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Cardiac Energy Metabolism: A Potential Novel Therapeutic Target in the Treatment of Ischemic Heart Diseases

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ABSTRACT

Despite decades of research, ischemic heart diseases (IHD) remain a major health problem in Jordan and worldwide. Ischemia is associated with serious and deleterious perturbations in biochemical, and functional characteristics of the heart. During ischemia, the heart increased it is reliance on glycolysis as an ultimate source for ATP production. However, fatty acid β-oxidation rates significantly increased at reperfusion. The metabolic dysregulation negatively impact both cardiac function and efficiency. Current treatment approaches of IHD mostly focus on increasing oxygen supply (e.g. thrombolytic agents) or decreasing oxygen demand (e.g. beta-blockers). However, therapeutic interventions aiming at improving cardiac efficiency of oxygen utilization have not gained enough interest. In this review, this review focused on the metabolic pathways of fatty acid and glucose oxidation, as well as the metabolic phenotype of the ischemic heart. Furthermore, this review will discuss the mechanisms of metabolic modulators and how they can improve cardiac function in ischemia-reperfusion condition.

Keywords: MicroRNAs, Obesity, Diabetes, Fatty acid oxidation, MED13, Lipid metabolism.

1. INTRODUCTION

Ischemic heart diseases are major health concerns that have reached epidemic proportions locally and worldwide. Myocardial ischemia in specific is one of the major causes of morbidity and mortality in Jordan[1]. It is associated with serious and deleterious perturbations in biochemical and functional characteristics of the heart. Particularly, energy metabolism is markedly altered [2]. In contrast to the normal heart, where mitochondrial oxidative phosphorylation of glucose and fatty acids accounts for 90% of myocardial adenosine triphosphate (ATP) production, the dynamic balance between glucose and fatty acid oxidation is perturbed in ischemic and post-ischemic hearts[3,4]. The metabolic dysregulation that lead to imbalance between glucose and fatty acid oxidation negatively impact both cardiac efficiency and function[5,6]. Although classical pharmacological and non-pharmacological treatment strategies can improve cardiac function and prolong survival in patients with ischemic heart diseases, these attempts are ultimately inadequate to prevent disease progression. Given the large number of patients with ischemic heart diseases, it is important to find novel therapeutic strategies to treat ischemic heart diseases and to prevent its long-term complications such as ischemia-induced ventricular remodeling, and heart failure.

Methods

A literature search was performed using two data electronic data bases (PubMed and web of science) without any limitations on the publication dates. Key search terms were used to identify relevant studies "metabolic modulator", "cardiac energy metabolism",

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"heart ischemia". Furthermore, keywords about animal models of ischemia-reperfusion, and obesity are used to include articles not found in the initial search. In addition, references of the included articles were examined to identify additional relevant references.

1. Cardiac Energy Metabolism

1.1 Energy metabolism in the heart

The heart must continuously generate large amounts of adenosine triphosphate (ATP) to sustain contractile function[6]. There are essentially no ATP reserves in the heart, and if myocardial ATP synthesis ceased, contractile function would fail within 5-6 heart beats[6,7]. The continuous synthesis of ATP in the heart is primarily met by the metabolism of fatty acids and carbohydrates (Fig.1).

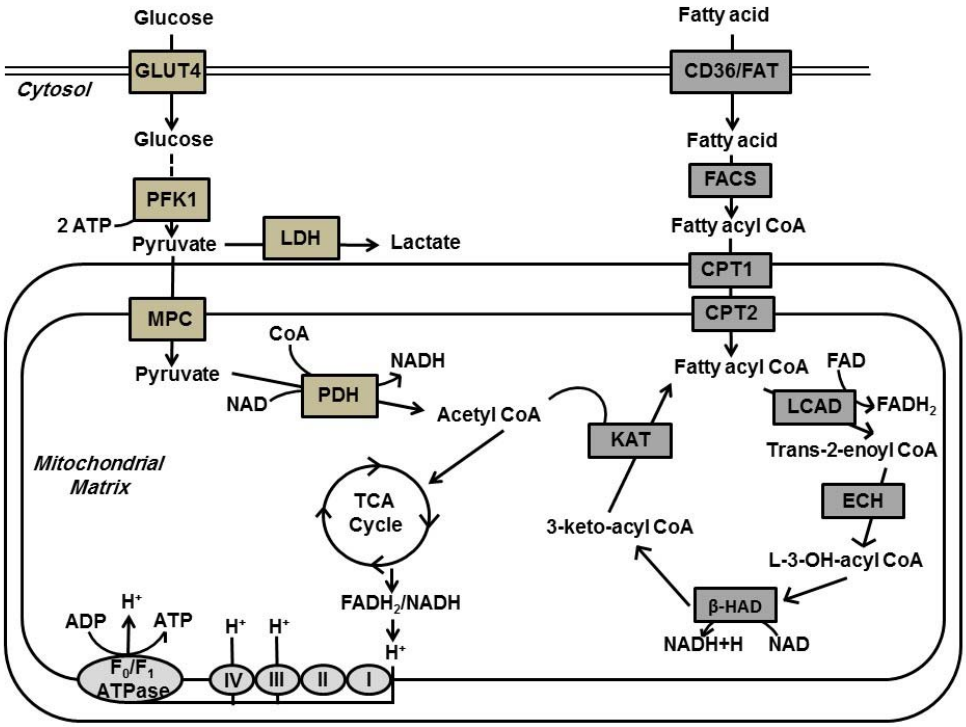

Figure 1: Overview of glucose and fatty acid metabolism

However, depending on availability the heart can also use ketones and amino acids as energy sources[6]. In the adult heart over than 90% of the ATP supply is generated from mitochondrial oxidative phosphorylation, with the remainder originating from glycolysis[8-10]. The majority of this mitochondrial ATP production normally originates from fatty acid β-oxidation. However, the heart can rapidly switch to other fuel sources (such as glycolysis and carbohydrate oxidation) depending on several factors, which includes contractile demand, nutritional status, hormonal influences, oxygen supply, transcriptional/translational and post-translational control of energy metabolic pathways, and/or the presence of underlying cardiac diseases[6-10].

Myocardial ischemia is a stress form on the heart in which energy metabolism is profoundly altered, due to a mismatch between energy supply and energy demand[4,5].

The causes of cardiac dysfunction and cell death that occur during and following myocardial ischemia are complex and multifactorial. However, it is now becoming clear that, in addition to the supply of energy to the heart, the source of energy used during and following myocardial ischemia also has a significant impact on the degree of ischemic injury [4,5,11,12]. Thus, optimization of energy metabolism is emerging as a novel approach for treating myocardial ischemia. Nonetheless, to maximize this potential therapeutic approach for treating ischemic heart disease, it is important to have a better understanding of how energy metabolism is controlled in the aerobic and ischemic heart, which is the primary focus of this review.

1.2 Fatty acid β-oxidation in the heart

Fatty acids β-oxidation is a major source of energy for the adult heart [6]. Fatty acids which are either free fatty acids bound to serum albumin, or fatty acids released from triacylglycerol (TG), enter the cardiomyocyte either by a carrier mediated pathway or facilitated diffusion. Once in the cytoplasm, fatty acids are converted into fatty acyl CoA esters by fatty acyl CoA synthetase[13]. The fatty acid moiety from fatty acyl CoA is then transferred to carnitine and is taken up into the mitochondria by the carnitine shuttle, carnitine palmitoyltransferase (CPT) 1 and 2 where it is converted back to long chain acyl CoA[6]. Once inside the mitochondria, fatty acids undergo β-oxidation. This oxidative process produces acetyl CoA that is used by the tricarboxylic acid (TCA) cycle to produce reducing equivalents that are used by the electron transport chain (ETC) for production of ATP [6].

A key site of fatty acid β-oxidation regulation in the heart is malonyl CoA inhibition of CPT1[14,15]. CPT1 inhibition results in decreased fatty acid uptake into the mitochondria, thereby reducing fatty acid β-oxidation[14,15]. In fact, the turnover of malonyl CoA is quite rapid[16]. The biosynthesis of malonyl CoA is controlled by acetyl CoA carboxylase (ACC), while its degradation is mediated by malonyl CoA decarboxylase (MCD)[17]. Two isoforms of acetyl CoA carboxylase, ACC1 and ACC2, are responsible for malonyl CoA production in the heart[18,19]. Various studies have provided direct evidence that ACC is an important regulator of fatty acid oxidation[18-20]. Increases in ACC activity increases malonyl CoA levels, and decreases cardiacfatty acid β-oxidation, while decreases in ACC activity and malonyl CoA increase fatty acid β-oxidation[18-20]. Studies in ACC2 deficient mice have confirmed that ACC2 is a key regulator of fatty acid β-oxidation in muscle[21]. In mice with a cardiac ACC2 deficiency a significant increase in cardiac fatty acid β-oxidation rates occurs[22].

Malonyl CoA decarboxylase (MCD) is primarily responsible for malonyl CoA degradation in the heart[6,16]. Although MCD was originally reported to be solely a mitochondrial enzyme in mammalian cells, it is also found in the cytoplasm and peroxisomes[24]. Since the initial identification of MCD in cardiac muscle, follow-up studies have shown that high MCD activity is associated with higher rates of fatty acid β-oxidation (primarily due to a decrease in malonyl CoA levels), in conditions such as fasting, diabetes, and ischemia[23-26].

1.3 Carbohydrate metabolism in the heart

Glucose and lactate are two other major sources of ATP for the heart[6]. Glucose use by the heart originates either from endogenous glycogen stores, or is transported into cardiac myocytes via glucose transporter 1 (GLUT1) and GLUT4[6,16]. The first part of the glucose metabolic pathway, glycolysis, is capable of synthesizing ATP in the absence of oxygen. Although glycolysis normally accounts for less than 10% of the heart's ATP production, its contribution to ATP production can increase during times of stress, such as during ischemia[6-9]. There are several key sites of regulation of flux through glycolysis, which includes glucose transport, supply of glucose from endogenous glycogen stores, initial phosphorylation of

glucose by hexokinase, phosphofructokinase-1 (PFK-1), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and pyruvate kinase[27].

The oxidation of pyruvate, derived either from glycolysis (glucose oxidation) or from lactate (lactate oxidation), accounts for the majority of carbohydrate-derived ATP [6,27]. The rate-limiting step for glucose and lactate oxidation is flux through the pyruvate dehydrogenase (PDH) complex[29]. PDH is regulated both by substrate/product ratios and by covalent modifications[29]. PDH activity is decreased by increased ratios of mitochondrial NADH/NAD^+ and acetyl-CoA/CoA[17]. Covalent modifications include phosphorylation and recently suggested acetylation[6,27,30]. Dephosphorylation and deacetylation of PDH is positively related to PDH activity, whereas phosphorylation and acetylation of PDH decreases its activity, thereby restricting the oxidation of pyruvate[27,30]. Increased PDH kinase (PDK) protein expression, which results in increased PDH phosphorylation, is a key mechanism involved in reduced PDH flux and glucose oxidation[31].

1.4 Energy production in the heart during and following ischemia

Ischemic heart disease has a profound effect on cardiac energy metabolism (Fig 2).

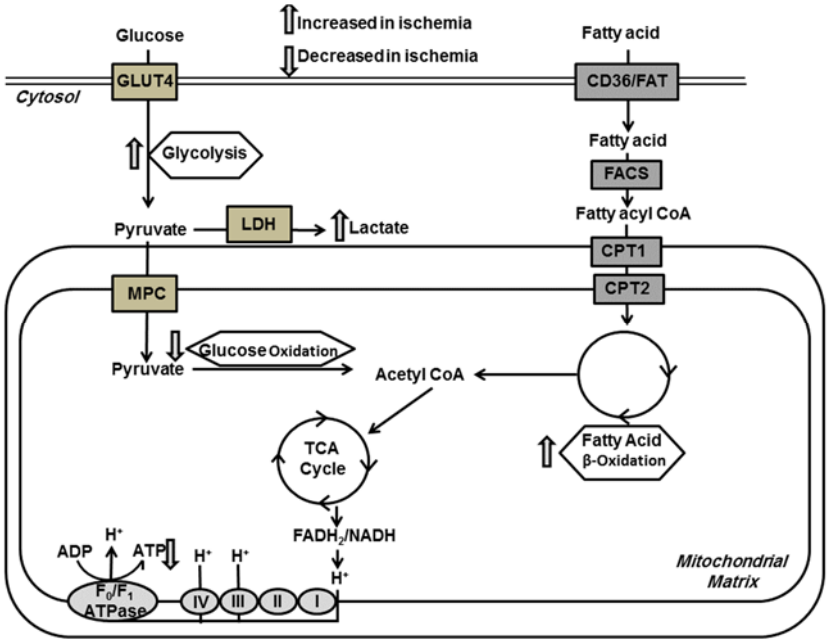

Figure 2: Major changes of cardiac energy metabolism during ischemia

Interruptions in O_2 and energy substrate supply to the heart result in a rapid loss of contractile function, depletion of high energy phosphates, and disturbances in ionic homeostasis[4-6,9]. Decreased O_2 supply to the heart inhibits both mitochondrial fatty acid and carbohydrate oxidation, thereby decreasing ATP production. Glycolysis becomes a very important source of energy in the ischemic heart, due to its ability to generate ATP in the absence of O_2 [32]. Increased glycolytic ATP helps to maintain/correct ionic homeostasis during mild to moderate ischemia. However, if glycolysis is uncoupled from the subsequent oxidation of pyruvate (due to reduced mitochondrial oxidative

metabolism), lactate, and H^+s will accumulate in the ischemic heart. Depending on the severity of ischemia, this can result in a substantial decrease in myocardial pH, which can result in the accumulation of Na^+ and Ca^{2+} in the myocardium[4-7,11,33].

If the ischemic myocardium is reperfused such as occurs during mechanical or pharmacological revascularization post-myocardial infarction (MI), a recovery of mitochondrial oxidative metabolism will occur in reversibly injured myocardium. However, the ATP needed for both mechanical work, as well as for the re-establishment of Na^+ and Ca^{2+} homeostasis, is primarily met by a rapid restoration of fatty acid β-oxidation to near pre-ischemic rates, which results in a corresponding decrease in glucose oxidation (via the Randle Cycle)[6,34,35]. Moreover, glycolysis rates remain high during reperfusion[4,7,12]. This increased uncoupling of glycolysis from glucose oxidation increases H^+ production. Unfortunately, the use of energy to re-establish altered ionic imbalances resulting from elevated H^+ production decreases cardiac function and efficiency[4,7,12,34]. In support of this concept, therapeutic strategies that inhibit fatty acid β-oxidation and increase glucose oxidation lessen the uncoupling of glycolysis from glucose oxidation, decrease H^+ production, and increase cardiac efficiency.

Several mechanisms contribute to this metabolic phenotype in the ischemic heart. Circulating fatty acid levels are elevated during and following ischemia, due in part to the activation of a stress-induced "fight or flight" sympathetic response [34,36]. Fatty acid β-oxidation rates also increase in response to decreased malonyl CoA levels, which was shown to occur secondary to AMPK activation and to decreased ACC activity during ischemia[14,16,26]. Ischemia-induced activation of AMPK has detrimental consequences, fatty acid β-oxidation recovers and provides the majority of the acetyl CoA for the TCA cycle at the expense of glucose oxidation, and glycolytic rates remain elevated[37,38]. As a result, proton production from uncoupled glucose metabolism persists into reperfusion, impairing pH recovery.

MCD inhibition is one approach to prevent the detrimental effects of high levels of fatty acids in the ischemic heart[16]. In MCD deleted (MCD-/-) mice, levels of cardiac malonyl CoA were significantly increased[23-26]. When subjected to reperfusion following global no-flow ischemia, hearts from MCD-/- mice exhibit an enhanced functional recovery compared to wild type (WT) littermate controls, due to an increased glucose oxidation rate[25]. Furthermore, novel MCD inhibitors increase recovery of cardiac function in rat hearts subjected to ischemia/reperfusion (I/R), and in pig hearts subjected to an in vivo demand induced ischemia[39]. Furthermore, it has been recently shown that MCD deletion reduced infarct size in mice subjected to an in vivo I/R protocol[12].

The importance of high fatty acid β-oxidation rates and low glucose oxidation rates to ischemic injury is supported by clinical studies showing that overcoming fatty acid inhibition of glucose oxidation improves both cardiac function and cardiac efficiency. As such, drugs that inhibit fatty acid β-oxidation are a new approach for treating ischemic heart diseases.

1.5 Energy metabolism in the heart following chronic ischemia

Ischemic damage to heart muscle (such as can occur following an acute MI) not only decreases the amount of viable heart muscle, but also result in adverse remodeling to the remaining viable myocardium, leading to the development of heart failure [2,3,6]. It is also clear that alterations in energy metabolism occur in this "remodeled" myocardium. As heart failure progresses, cardiac energetics become compromised, resulting in decreased myocardial phosphocreatine content[40]. Defects in the rates of O_2 consumption and mitochondrial ETC activity also

occur in advanced stages of heart failure, which decrease ATP generation[41]. Thus, the failing heart in chronic ischemia is often thought of as an "engine out of fuel"[42].

Alterations in energy substrate metabolism accompanying ischemic-induced heart failure are complex, and are partly dependent on the stage/severity of the syndrome. There is not a clear consensus as to what changes in fatty acid and carbohydrate oxidation occur in heart failure. Fatty acid β-oxidation rates have been shown to be increased [43], decreased [44], or unchanged in patients with HF [45]. Similar to what has been observed with fatty acid β-oxidation rates, there is a lack of consensus involving the changes in glucose oxidation rates in the chronically ischemic failing heart. However, an elevation in glycolytic rates in the chronically ischemic heart is consistent[11,12,32,46]. Results from Lopaschuk lab reported increased uncoupling of glycolysis from glucose oxidation, accompanied by an enhanced H^+ production, and decreased efficiency of hearts subjected to permanent coronary artery ligation (CAL) [47]. Alterations in cardiac fatty acid and glucose utilization in heart failure patients may negatively impact cardiac efficiency, and may thus represent a viable therapeutic target.

Studies involving heart failure secondary to pressure overload also show variable results. In a rat model of severe end-stage heart failure, a depression in overall oxidative metabolism is seen, as well as a decrease in both fatty acid (i.e. oleate) and glucose oxidation[48]. This contrasts with findings in the canine model of severe heart failure induced by rapid ventricular pacing, where decreased rates of fatty β-oxidation and increased rates of glucose oxidation are observed[49]. Furthermore, hypertrophic hearts from spontaneously hypertensive rats have decreased mitochondrial oxidation and increased glucose uptake (suggesting increased glycolysis)[50]. Interestingly, stimulation of glucose oxidation in these rats not only improves overall cardiac energetics, but overall cardiac function as well. A study in which fatty acid β-oxidation was decreased by heterologous deletion of CPT-1β in mice was also associated with a worsening of cardiac hypertrophy and function following a transverse aortic constriction (TAC)[51]. A recent study by Rong Tian's group also showed that cardiac deletion of ACC2 (which decreases malonyl CoA and increases fatty acid β-oxidation) could also improve cardiac energetics and function in TAC mice[52]. Moreover, recent studies observed that both glucose oxidation and fatty acid β-oxidation decrease very early during the development of cardiac hypertrophy in mice subjected to an abdominal aortic constriction (AAC), leaving the heart in an energy deficient state[53,54].

2. Novel Treatment strategy using metabolic modulators

2.1 Treating ischemic heart diseases by targeting mitochondrial oxidative phosphorylation

The excessive reliance on fatty acids as an energy source contributes to a decrease in cardiac efficiency in the reperfused ischemic heart [3-7]. The main consequence of high fatty acid β-oxidation rates is a parallel inhibition of glucose oxidation, despite the presence of high glycolysis rates[3-7]. The subsequent uncoupling of glycolysis from glucose oxidation results in lactate and H^+ accumulation during reperfusion, which decreases cardiac efficiency[34]. A considerable amount of data from clinical and experimental studies confirms the beneficial effects of targeting cardiac energy metabolism as an approach to treat ischemic heart disease[3-15]. Pharmacological interventions aimed to decrease fatty acid β-oxidation, while increasing glucose oxidation may provide a novel therapeutic strategy to increase mitochondrial ATP production, cardiac function, and efficiency in acute and chronic ischemic/reperfused heart. The main targets for metabolic modulators are pathways involved in fatty acid availability, uptake, and β-oxidation, the rate limiting

enzyme of glucose oxidation (PDH), and Glucose–insulin–potassium (GIK) therapy (Fig 3).

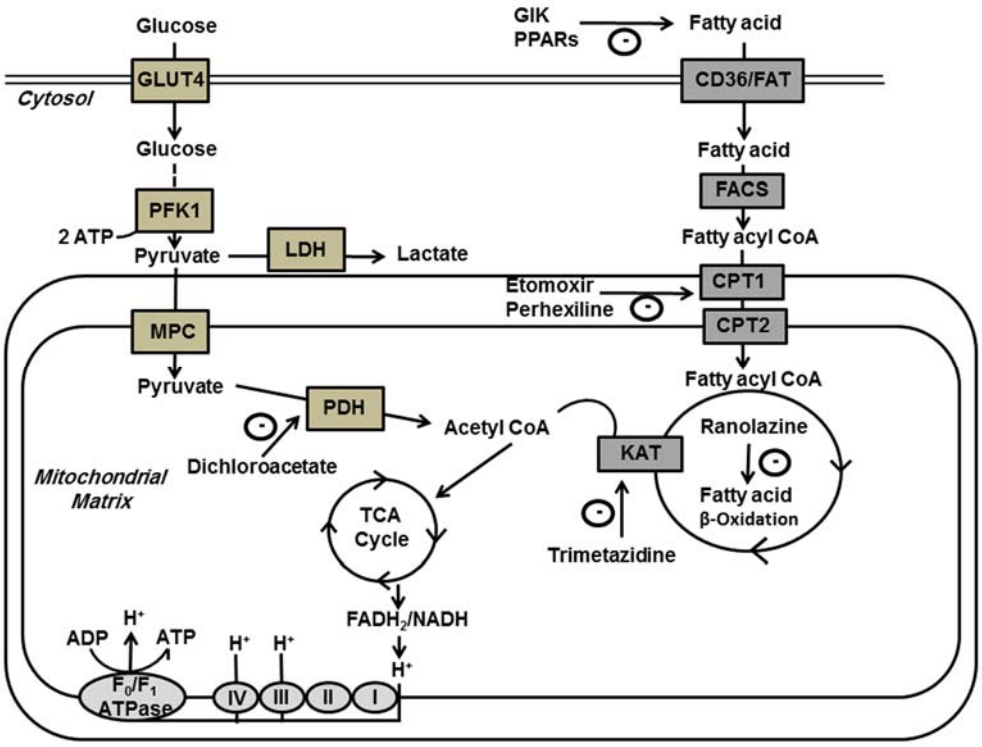

Figure 3: Main enzyme targets of metabolic modulators

2.2 Peroxisome proliferator activated receptor (PPAR) ligands

The peroxisome proliferator-activated receptors (PPARs) considered the main transcriptional regulators of fatty acid β-oxidation[55]. Various types of ligands are able to bind and modulate the activity of PPARα, δ, and γ including fatty acids, and the genes regulated by each type of the PPARs vary depending on the tissue type[56]. For example, skeletal muscles PPARδ, but not PPARα, upregulates the protein expression of CPT1[57]. PPAR isoforms are also differentially expressed between various tissue types[56]. While PPARδ protein tends to be ubiquitously expressed, PPARα is predominantly expressed in high metabolic tissues (i.e. heart, skeletal muscle, and liver), while PPARγ is predominantly expressed in adipose tissue[55-58].

The fibrates class of drugs targets PPARα[59]. Fibrates decrease circulating free fatty acids, primarily by upregulation of hepatic fatty acid β-oxidation enzymes[60]. It is suggested that the decrease in circulating plasma free fatty acids would decrease cardiac fatty acid uptake and oxidation, which may explain the beneficial effects of using fibrates in the treatment of ischemic heart diseases. Indeed, previous studies showed that fibrates can reduce the size of cardiac tissue infarction and enhance the recovery in various post-ischemic animal models [61]. This was explained by the ability of the fibrates to increase the use of fatty acid by extra-cardiac tissues such as liver, which contributes to the noticed reduction in myocardial fatty acid β-oxidation accompanied by increases in cardiac glucose oxidation rates, eventually leading to enhanced post-ischemic recovery[62]. In support of this notion, a

recent study by Song et al. observed a cardioprotective effect of PPARα ligand (WY-14643) in rat model of ischemia-reperfusion injury [63].

Another important PPAR ligand is the antidiabetic drug thiazolidinedione (TZD), which can specifically activate PPARγ. Previous animal and clinical studies showed that TZD admistration lowers plasma free fatty acids levels; in addition, TZD increases myocardial glucose uptake and oxidation[64-66]. The switch in substrate preference from fatty acids to glucose utilization has a potential therapeutic value in ischemic and post-ischemic heart tissue. In support, treating various animal models of ischemia-reperfusion (I/R) with TZD protect myocardium from I/R injury[64-67].

Moreover, oral administration of rosiglitazone (TZD derivatives) improves post-ischemic recovery in ischemia-reperfusion rat model[67].

On the other hand, safety issues have been raised based on clinical and experimental reports, PPARγ transgenic mice developed dilated cardiomyopathy [68]. In addition, recent clinical trials linked the use of TZD to the exacerbation of heart failure in diabetic patients. Prospective randomized clinical trial (PROFIT-J study) demonstrated that the long-term use of pioglitazone did not lead to any reductions in cardiovascular events[69]. However, a recent open-label extension study indicated that the use of lobeglitazone has a beneficial clinical benefit on glucose and lipid levels, and safety on long term use[70]. Thus, safety of using TZDs in the treatment of ischemic heart diseases is an important issue that needs further evaluation.

2.3 Carnitine palmitoyl-transferase I inhibitors

The rate limiting enzyme of fatty acid uptake is CPT1. Various important CPT1 inhibitors have been developed and used in the treatment of ischemic heart diseases, such as etomoxir[71]. In rat heart, administration of the CPT1 irreversible inhibitor etomoxir results in significant decrease in cardiac fatty acid β-oxidation concomitant with an increased levels of glucose uptake and oxidation, which lead to improvement in myocardial function and metabolism post infarction in both ischemic and diabetic models[72,73]. However, positive outcomes of etomoxir use could not be translated in clinical trials, etomoxir for the recovery of glucose oxidation (ERGO) study indicates high levels of liver enzymes and no beneficial effects in echocardiographical parameters of congestive heart failure patients[74]. Other CPT 1 inhibitors like perhexiline showed anti-anginal effects when used in low doses, however, high doses of perhexiline were found to be toxic due to phospholipid accumulation[75].

2.4 Fatty acid β-oxidation enzyme partial inhibitors

Trimetazidine and ranolazine are partial fatty acid β-oxidation inhibitors that competitively inhibit fatty acid β-oxidation enzymes which reciprocally stimulate cardiac glucose oxidation, this improves the coupling between glycolysis and glucose oxidation which should be beneficial in the setting of ischemia. Recent clinical trials showed promising results regards the use of trimetazidine in the treatment of ischemia[76,77]. Intravenous administration of trimetazidine improves cardiac function, decreases nitrates consumption, and enhances the resolution of ST-segment elevation in acute myocardial infarction[78]. Trimetazidine has also been shown to have comparable effectiveness as thiotriazoline in treating stable angina pectoris[79]. Combination treatment with metoprolol markedly decreases recurrence of anginal attach, nitrates consumption, and the grade of anginal pain in patients with stable angina[80].

Ranolazine attenuates postischemic myocardial dysfunction and reduces ischemic zone in rabbits, by inhibiting late sodium current channels. Interestingly, ranolazine is approved in clinical use for the treatment of

stable angina[81]. In patients with chronic angina and acute coronary syndrome, ranolazine reduced recurrent ischemic events regardless of revascularization[82]. Both anti-ischemic and anti-arrhythmic additive effects of ranolazine were shown in anginal patients when added to other aniti-aniginal drugs such as atenolol, amlodipine, or diltiazem[83].

2.5 Glucose oxidation activators

Direct stimulation of the rate limiting enzyme of glucose oxidation pyruvate dehydrogenase complex (PDC) is another applicable approach to treat ischemic heart diseases. PDC can be indirectly activated by inhibiting its kinases which lead to a decrease in PDH phosphorylation and hence increasing PDH activity. Dichloroacetate (DCA) stimulates mitochondrial glucose oxidation via the inhibition of PDK activity. Post-ischemic recovery and myocardial function was improved by DCA treatment in various animal models[84-88]. Moreover, DCA attenuates cardiac contractile dysfunction in ischemia-induced Ventricular fibrillation rat model[86]. In vivo, direct stimulation of glucose oxidation in mice with dichloroacetate, results in a marked decrease in infarct size following left anterior descending coronary artery ligation[12]. Clinical application of DCA is very limited due to the fact that the half-life of DCA is very short[88]. However, in a small clinical trial, nine patients with angina were injected with a dose of 35 mg/Kg of DCA intravenously before cardiac catheterization[89]. Left ventricular stroke volume and cardiac efficiency were significantly improved in anginal treated patients. This result was attributed to the improved coupling between glycolysis and glucose oxidation and decreased levels of plasma lactate concentration[89].

2.6 Glucose–insulin–potassium (GIK) therapy

Cardioprotective effects of GIK was originally proposed as increasing glucose utilization and lowering free fatty acids level would shift the cardiac energy metabolism toward glucose metabolism in the setting of ischemia[90]. The shift toward glucose preference showed to be beneficial in various models of myocardial infarction, GIK infusion limits heart tissue infarct size and improves post-ischemic cardiac function[91,92]. Furthermore, GIK reduces infarct size in rats subjected to 30 min regional ischemia when administered at the time of coronary reperfusion[91]. There is no consensus regarding the beneficial effects of GIK therapy in myocardial ischemia[93]. Safety and efficacy of GIK therapy was recently evaluated in coronary artery bypass graft surgery and percutaneous coronary intervention, GIK did not show obvious cardioprotective effects in ischemic patients[94]. Moreover, more clinical complications were reported in percutaneous coronary intervention patients treated with GIK compared to control [95]. This may be related to the complex effects of insulin on hall body energy metabolism, and on levels and availability of various metabolites including glucose, and free fatty acids. Further evaluation of GIK therapy is needed with special attention to doses, types of patient's sample, and the time of drug admistration.

Summary and Conclusions

An excessive reliance on fatty acids as an energy source contributes to a decrease in cardiac efficiency in the reperfused ischemic heart. The main consequence of high fatty acid β-oxidation rates is a parallel inhibition of glucose oxidation, despite the presence of high glycolysis rates. The subsequent uncoupling of glycolysis from glucose oxidation results in lactate and H^+ accumulation during reperfusion, which decreases cardiac efficiency. There is ongoing effort to validate metabolic modulators as a novel therapeutic approach in the treatment of ischemic heart diseases. A propitious strategy of inhibiting fatty acid β-oxidation and improves the coupling between glycolysis and glucose oxidation by targeting the rate limiting steps of fatty acid and glucose oxidation. Enzyme targets include CPT1, PPARs, and PDC, as well as modulation of insulin, glucose, and free fatty acid levels. Among the limitations of using this strategy is the concern

about the toxic accumulation of the non-oxidized fatty acids in vital tissues such as adipose, liver, and the heart. The safety of using metabolic modulators in the short or long term treatment of ischemic heart diseases is an important issue that need to be addressed in the future research. Nonetheless, optimization of energy metabolism is emerging as a novel approach for treating myocardial ischemia.

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عمليات القلب الأيضية: كعلاج حديث محتمل لانقطاع التروية الدموية عن عضلة القلب

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ملخص

بالرغم من السنوات الطويلة من البحث العلمي، ما تزال أمراض القلب التاجية من أهم المشاكل المرضية في الأردن والعالم. انقطاع التروية الدموية عن عضلة القلب يؤدي إلى اختلالات أيضية ووظيفية، يزداد اعتماد القلب وبشكل ملحوظ على استخدام الجلوكوز كمصدر أساسي لإنتاج الطاقة.

وبالرغم من ذلك، فإن معدلات أكسدة الأحماض الدهنية يتزايد باضطراد عند استعادة التروية الدموية لعضلة القلب، كل هذه التغييرات في عمليات الأيض لها تأثيرات سلبية على وظيفة وكفاءة العضلة القلبية. تعتمد طرق العلاج الحالية لهذه المشكلة على زيادة تزويد عضلة القلب بالأكسجين أو تقليل الإجهاد على القلب. ولكن زيادة كفاءة القلب في استخدام الأكسجين المتوفر لم تعطِ لغاية الان القدر الكافي من البحث والتركيز بالرغم من أهميتها. في هذه المراجعة العلمية، سيتم التركيز على أهم العمليات الأيضية في القلب وطبيعة التغييرات التي تحدث خلال فترة انقطاع التروية الدموية عن العضلة القلبية. كما سيتم مناقشة أهم الطرق العلاجية الحديثة التي تستهدف تغيير العمليات الأيضية للقلب والتي تؤدي إلى تحسين وظائف القلب خلال وبعد انتهاء انقطاع التروية الدموية.

الكلمات الدالة: السمنة، السكري، عمليات القلب الأيضية.

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