCFAs, > 12 carbons), medium-chain fatty acids (MCFAs,

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6–12 carbons) and short-chain fatty acids (SCFAs, 1–6 carbons). LCFAs have been reported to be involved in β-oxidation in the process of cardiac energy metabolism [7–9]. MCFAs serve as the metabolic therapy in cardiac disease [10–12]. As for SCFAs, previous studies have shown that they are involved in the regulation of brain-gut-microbiome axis, which has been considered as a promising approach to understand the pathogenesis of nervous system diseases [13–15]. However, recent findings have demonstrated that SCFAs can also play a crucial role in cardiac energy metabolism [16, 17].

In this review, we aim to summarize the recent studies of three predominant SCFAs in MIRI and discussed the significance of SCFAs in the cardiovascular system.

Cardiac Metabolism: In Normal and MIRI Conditions

Myocardial metabolism is intricately related to cardiac function. As a highly energy-demanding organ, heart needs to consume various substrates including FAs, glucose and ketone bodies. Fatty acid oxidation (FAO) and aerobic oxidation of glucose are the main sources of energy for normal myocardial metabolism, of which 60–90% comes from FAO, while the remaining 10–40% of energy supply comes from glucose and lactose oxidation, and very little is from amino acid and ketone body metabolism [18].

In the cytoplasm of cardiomyocytes, most LCFAs converted into FA-acyl-CoAs, which are transported into mitochondria for β-oxidation via carnitine palmitoyltransferases (CPT-1 and CPT-2). The subsequent production of acetyl coenzyme A (acetyl-CoAs) is involved in the production of ATP in the TCA cycle. SCFAs and MCFAs can freely diffuse into mitochondria, followed by activation to generate lipoyl-CoA [19].

Cardiac substrate metabolism is considered as the primary determinant in MIRI since the abruptly shifted energy production during the convertion from normoxia to ischemia and further reperfusion [20, 21]. When the blood supplying to the myocardium is suddenly interrupted, cardiac metabolism responds rapidly to this change, which is manifested as the inhibited oxidative metabolism of fatty acids, carbohydrates, ketones as well as amino acids in hypoxia with concomitant activation of anaerobic glycolysis, preserving the utilization of limited oxygen. During reperfusion, however, with the entry of oxygen and the excretion of ischemic metabolites, the intracellular pH is suddenly normalized, and the oxidative metabolism of various substrates begins to be specifically initiated, and the dynamic relationship between fatty acid β-oxidation and glucose oxidation is disturbed leading to sustained changes in aerobic glycolysis, which is reflected in the gradual shift of the fuel source for fatty acid oxidation to the uptake and utilization of glucose [22]. These metabolic changes are not merely the result of reperfusion injury but largely determine the actual damage to the heart after an ischemic episode.

General Properties of Short-Chain Fatty Acids

The SCFAs, also known as volatile fatty acids, are a group of saturated fatty acids which contain one to six atoms. The SCFAs exist as straight- or branch-chained compounds which include formic, acetic, propionic, butyric, isobutyric, valeric and isovaleric. The SCFAs are mainly derived from the fermentation of fiber-rich diets by the anaerobic bacteria. Acetate (60–75%), propionate (15–25%), and butyrate (10–15%), the predominant forms of SCFAs, are produced through different microbial fermentation. Acetate is produced by most gut anaerobes like Bifidobacterium spp. and Akkermansia muciniphila et al. Butyrate is mainly produced by Coprococcus eutactus and Faecalibacterium prausnitzii. Bacteroides spp. and Veillonella spp. are the principal anaerobes to form propionate [23–27]. Besides the fermentation of carbohydrates, proteolysis also contributes to the SCFA production which produces peptides and amino acids that can be utilized for energy or biosynthetic processes [23].

Pyruvate and acetyl-CoA are key points in fermentative metabolism, which are produced from carbohydrates by intestinal bacteria through glycolytic pathways [26]. Acetate is produced from pyruvate by acetyl-CoA or via Wood-Ljungdahl pathway. Three pathways, known for the formation of propionate, include the acrylate pathway, the succinate pathway and the propanediol pathway. Butyrate is produced through two different pathways for the final step from butyral- CoA, which pursues either via butyryl-CoA/acetate-CoA transferase or via phosphotransbutyrylase and butyrate kinase [28].

SCFAs are absorbed rapidly and efficiently by intestinal epithelial cells via at least four ways, including nonionic diffusion [25], exchange with bicarbonate in a ratio of 1:1 [29–31], co-transportation with cations via H^+-coupled monocarboxylate transporters (MCT1, MCT2 and MCT4) [32], as well as Na^+-coupled monocarboxylate transporter 1 (SMCT1, also known as SLC5A8) [33]. Monocarboxylate transporter (MCT) and sodium-coupled monocarboxylate transporter (SMCT), two major transporters for SCFAs, locate in the digestive tract [34]. MCT1 (also known as SLC16A1) was first identified and existed in intestinal epithelial cells as well as in the heart, kidney, and epididymis [35]. The MCT family, of which only MCT1-MCT4 have been demonstrated to catalyse proton-coupled transport of monocarboxylates [27]. MCT1 is expressed in both the apical and basolateral membrane of colonic epithelium,

whereas MCT4 (also known as SLC16A3) is specifically in the basolateral membrane [36]. Both MCT1 and SMCT1 are the transporters for lactate, pyruvate, and SCFAs. One discrepancy between them is their existing form. MCT1 is H^+-dependent, while SMCT1 is Na^+-dependent [34, 36]. SMCT1, expressed in the brush border of enterocytes, regulates the uptake of SCFAs produced by bacterial fermentation in the large intestine [36–38].

Once absorbed by colonic epithelial cells, SCFAs move into the portal vein. Propionate and butyrate are both metabolized by the liver and served as materials for gluconeogenesis (Fig. 1), whereas acetate is used for lipogenesis and taken up by muscle tissue and adipose [39]. Butyrate, as fecal for colonocytes, is important in the regulation of colonic epithelial cell proliferation and differentiation [40].

Different Types of SCFAs in MIRI

Acetate

Acetate is found mainly in the form of esters in fruits or vegetable oils, whereas as a free acid in the tissues, excretions and blood of animals, since aqueous solution of acetate is moderately weakly acidic and corrosive. Many microorganisms can convert different organic substances into acetate through fermentation. Recent studies have testified some mixture of acetate, including dichloroacetate, glatiramer acetate, gossypol acetic acid.

Pyruvate dehydrogenase complex (PDH), a mitochondrial multienzyme complex that oxidatively decarboxylates pyruvate to form carbon dioxide, can be activated by dichloroacetate (DCA) through inhibiting pyruvate dehydrogenase kinase (PDK) which stimulates glucose oxidation. PDH is regulated by inhibition of acetyl-CoA and nicotinamide adenine dinucleotide (NADH2) and by reversible phosphorylation of PDH. Wambolt et al. found that the beneficial effect of enhanced glucose oxidation may increase the ratio of intramitochondrial NADH2 / oxidized nicotinamide adenine dinucleotide (NAD), which would thereby enhance the mitochondrial oxidative phosphorylation potential [41]. Li et al. revealed that under I/R conditions, DCA not only regulates phosphorylated level of PDH, but also modulates AMPK signaling pathway in mice hearts [42]. Interestingly, in a Wang's study, results showed that DCA increased carbohydrate oxidation and the ratio of glucose oxidation to glycolysis in the setting of ischemia and reperfusion, but did not improve functional recovery of cardiac efficiency. In another group, it was found that elevated glucose and insulin levels improved functional recovery of cardiac efficiency, but did not increase carbohydrate oxidation and the ratio of glucose oxidation to glycolysis. These data supported the notion that increased level of myocardial glucose is beneficial in the setting of ischemia and reperfusion. However, the protective effect appeared not to be mediated by shifting the balance between carbohydrate and fatty acid oxidation [43].

Glatiramer acetate (GA) is a random sequence acetate salt polypeptide with a length of 40–100 amino acids and a molecular weight of roughly 7300 Kd, which is used for treatment of multiple sclerosis. Research by Du et al. suggested that GA could reduce oxygen-glucose deprivation/reperfusion-induced (ODG/R-induced) inflammation and oxidative stress by inhibiting the expression of TNF-α, IL-6, ICAM-1, and VEGF, and suppressing ROS production via reduced NADPH oxidase 1 (NOX1) expression. They also demonstrated that GA could downregulate the

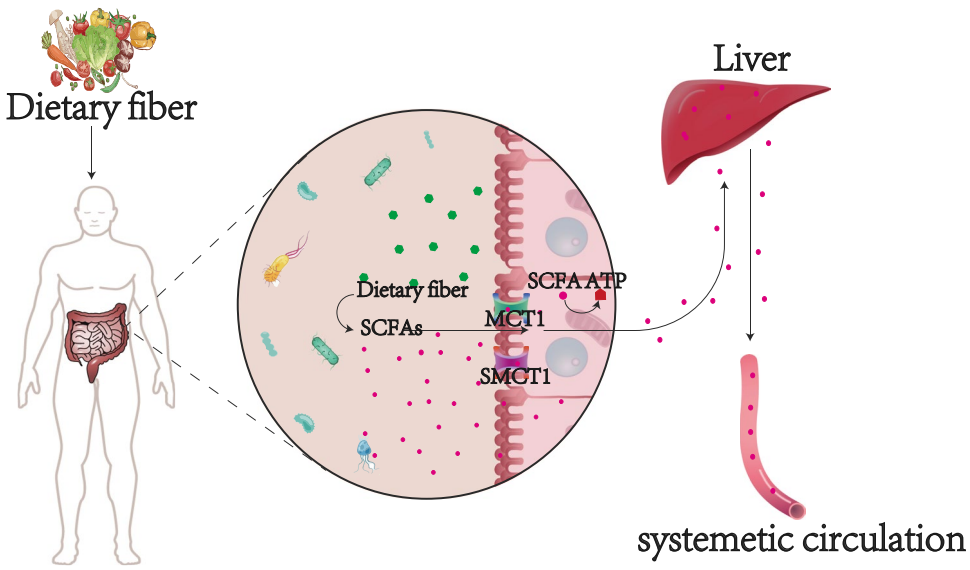

Fig. 1 The transportation and absorption of SCFAs in the body (created with Reactome library, with permission)

expression of ICAM-1 and VEGF by repressing Egr-1 expression, a transcriptional factor recognized as a mediator of MI-related inflammation and cellular injury [44].

Gossypol acetic acid (GAA), a natural product isolated from the seeds of cotton plants, has been shown to exert anti-oxidative stress and anti-lipid peroxidation effects on rats. Due to its iron-chelating capacity, Lin et al. focused on the benefits of GAA in I/R-induced ferroptosis. The data revealed that GAA preserved H9C2 cells against ferroptotic cell death by reducing the production of malondialdehyde and reactive oxygen species and downregulating the mRNA levels of Ptgs2. Additionally, GAA significantly alleviated myocardial infarct size, abated lipid peroxidation, and reduced ACSL4 and NRF2 expression even in the protein level, indicating that GAA may play a cardioprotective role in ferroptosis-induced cardiomyocyte death [45].

Propionate

As an important intermediate metabolite, propionate participates in the TCA cycle and produces ATP through oxidative metabolism to meet the energy demands of cells. N, S-dipropionyl cysteine ethyl ester (DPNCE), a synthetic bifunctional compound, has the antioxidant effects of cysteine and the anaplerotic effects of propionate. In an ischemia/reperfusion rat model, DPENCE treatment was found to significantly increase the concentrations of arterial propionate and cysteine and myocardial propionate uptake, while it did not affect blood pressure or myocardial contractile function, indicating that there might be other treating targets for propionate [46].

The latest research by Deng et al. demonstrated the critical role of propionate in MIRI. The data showed that Ang II may aggravate MIRI through caveolin-1(CAV-1)/angiotensin-converting enzyme 2(ACE2) axis, and propionate could reverse the exacerbating injury through GPR41, indicating that it is a promising metabolic target for the treatment of MIRI by regulating the intestinal flora [47].

Butyrate

Butyrate is absorbed by intestinal mucosal cells and enters the blood circulation, then enters the liver and participates in the TCA cycle, in which butyrate reacts with other metabolites to produce energy. Butyrate not only provides energy supply, but also affects the blood sugar balance and participates in the process of cell growth and differentiation. Proper butyrate intake can regulate the balance of flora, inhibit the growth of harmful bacteria and promote intestinal peristalsis.

Sodium butyrate, an inhibitor of histone deacetylase (HDAC), has been shown to inhibit the expression of High mobility group box 1 protein (HMGB1) which has an important role in MIRI. Previous studies have demonstrated that HMGB1 promotes cell injury during MIRI and also increases the release of early pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Administration of HMGB1 A box peptide, a specific HMGB1 antagonist, protected myocardium against reperfusion injury and inhibited the release of TNF-α and IL-6 [48, 49]. Therefore, Hu et al. conducted research to analyze the effect of sodium butyrate preconditioning on MIRI. The data showed that pretreatment with sodium butyrate significantly reduced the infarct size of myocardium, in line with the decreased levels of lactate dehydrogenase (LDH) and creatine kinase (CK). In addition, sodium butyrate was found to significantly inhibit the expression of TNF-α, IL-6 and HMGB1 induced by MIRI [50].

Dietary fiber supplementation mediated increase of butyrate shows to be protective against myocardial infarction, hypertension, and other diseases [51, 52]. The activation of G protein-coupled receptors (GPCRs) and the inhibition of HDACs have been the focus of recent studies since SCFAs can act as signaling molecules in both ways. Meanwhile, accumulating studies suggested that the gut-brain neural mechanism may also contribute to the beneficial effects of butyrate [53–55]. The vagus nerve, a major bidirectional connection between the body and the brain, has been the focus in recent researches of the gut-brain axis [56]. As a key member of the gut-brain axis, the vagus nerve innervates many gastrointestinal organs in addition to cardiopulmonary organs such as heart, lungs, aortic arch and trachea [57]. Based on this, Yu et al. conducted a series of studies on the relationship between butyrate and the vagus nerve, which found that butyrate treatment significantly improved myocardial I/R injury via a gut-brain neural circuit, and this cardioprotective effect was likely mediated by suppression of the sympathetic nervous system [58]. In Table 1, we summarized the protective effects and mechanisms of the main SCFAs on injured myocardium.

Therapeutic Intervention

Cardiovascular health factors include cholesterol, blood pressure, and blood sugar control. Despite conventional treatment of MIRI has played a role in clinical practice, many links between SCFAs and cardiovascular health factors make SCFAs a new target for future treatments. Increasing SCFAs content by increasing dietary fiber content and regulating intestinal flora abundance, as well as enhancing intestinal SCFAs absorption efficiency, are currently commonly used strategies.

Table 1 The effects and mechanism of main SCFAs in MIRI

SCFA	Effects	Mechanism	References
Acetate	Normalize postischemic function of heart	Increase glucose oxidation and decrease glycolysis	[41]
	Ameliorate cardiac dysfunction	Modulate the AMPK signaling pathway	[42]
	Protect against oxygen-glucose deprivation/reperfusion-induced injury in H9c2 cells	Inhibit Egr-1	[44]
	Alleviate myocardial infarct size	Increase the protein level of GPX4	[45]
Propionate	Improve I/R injury	Affect CAV-1/ACE2 axis	[47]
Butyrate	Protect myocardium against reperfusion injury	Inhibit the expression of HMGB1	[48, 49]
	Reduce the infarct size	Inhibit the expression of inflammatory mediators	[50]
	Improve I/R injury	Suppress the sympathetic nervous system	[58]

Dietary Interventions

Increasing evidence indicated that diets with low animal protein and high vegetable and fiber intake are associated with the prevention of CVD [59, 60]. Habitual diet plays a critical role in impacting the composition of the gut microbiota and its metabolite. Several diets were designed for intervention of MIRI. The Mediterranean diet (MD), a recognized healthy dietary pattern, is characterized by high-level consumption of cereals, fruit, vegetables and legumes. A cohort of Italian individual study found that regardless of the diet type, subjects who consume more fruit, legumes and vegetables have higher levels of fecal SCFAs. In addition, enrichment of fiber-degrading bacteria in the gut is promoted in habitual vegetarian [61]. A study by Kaye et al. of the effect of lack of prebiotic fiber on cardiac function in mice, revealing that mice with deficient prebiotic fiber predisposed to suffer hypertension and consequential cardiac remodeling, while the impairment could be reversed by reintroduction of SCFAs, indicating the cardioprotective effect of SCFAs and the importance of maintaining a healthy, SCFA-producing microbiota for cardiovascular health [62]. Taken together, it is a promising metabolic intervention of microbiota through consumption of diets rich in diverse vegetable foods.

Probiotics and Prebiotics

Prebiotics are defined as non-digestible food ingredients which can shape the composition and metabolism of gut microbiota, thereby providing health benefits to the host. Probiotics, widely accepted by the public, have exhibited therapeutic effects on some gastrointestinal disorders. Lactobacillus plantarum 299v (Lp299v) is a human commensal that can survive through the gastrointestinal tract without being affected by stomach acid. It is an antioxidant with anti-cancer, anti-inflammatory, anti-obesity and anti-diabetic properties [63]. A series of corresponding researches demonstrated that Lp299v displayed cardiovascular protective effects in mouse models. Based on this, Malik et al. also explored its possible effects on cardiovascular disorders in humans. He conducted a pilot study of 21 men with stable coronary artery disease (CAD) who were daily supplied with Lp299v for six weeks, showing that Lp299v significant enhanced vascular endothelial function and mitigated inflammation in men with CAD. This phenomenon indicated that circulating gut-derived metabolites, especially SCFAs, were likely contributing to these improvements [64]. Tunapong et al. conducted a series of studies on the role of prebiotics, probiotics, and synbiotics in ameliorating cardiac sympathovagal imbalance in obese insulin-resistant rats, finding that they shared similar efficacy in improving insulin resistance, reducing dyslipidemia and BP, attenuating LV dysfunction via improving cardiac mitochondrial dysfunction and reducing oxidative stress [65]. Tang et al. explored that infiltration of $CX3CR1^{+}$ monocytes to the peri-infarct zone was decreased in antibiotic-treated (ABX) mice, while the mice survival rate was improved after transplantation of monocytes or dietary SCFA supplementation. He also found that supplementing ABX mice with a Lactobacillus probiotic before MI surgery recovered myeloid cell proportions, altered the composition of SCFAs towards propionate, thereby displaying cardioprotective effects [66]. Chen et al. revealed that the composition of the gut microbiota in people with heart failure is different from those with healthy status, and characterized with reduction in SCFA-producing bacteria in patients and increase in the microbial potential to produce trimethylamine N-oxide (TMAO) and lipopolysaccharides [67]. In conclusion, these studies shed light on the potential modulatory effects of probiotics and prebiotics on microbiome, and SCFAs may provide promising treatment strategies for MIRI. However, more researches are needed to explore the mechanism and possible adverse effects of probiotics and prebiotics in treating MIRI.

Conclusion

Accumulating evidence suggests that SCFAs play important roles in CVDs. The SCFAs mediated regulation of intestinal barrier to modulate the inflammatory response of the

immune and surrounding tissues plays important roles in the myocardial infarction or HF progression. Their energy homeostasis enhancing and lipid buffering capacity via metabolic regulation and gut-brain axis also make a great contribution to CVDs progression.

In this review, we clarified the critical roles of the different SCFAs in MIRI. Acetate, propionate, and butyrate, the predominant SCFAs, displayed anti-inflammatory and metabolic regulatory functions during MIRI. Recent studies also showed that acetate could exhibit anti-ferroptotic feature [45], propionate could mitigate MIRI by suppressing Ang II through CAV-1/ACE2 axis via GPR41 [47], and butyrate could ameliorate MIRI by pressing sympathetic nervous system via gut-brain neural circuit [58]. We also summarized the related studies of SCFAs interventions. Consuming fiber-rich foods or supplementing SCFA-producing probiotics and prebiotics can make some contributions in improving cardiac function.

However, there are still some limitations regarding to the direct participatory role of SCFAs on MIRI. Existing studies on SCFAs are mostly restrict to phenotypes, is also lack of clinical evidences. It is noteworthy that supplementation of SCFAs exists as a compound instead of a monomer. Whether their effectiveness would be affected through digestion remains unclear. In recent years, many studies have confirmed that the active ingredients of traditional Chinese medicine (TCM) as a therapeutic intervention to treat CVDs by interacting with microbial metabolites. Studies have shown that TCM gradually plays an important role in the progression of metabolic syndrome by regulating the level of intestinal flora SCFAs, but there is a lack of relevant studies on MIRI. Additionally, current researches have focused on increasing the concentration of SCFAs in the peripheral circulation to mitigate MIRI through the intestinal flora, whereas the specific mechanisms by which SCFAs enter the intracellular mitochondria to act have not been elucidated. Existing therapeutic modalities are not sufficiently associated with the pathophysiologic mechanisms of MIRI. Due to these limitations about the current research of SCFAs, it would be urgently needed to conduct further researches on the intrinsic mechanisms of most individual SCFAs and how they function in different types of cells in the heart. Additionally, the structural analysis of effective components also requires more research.

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Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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