The Roles of Thiamine in Myocardial Infarction Possible Genetic and Cellular Signaling Mechanisms

Khanh vinh quốc Lương
Vietnamese American Medical Research Foundation
Westminster, California, United States

Lan Thị Hoàng Nguyên
Vietnamese American Medical Research Foundation
Westminster, California, United States
1 Introduction

The relationship between thiamine and myocardial infarction (MI) has been previously reported in the literature. In thiamine-deficient (TD) rats, electrocardiograms (ECGs) showed marked bradycardia as well as T wave and ST-segment changes. These changes usually disappear within a few hours of thiamine administration (Weiss et al., 1938). Beriberi heart disease is a very rare disease caused by thiamine deficiency. Bello et al. (2011) described two patients who presented with fatal cardiac beriberi, an acute MI and extensive colliquiative myocytolysis. Another beriberi heart patient presented with chest discomfort, diffuse ST-segment depression in the ECG with ST-segment elevation in a VR, and rapidly evolving congestive heart failure leading to cardiogenic shock. An emergency coronary angiogram was performed that showed normal coronary arteries. Right heart catheterization showed a high-output state with elevated filling pressures suggesting high-output heart failure. The echocardiography confirmed normal left and right ventricular contraction. After a single dose of intravenous thiamine (100 mg), the patient's hemodynamic status dramatically improved within minutes, allowing for rapid discontinuation of hemodynamic support. Subsequent ECGs showed complete resolution of ST-segment abnormalities. Serial lactate measurements, red blood cell transketolase (Tk) activity, and the thiamine pyrophosphate (TPP) response test were concordant with thiamine deficiency (Loma-Osorio et al., 2011). In addition, beriberi heart patients also demonstrated ST-segment elevation and myocardial damage without coronary artery stenosis, and they improved rapidly after thiamine was administered (Ito et al., 2002; Kawano et al., 2005a). Daly and Dixon (2009) described a patient who presented acutely with Wernicke's encephalopathy, chest pain, ST-segment elevation, and congestive cardiac failure associated with hypotension. Coronary angiography demonstrated no abnormalities. The patient’s hemodynamics improved significantly in the short-term following intravenous thiamine replacement, with complete resolution of all ST-segment abnormalities and normalization of left ventricular function at the six-week follow-up. Interstitial fibrosis and a variation in the size of the myocardial fibers were the main findings after thiamine treatment in these patients (Kawano et al., 2005b). An electron microscopy study on myocardial lesions in TD rats revealed changes in the heart muscle, including a decrease in electron density of the mitochondrial matrix, swelling and rupture of the mitochondria, reduction and derangement of cristae, mitochondrial degeneration, enlargement and destruction of cisternae of the sarcoplasmic reticulum, appearance of large vacuoles, and disappearance of cross striation in myofibrils (Suzuki, 1967). Tylicki et al. (2008) observed the effects of MnCl₂ and TPP changes on EEG and pyruvate dehydrogenase complex (PDC) enzyme activity in the hearts of rats after MI induction. TPP also plays the important role of the positive regulatory effector of pig heart PDC (Strumilo et al., 1999). In isoprenaline-induced MI rats, male rats developed much more severe myocardial necrosis than female rats and concomitantly exhibited significantly greater reduction in myocardial thiamine during acute ischemia compared with female subjects (Wexler and Lutmer, 1973). Two hours before the start of the experiment, thiamine administration (200 mg/kg) substantially reduced the myocardial ischemic lesion in a rat model of experimental MI (Vinogradov et al., 1991). Benfotiamine, a fat-soluble thiamine analog, accelerated the healing of ischemia in the limbs of diabetic mice (Gadau et al., 2006) and improved the functional recovery of the infarcted heart via activation of the pro-survival glucose-6-phosphate dehydrogenase/Akt signaling pathway and modulation of the neurohormonal response (Katare et al., 2010). Thiamine has a cyto-protective effect on cultured neonatal rat cardio-myocytes under hypoxic insult, and it also protects the cardio-myocytes against hypoxia-induced apoptosis (Shin et al., 2004). A single thiamine administration yielded a marked anti-ischemic protective effect on the heart (Shneider, 1991). The beneficial effects of TPP were demonstrated in the treatment of
experimental MI in dogs and rats. There were beneficial hemodynamic changes, including significantly decreased heart rate, increased stroke volume, decreased systemic vascular resistance, and decreased myocardial O₂ consumption, in the MI group compared with the control group (Larriue et al., 1987a & 1987b). Thiamine also has a cardiovascular effect. High doses of thiamine in the dog decreased the mean peripheral pressure by up to 25%, left ventricular pressure by up to 15%, coronary sinus blood flow by up to 31%, and myocardial oxygen consumption by up to 45% (Freye et al., 1976). These findings suggest that thiamine may play a role in MI. In this paper, we further discuss the potential role of thiamine in MI, along with the possible genetic and cell signaling mechanisms involved.

2 The Genomic Role of Thiamine in Myocardial Infarction

2.1 Diabetes Mellitus (DM)

DM increases the risk of cardiovascular disease (CVD) (Bornfeldt and Tabas, 2011). In a systematic review and meta-analysis study, stress hyperglycaemia with MI is associated with an increased risk of inhospital mortality in patients with and without diabetes (Capes et al., 2000). According to the Cooperative Cardiovascular Project, higher glucose levels are associated with a greater risk of mortality in patients without known diabetes compared with diabetics (Kosiborod et al., 2005). In addition, the relationship between thiamine and DM has been previously reported in the literature. Acute TD was reported in a child with diabetic ketoacidosis (Clark et al., 2006). In addition, plasma thiamine levels are decreased by 76% in type 1 diabetic patients and 75% in type 2 diabetic patients and are associated with increased renal clearance and fractional excretion of thiamine (Thornalley et al., 2007). Furthermore, the thiamine transporter protein concentration has been shown to be increased in the erythrocyte membranes of type 1 and type 2 diabetic patients. Therefore, changes in thiamine levels may be masked by an increase in thiamine transporter expression. The dysfunction of endothelial cells has been known to play a major role in both micro- and macro-vascular complications of DM. Diabetic cardiomyopathy can progress to overt heart failure with increased mortality. Thiamine repletion prevented diabetes-induced cardiac fibrosis in an experimental model of diabetes (Kohda et al., 2008). High-dose benfotiamine rescued cardiomyocyte contractile dysfunction in streptozotocin-induced DM (Ceylan-Isik et al., 2006). Additionally, thiamine reversed hyperglycemia-induced dysfunction in cultured endothelial cells (Ascher et al., 2001). Thiamine and benfotiamine have been demonstrated in vitro to counteract the damaging effects of hyperglycemia on cultured vascular cells (Beltramo et al., 2004). In addition, thiamine has been reported to improve endothelial vasodilatation in patients with hyperglycemia (Arora et al., 2006). Benfotiamine and fenofibrate ameliorated the diabetes-induced vascular endothelial dysfunction and nephropathy in rats (Balakumar et al., 2009). Benfotiamine also attenuated nicotine- and uric acid-induced vascular endothelial dysfunction in rats (Balakumar et al., 2008). The daily intake of thiamine was positively correlated with the circulating level of endothelial progenitor cells and vascular endothelial function in type 2 diabetic patients (Wong et al., 2008). Treatment with benfotiamine prevented sodium arsenite-induced vascular endothelial dysfunction and oxidative stress (Verma et al., 2010) and counteracted smoking-induced vascular dysfunction in healthy smokers (Stirban et al., 2012).
2.2 The Renin-Angiotensin System (RAS)

The primary function of the RAS is to maintain fluid homeostasis and regulate blood pressure. The angiotensin-converting enzyme (ACE) is a key enzyme in the RAS that converts angiotensin (AT) I to the potent vasoconstrictor AT II (Johnston, 1994). The activation of the RAS plays a critical role in the pathophysiology of MI by inducing the up-regulation of angiotensin II type 1 receptor, ACE, and collagen I mRNAs (Qi et al., 2012). Elevated baseline plasma renin activity (PRA) is associated with cardiac morbidity and mortality in CAD patients who otherwise have normal left ventricular function and no previous MI or heart failure (Muhlestein et al., 2010). RAS blockade with ACE inhibitors or angiotensin receptor blockers (ARBs) improves cardiac remodeling and outcomes in patients (White et al., 2005). Impaired post-infarction cardiac remodeling in chronic kidney disease is due to an excessive renin release (Ogawa et al., 2012). The inhibition of brain angiotensin III, one of the main effector peptides of the RAS in the brain, attenuates sympathetic hyperactivity and cardiac dysfunction in rat post-MI (Huang et al., 2012). A direct renin inhibitor (DRI), aliskiren, when combined with ACE inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs), improved the extent of myocardial salvage after AMI compared with an ACEI or ARB alone and was associated with a decrease in circulating CD14⁺CD16⁻ monocytes (Ozaki et al., 2012). In a hypertensive rat model subjected to experimental MI, ejection fraction (EF) and left ventricular end-diastolic pressure (LVEDP), key functional indices of heart failure, were improved by treatment with a combination of ACE and direct renin inhibition compared with either agent used alone (Connelly et al., 2013). The RAS activity may be modified by variants of the genes that code for the functional proteins in this pathway. A combination of three common polymorphisms of RAS genes (ACE Ins/Del, angiotensin receptor type 1 [AGTIR] A1166C, and angiotensinogen [ATG] M235T) are linked to adverse events in patients with CAD (Dzielińska et al., 2011). There were significant differences in the distribution of genotypes for the AGT Thr174Met polymorphism between patients with ST-elevation myocardial infarction (STEMI) and healthy subjects. The most powerful predictor of STEMI was the Thr/Met genotype and the Met174 allele of the AGT Thr174Met gene polymorphism (Konopka et al., 2011). The DD genotype of ACE may be a genetic risk factor for cardiovascular events in hypertensive patients in Japan (Kato et al., 2011). There was a significant association between the AGT gene polymorphism and the extent of CAD in Greek patients with a history of MI (Karayannis et al., 2010). Men who carry the ACE DD genotype and have high total cholesterol, high LDL cholesterol, and low HDL cholesterol levels may be predisposed to the development of more severe CAD (Borzyszkowska et al., 2012). An interaction between thiamine and the RAS has been observed. Thiamine attenuates hypertension and metabolic abnormalities in spontaneously hypertensive rats (SHRs). Thiamine repletion down-regulates the expression of angiotensinogen (-80%), ACE (-77%), and angiotensin type 1 receptor (-72%) mRNAs in SHRs (Tanaka et al 2007). In addition, oxidative DNA damage induced by angiotensin II was completely prevented by benfotiamine (Schmid et al., 2008). These observations suggest that thiamine affects ACE activity in MI patients.

2.3 The Reduced Form of the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase (NOX) Enzyme Complex

NOX mediates critical physiological and pathological processes, including cell signaling, inflammation, and mitogenesis, by generating reactive oxygen species (ROS) from molecular oxygen. NOX family enzymes are the major sources of ROS that are implicated in the pathophysiology of many cardiovascular diseases. An increase in NOX2, NOX4, p22phox, and p67phox mRNAs was also found in mice post-MI
(Doerries et al., 2007; Looi et al., 2008; Zhao et al., 2009). NOX5 expression is increased in intramyocardial blood vessels and cardiomyocytes after AMI in humans (Hahn et al., 2012). Furthermore, NOX4 mRNA and protein levels were up-regulated in peripheral muscles after hindlimb ischemia in mice (Craige et al., 2011). Taken together, the aforementioned studies indicate that NOX isoforms are up-regulated at the mRNA level. NOX generated large amounts of ROS, which have direct cytotoxic effects (Elahi et al., 2009; Griendling and FitzGerald, 2003). NOX can also indirectly cause damage by enhancing the inflammatory response (Cave et al., 2006). Specific knock-down of Nox4 mRNA by siRNA caused a decrease in ROS production and a decrease in NOX activity. Moreover, Nox4 silencing decreased PAI-1 expression, release, and activity; p38 MAPK pathways activation; and NFκB activation (Jaulmes et al., 2009). A variant of p22phox, which is involved in the generation of ROS in the vessel wall, is associated with the progression of coronary atherosclerosis (Cahilly et al., 2000). Goliash et al. (2011) demonstrated a protective association between the -930A>G promoter polymorphism in the p22phox gene and the development of MI in young individuals (≤ 40 years). The expression of Nox4 is significantly down-regulated by benfotiamine treatment under both normo- and hyper-glycemic conditions (Frazer et al., 2012). Taken together, these results indicate that thiamine may have a beneficial role in MI by suppressing NOX expression.

2.4 Poly (ADP-ribose) Polymerases (PARPs)

PARPs comprise a family of enzymes that share a conserved catalytic domain and support mono- or poly (ADP-ribosyl) transferase activity using NAD+ as a donor of ADP-ribosyl units. PARPs are involved in a wide range of molecular and cellular processes, including maintenance of genome stability, regulation of chromatin structure, transcription, cell proliferation, and apoptosis (Krishnakumar and Kraus, 2010). AMI-induced increases in plasma tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) are associated with the activation of PARP-1 in circulating mononuclear cells (Yao et al., 2008). The activation of PARP-1 was demonstrated in circulating leukocytes during MI and was inhibited by the administration of the pharmacologic PARP inhibitor INO-1001 in rats (Murthy et al., 2004; Tóth-Zsámbokí et al., 2006). Excessive PARP-1 activation is an important cause of infarction and contractile dysfunction in heart tissue during interruptions of blood flow. A strong association between PARP-1 hyper-activation and impairment of mitochondrial respiratory chain complex I function was demonstrated in reperfused mouse hearts (Zhou et al., 2006). Treatment with the PARP inhibitor PJ34 began 1 week after the onset of diabetes. PJ34 restored normal vascular responsiveness and significantly improved cardiac dysfunction, despite the persistence of severe hyperglycemia. The beneficial effects of PARP inhibition persisted even after several weeks of treatment discontinuation (Pacher et al., 2002). These findings suggest a role of PARP-1 activation in the development of myocardial and endothelial dysfunction in diabetes. PARP-1 contributes to the development of MI in diabetic rats and regulates the nuclear translocation of apoptosis-inducing factor (Xiao et al., 2004). In a rat model of MI, suppression of PARP-1 activation by 3-aminobenzamide demonstrated long-term, beneficial morphological and functional effects in reperfused myocardium (Liaudet et al., 2001). Myocardial post-ischemic injury is reduced by PARP-1 gene disruption (Pieper et al., 2000). In addition, the suppression of TNF-α, IL-10, and nitric oxide (NO) production was found in the absence of functional PARP (Yang et al., 2000). These findings provide direct evidence that PARP activation participates in the development of delayed cell injury and delayed mediator production in myocardial reperfusion injury. Furthermore, thiamine has a cyto-protective effect on cultured neonatal rat cardio-myocytes under hypoxic insult, and it also inhibits PARP cleavage and DNA fragmentation (Shin et al., 2004). Benfotiamine prevents bacterial endotoxin-induced inflammation and PARP
cleavage in mouse macrophage cell lines (Yaday et al., 2010). Adenosine thiamine triphosphate (ATTP), a new thiamine derivative, has been identified in small amounts in the mouse brain, heart, skeletal muscle, liver, and kidneys (Frédérick et al. 2009), and it has been shown to inhibit PARP-1 activity (Tanaka et al., 2011). These findings suggest that thiamine may have a protective role in MI by down-regulating PARP.

2.5 The Advanced Glycation End Products (AGEs)

AGEs are a heterogeneous group of macromolecules formed by the non-enzymatic glycation of proteins, lipids, and nucleic acids. Receptors for AGEs (RAGEs) are multi-ligand receptors, and their ligands are also likely to recognize several receptors that mediate their biological effects (Bierhaus et al., 2006). AGEs act through receptor-independent and -dependent mechanisms to promote vascular damage, fibrosis, and inflammation associated with accelerated atherogenesis. Diabetic RAGE transgenic mice that overexpress RAGE in vascular cells exhibited exacerbation of the indices of nephropathy and retinopathy, which was prevented by inhibiting AGE formation (Yonekura et al., 2005). Diabetic RAGE-null mice were significantly protected from the adverse impact of I/R injury in the heart (Bucciarelli et al., 2008). These findings demonstrate both novel and key roles for RAGE in I/R injury in the diabetic heart. An inverse association between cardiac troponin-I and soluble RAGEs was demonstrated in patients with NSTEMI (McNair et al., 2009 & 2011). Plasma levels of soluble RAGEs are associated with endothelial function and predict cardiovascular events in non-diabetic patients (Chiang et al., 2009), cardiovascular mortality in patients with end-stage renal disease (Koyama et al., 2007), restenosis following percutaneous coronary intervention (McNair et al., 2010), and the development of post-infarction heart failure (Raposeiras-Roubin et al., 2012). The -374T/A RAGE polymorphism is an independent protective factor for cardiac events in both non-diabetic and diabetic patients with CAD (Falcone et al., 2008; Picheth et al., 2007; dos Santos et al., 2005). The -429 T/C and -374 T/A polymorphisms of the RAGE gene are not risk factors for coronary artery disease in a Slovene population with type 2 diabetes and in Chinese patients with diabetic nephropathy (Kirbis et al., 2004; Poon et al., 2010). The RAGE Gly82Ser polymorphism is not associated with cardiovascular disease in the Framingham offspring study (Hofmann et al., 2005). Furthermore, thiamine and a benfotiamine supplement prevented tissue accumulation and increased the urinary excretion of protein glycation and oxidation and nitration adducts associated with experimental diabetes (Karachalias et al., 2010). Karachalias et al. (2005) reported that, in streptozotocin-induced (STZ) diabetic rats, the hydroimidazolone of AGE residues derived from glyoxal and methylglyoxal (G-H1 and MG-H1, respectively) increased by 115 and 68%, respectively, and thiamine and benfotiamine normalized these residues. However, in diabetic-induced rats, N-carboxymethyl-lysine (CML) and N-carboxyethyl-lysine (CEL) residues increased by 74 and 118%, respectively, and only thiamine normalized these residues. Serum markers of endothelial dysfunction, oxidative stress, and AGE increased after a meal high in AGE content, and benfotiamine significantly reduced these effects (Stirban et al., 2006). The addition of benfotiamine enhanced Tk activity and decreased the expression of AGE and RAGE in a peritoneal dialysis model of uremic rats (Kihm et al., 2011). The combined administration of thiamine and vitamin B6 to patients with diabetic nephropathy decreased DNA glycation in leukocytes; however, vitamin B6 alone did not have such an effect (Polizzi et al., 2012). Taken together, these findings suggest that thiamine may have a role in MI by modulating AGEs.
3 The Non-genomic Role of Thiamine in Myocardial Infarction

3.1 Matrix Metalloproteinases (MMPs)

MMPs are proteolytic enzymes that are responsible for remodeling the extracellular matrix and regulating leukocyte migration through the extracellular matrix. This migration is an important step in inflammatory and infectious pathophysiology. MMPs are produced by many cell types, including lymphocytes, granulocytes, astrocytes, and activated macrophages. There is growing evidence that MMPs play an important role in the pathogenesis of MI. In patients with STEMI, circulating levels of MMP-2, measured early and even before reperfusion therapy, are strongly associated with infarct size and LV dysfunction (Nilsson et al., 2012). Increased plasma levels of MMP-9 predict future coronary revascularization in AMI patients (Wang et al., 2013). The MMP-9 and myeloperoxidase (MPO) values in patients with non-obstructive CAD were significantly higher than in patients with no coronary plaque. The levels of MMP-9 and MPO were significantly correlated with the Framingham risk score (Hou et al., 2013). Serum levels of MMP-1, MMP-9, and IL-6 were elevated in patients with CAD and, to a greater extent, in patients with acute coronary syndromes. MMP-1, MMP-9, and IL-6 are associated with more extensive and severe CAD (Tanindi et al., 2011). The MMP-2-1575 (rs243866) gene polymorphism is associated with a risk of developing MI in Mexican individuals (Pérez-Hernández et al., 2012). There is a trend of the MMP-1 and MMP-12 polymorphisms toward the prediction of future clinical events in patients with CAD (Iguirim-Souissi et al., 2011). In an Indian population, serum MMP-3 levels were significantly elevated at the presentation of acute MI compared with controls (36.8%) and were more associated with the 6A genotype (Shalia et al., 2010). A systematic review and meta-analysis provided strong evidence regarding the association of the MMP-3 and MMP-9 genes with the development of CAD (Wang et al., 2011; Niu and Qi, 2012). However, MMP-9 has also been shown to be up-regulated in the TD mouse brain (Calingasan and Gibson, 2000; Beauchesne et al., 2009). Thiamine prevents diabetes-induced cardiac fibrosis and decreases MMP-2 activity in the heart of diabetic rats (Kohda et al., 2008). Moreover, thiamine and benfotiamine correct the increase in MMP-2 activity that results from high glucose levels in human retinal pericytes, while increasing TIMP-1 (Tarallo et al., 2010). Together, these studies suggest that thiamine may play an important role in the pathological processes of MI by down-regulating the levels of MMPs and regulating the levels of TIMPs.

3.2 The Mitogen-Activated Protein Kinase (MAPK) Pathways

MAPK provide a key link between the membrane-bound receptors that receive these cues and the changes in gene expression patterns, including the extracellular signal-regulated kinase (ERK) cascade, stress-activated protein kinases/c-jun N-terminal kinase (SAPK/JNK) cascade, and p38 MAPK/RK/HOG cascade (Hipskind and Bilbe, 1998). Myocardial ischemia activates a number of kinases, including members of the p38 MAPK family (p38s) (Tanno et al., 2003; Kumphune et al., 2010). Compared with the control group, levels of p-ERK1/2, p-JNK, and p38 were significantly increased in the isoproterenol-induced, AMI-treated group (Guo et al., 2012). In the minutes after experimental MI, ERK1/2, JNK1/2, and p38α MAPK are all activated in both the ischemic myocardium and unaffected portions of the left ventricle of mice and rats (Ren et al., 2005; Yoshida et al., 2001). Treatment with SB203580, a p38α and p38β inhibitor, resulted in reduced myocardial fibrosis, reduced TNF-α and collagen I levels, and increased LV contractile function (Yin et al., 2008). MAPKs also have a role in atherosclerotic development. When mouse peritoneal macrophages were treated with oxLDL, ERK1/2, p38α MAPK, and JNK1/2 were activated.
within 15 minutes (Rahaman et al., 2006). oLDL-induced foam cell formation in the J774 macrophage cell line was found to be blocked by administration of the p38 MAPK inhibitor SB203580 (Zhao et al., 2002). Macrophages lacking JNK2 displayed suppressed foam cell formation caused by defective uptake and degradation of modified lipoproteins and exhibited an increased binding of the modified lipoproteins (Ricci et al., 2004). Moreover, benfotiamine was shown to modulate the macrophage response to bacterial endotoxin-induced inflammation by preventing the activation of p38 MAPK and stress-activated kinases (SAPK/JNK) (Yaday et al., 2010).

### 3.3 Prostaglandins (PGs)

PGs play a role in inflammatory processes. Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. Plasma 8-iso-PG F2α levels, markers of oxidative stress, were significantly elevated in patients with AMI compared with patients with stable CAD and patients with no significant CAD (Elesber et al., 2006). Following reperfusion by primary percutaneous coronary intervention in AMI, oxidative stress and an inflammatory response are induced immediately. A rise in 8-iso-PG F2α during ischemia indicates that ROS generation may also take place during severely reduced coronary blood flow and hypoxia (Berg et al., 2005). COX-2 has been found to be up-regulated in atherosclerotic plaques (Kuge et al., 2007). Selective COX-2 inhibition protects against myocardial damage in experimental acute ischemia (Carnieto et al., 2009). MI size in celecoxib-treated rats was significantly reduced compared with the control group (Lada-Moldovan et al., 2009). However, COX-2 inhibitors recently were reported to be associated with MI and cardiovascular risk (Canon and Canon, 2012; Schjerning Olsen et al., 2011), which refecoxib was withdrawn from the U.S. market. Pharmacological activation of the PGE2 receptor EP4 improves cardiac function after myocardial I/R injury (Hishikari et al., 2009). Reduced cardiac remodeling and function was observed in cardiac-specific EP4 receptor knockout mice with MI (Qian et al., 2008). Deletion of microsomal PG synthetase-1 leads to eccentric cardiac myocyte hypertrophy, LV dilation, and impaired LV contractile function after AMI (Degousee et al., 2008). The CC genotype of the prostacyclin synthase (PGIS) gene (CYP8A1) or the -763CC genotype of PGIS2 is associated with MI (Lemaitre et al., 2009; Xie et al., 2009). The COX-2 gene has been associated with ischemic heart disease and stroke risk (Cipollone et al., 2004; Orbe et al., 2006). The Helsinki sudden death study demonstrated that the COX-2 gene promoter polymorphism was associated with coronary artery disease in middle-aged men. Men carrying the minor C allele had larger areas of complicated lesions and a higher number of coronary arteries that had over 50% stenosis compared with men representing the common GG genotype (Huuskonen et al., 2008). Moreover, the expression of COX-2 mRNA and PGE2 was selectively increased in vulnerable regions during the symptomatic stages of TD encephalopathy in animal models (Gu et al., 2008). Up-regulation of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) expression was observed in breast cancer cell lines transfected with the thiamine transporter (ThTr2) gene, and down-regulation was observed after the suppression of ThTr2 with siRNA vectors (Liu et al., 2004). Over-expression of 15-PGDH inhibited IL-1β-induced COX-2 expression (Tai et al., 2007). In murine macrophages, benfotiamine also blocked the expression of COX-2 and its product, PGE2, by LPS-induced cytotoxicity (Yaday et al., 2009). In addition, benfotiamine significantly prevented LPS-induced macrophage death and monocyte adhesion to endothelial cells (Yaday et al., 2010). These anti-inflammatory effects of benfotiamine are mediated through the regulation of the arachidonic acid pathway in macrophages (Shoeb and Ramana, 2012). These findings suggest that thiamine may play a role in modulating the inflammatory process in MI.
3.4 Reactive Oxygen Species (ROS)

ROS are produced by activated phagocytes as part of their microbicidal activities. A decrease in the blood supply to the heart caused by atherosclerosis or thrombosis is known to induce MI. Following ischemia, ROS are produced during the reperfusion phase (Espot and Nelton, 2000). Antioxidants decrease reperfusion-induced arrhythmias in MI with ST elevation (Hicks et al., 2007). During ischemia and reperfusion, ROS can be produced by both endothelial cells and circulating phagocytes. The sources of ROS in cardio-myocytes could be the mitochondrial electron transport chain, nitric oxide synthase (NOS), NOX, xanthine oxidase, lipooxygenase/COX, and/or the auto-oxidation of various substances, particularly catecholamines (Misra et al., 2009). MI was reported secondary to unintentional ingestion of hydrogen peroxide in a case study of a 60-year-old woman (Islamoglu et al., 2012). SOD1 over-expression in the para-ventricular nucleus improves post-infarct myocardial remodeling and ventricular function (Gao et al., 2012). Antioxidant vitamins reduce oxidative stress and ventricular remodeling in patients with AMI (Gasparetto et al., 2005). The inhibition of ROS production reduced adverse remodeling and improved LV contractile function, and it may therefore hold therapeutic potential for the treatment of chronic heart failure following AMI (Grieve et al., 2004). Cardiac oxidative stress is involved in heart failure that is induced by thiamine deprivation in rats (Gioda et al., 2010). In vitro, thiamine inhibits lipid peroxidation in rat liver microsomes and free radical oxidation of oleic acid (Lukienko et al., 2000). Benfotiamine promotes a reduction in ROS that is induced by advanced glycated albumin in macrophages (de Souza Pinto et al., 2012). In primary human peritoneal mesothelial cells and in a rat model of peritoneal dialysis, the addition of benfotiamine enhanced Tk activity and decreased the expression of AGEs and their receptors (Kihm et al., 2011). These data suggest that benfotiamine protects the peritoneal membrane and remnant kidney in a rat model of peritoneal dialysis and uremia. Thiamine rescues hepatocytes from iron-catalyzed oxidative stress by decreasing lipid peroxidation, mitochondrial damage, protein damage, and DNA oxidation (Mehta et al., 2011). These findings suggest that thiamine modulates oxidative stress in MI.

3.5 Nitric Oxide Synthase (NOS)

NOS is an enzyme that is involved in the synthesis of nitric oxide (NO), which regulates a variety of important physiological responses, including cell migration, the immune response, and apoptosis. Endothelial nitric oxide synthase (eNOS) and NO may play an important role in attenuating cardiac remodeling and apoptosis after MI. There is a close relationship between eNOS activity and the development of insulin resistance and macro-vascular disease in AMI patients (Li et al., 2012). eNOS-deficient mice developed more severe LV dysfunction and remodeling after MI than wild-type mice (Scherrer-Crosbie et al., 2001), whereas endothelial overexpression of eNOS has been shown to attenuate LV dysfunction in mice after MI (Jones et al., 2003). Deficiency in NOS-3 resulted in coronary artery hypoplasia in fetal mice and spontaneous MI in postnatal hearts (Liu et al., 2012). Inhibition of MAPK signaling by eNOS gene transfer improves ventricular remodeling after MI through the reduction of inflammation (Chen et al., 2010). There is a significant association between the eNOS T-786C polymorphism, CAD, and coincident putative risk factors in type 2 DM individuals of the South Indian population (Narne et al., 2012). The E298D polymorphism of the eNOS gene is associated with MI occurrence in the Greek population (Dafni et al., 2010). Increased brain eNOS expression was demonstrated in TD animals (Kruse et al., 2004). In murine macrophages, benfotiamine also blocks the expression of iNOS by LPS-induced cytotoxicity (Yadav et al., 2009). Benfotiamine reduces oxidative stress and activates eNOS to enhance the generation
and bioavailability of NO, and it subsequently improves the integrity of vascular endothelium to prevent sodium arsenite-induced experimental vascular endothelial dysfunction (Verma et al., 2010).

4 Conclusions

This paper reviewed the relationship between thiamine and MI. Genetic studies provide opportunities to determine which proteins link thiamine to MI pathology. Thiamine is also able to act through numerous non-genomic mechanisms, including protein expression, oxidative stress, inflammation, and cellular metabolism. These findings suggest that thiamine may play an important role in MI. Therefore, further investigation of thiamine in MI patients is warranted.

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