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METHYLGLYOXAL: A MOLECULE IN DIABETIC CARDIOVASCULAR DISEASES

DEVIPRIYA NAGARAJAN*, SUNILGOWDA SUNNAGHATTA NAGARAJA[1]

*[1] *School of chemical & biotechnology, Sastra university, Thanjavur, Tamil nadu, India.*

ABSTRACT

Diabetes mellitus, a chronic metabolic disorder, exerts pathophysiological effects on the heart leads to impaired myocardial function, cardiac failure and dysfunction. Methylglyoxal (MG) is a protein and nucleic acid modifying agent which is accelerated under diabetic conditions and act as a major component in the diabetic environment. MG has been reported to affect cardiac fibroblasts function, induce peritoneal fibrosis, modifies platelet-derived growth factor receptor. In this review, the role of MG on atherosclerosis, ischemic reperfusion, angiogenesis under diabetic conditions were reviewed and discussed. Studies showed that MG triggers free radicals, alters cell signalling mechanism, stimulates apoptosis and modifies extracellular matrix proteins. The review suggests that MG can acts as a target molecule to develop pharmacological agents which might help to improve current treatment strategies towards cardiac dysfunction in diabetic condition.

KEYWORDS: *MG; Diabetes; Fibrosis; Cardiac dysfunction; Ischemia.*

DEVIPRIYA NAGARAJAN*
School of chemical & biotechnology, Sastra university, Thanjavur, Tamil nadu, India.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by a deficiency in the insulin production (type 1 diabetes; T1DM) or the effect of insulin in cells (type 2 diabetes; T2DM). Diabetes has become an epidemic disease and it is estimated that by the year 2025, it will affect over 300 million people worldwide. [1] Diabetic complication is the principle causes of morbidity and mortality in humans. Acute complications include hypoglycemia, hyperosmolar hyperglycemic state and diabetic ketoacidosis. Chronic complications include retinopathy, nephropathy, ischemic heart disease, neuropathies, peripheral vascular and cerebrovascular disease.[2] Diabetic patients are at higher risk of developing serious complications including cardiomyopathy, characterized by myocellular hypertrophy and myocardial fibrosis. The increased levels of blood glucose and ketones in people with diabetes result in elevated levels of reactive aldehyde, in particular, methylglyoxal (MG). [1] Increased formation of MG can promote the pathology of diabetic complications. In this review, structure, formation and physiological concentration and role of methylglyoxal were discussed. In addition, our discussion suggested that methylglyoxal can acts as a pathological link between diabetes and heart disease and as a therapeutic target for the both diseases.

METHYLGLYOXAL: FORMATION, METABOLISM AND GLYCATION

Methylglyoxal or pyruvaldehyde (Figure 1) is a highly reactive electrophilic α, β-dicarbonyl compound and is derived from metabolic intermediates of carbohydrates, proteins and fatty acids [4]. Majority of MG is derived from the metabolites of carbohydrate metabolism, such as glucose and fructose through non-enzymatic degradation of the triose phosphate intermediates of glycolysis, dihydroxyacetone phosphate and glyceraldehydes 3-phosphate. It is also formed by spontaneous fragmentation of a Schiff base during the Maillard reaction[4,5]. Minor sources of MG are autoxidation of glucose and degradation of glycated proteins[5], and also oxidation of acetone in the catabolism of ketone bodies during diabetic ketoacidosis[6], aminoacetone produced from L-threonine and glycine[7] and lipid peroxidation[8]. The concentration of MG is in the range of 256 nM in blood (2.4 μM in diabetics), 1μM in plasma and 15 μM in urine in healthy humans. The intracellular MG level is much higher than the plasma MG level in the diabetic condition as diabetic tissues are chronically exposed to high MG levels, which can cause intracellular MG accumulation (≤300 μM).[9] There is a equilibrium mixture of both free and bound form of methylglyoxal and complication arises in metabolism because of vary in steady state concentration. In rat tissues normal free methylglyoxal concentration vary from 0.16μM in blood. In contrast bound methylglyoxal concentration varies from >100μM and it is 2-3 folds higher than the free methylglyoxal concentration. [4, 9]

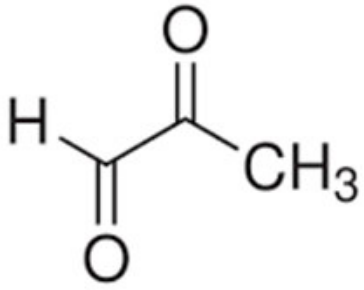

Figure 1
Structure of Methylglyoxal

The extent of MG accumulation in tissues and plasma is dependent upon its relative rates of generation and detoxification in the cells. Once MG is formed, it spontaneously reacts with glutathione (GSH) to form a hemithioacetal, which is then successively detoxified to D-lactate by the highly efficient and ubiquitous glyoxalase system, which consists of two key enzymes, glyoxalase-I (lactoylglutathione lyase) and glyoxalase II (hydroxyacylglutathione hydrolase).[10] D-Lactate dehydrogenase then converts D-lactate to pyruvate, which can be used for gluconeogenesis, lipogenesis, or oxidation in the tricarboxylic acid (TCA) cycle. [11] Under normal conditions, 99.7% of MG is metabolized via the glyoxalase system and remaining 0.3% of MG forms glycation adducts. [12] As GSH plays a key role by binding MG and presenting it to glyoxalase I, the enzymes involved in the synthesis and recycling of GSH, including glutathione peroxidase and glutathione reductase are also necessary for the metabolism of MG. [13] Minor pathways of MG detoxification include aldehyde dehydrogenase (ALDH)-catalyses the oxidation of MG to pyruvate; and aldose reductase (AR) - metabolizes MG mainly by means of the formation of hydroxyacetone.[14] Under normal physiological conditions, tissue levels of MG are maintained at a low level through the detoxification pathways, while in diabetes, both hyperglycaemia and oxidative stress are associated with GSH depletion and impairs detoxification of MG and consequently increase production and accumulation of MG. [15] The protein

glycation is a new mechanism through which MG aggravates ischemia-reperfusion injury (Figure 2). [16] Moreover, traces of MG which is not degraded by the glyoxalase system or aldose reductase, reacts non-enzymatically with arginine or lysine residues of proteins[17] to form irreversible advanced glycation end products (AGEs). In diabetes mellitus, excessive methylglyoxal accumulation results in dicarbonyl stress and forms other AGE related compounds. [18] Arginine residues are more common in functional domains of protein than lysine residues. The AGEs produced by the reaction between MG and arginine are hydroimidazolone Nε-(5-hydro-5-methyl-4-imidazolon-2-yl)- ornithine and argpyrimidine whereas reaction with lysine yields AGEs, Nε-carboxyethyllysine (CEL). In addition, MG can react irreversibly with lysine dimer 1,3-di(Nε-lysino)-4-methyl-imidazolium (MOLD). [19] MG can also cross-link arginine and lysine residues to form the adduct 2-ammonio-6-{(2-[(4-ammonio-5-oxido-5-oxopentyl)amino]-4-methyl-4,5-dihydro-1H-imidazol-5-ylidene) amino} hexanoate (MODIC). [20] MG-derived hydroimidazolones (MG-Hs) are formed as three structural isoforms: MG-H1, MG-H2 and MG-H3. MG-H1 is the most important MG-derived AGE, as it accounts for >90% of all MG adducts. [21] The important MG-H1-modified proteins are albumin, collagen[22], haemoglobin[23] and lens proteins[21]. DNA is also susceptible to glycation by MG on reaction it forms two imidazopurinone structural isomers, 3-(2'-deoxyribosyl)-6,7-dihydro-6,7-dihydroxy-6/7-methylimidazo-[2,3-b]purine-9(8)one(MGdG). DNA glycation by MG also forms two stereoisomers, N2-modified derivatives, N2-(1,R/S-carboxyethyl)-deoxyguanosine (CEdG). LC-MS/MS analysis of urinary excretion of CEdG in streptozotocin-induced diabetic rats indicated a 4-fold increase in CEdG excretion in diabetes with respect to normal healthy control rats. [24] DNA Glycation results in DNA strand breaks[25], nucleotide transversions[26], DNA–DNA and protein cross-links[27], and glycation of the nucleosomal protein histone H2A. [28]

Methylglyoxal metabolism and its effects

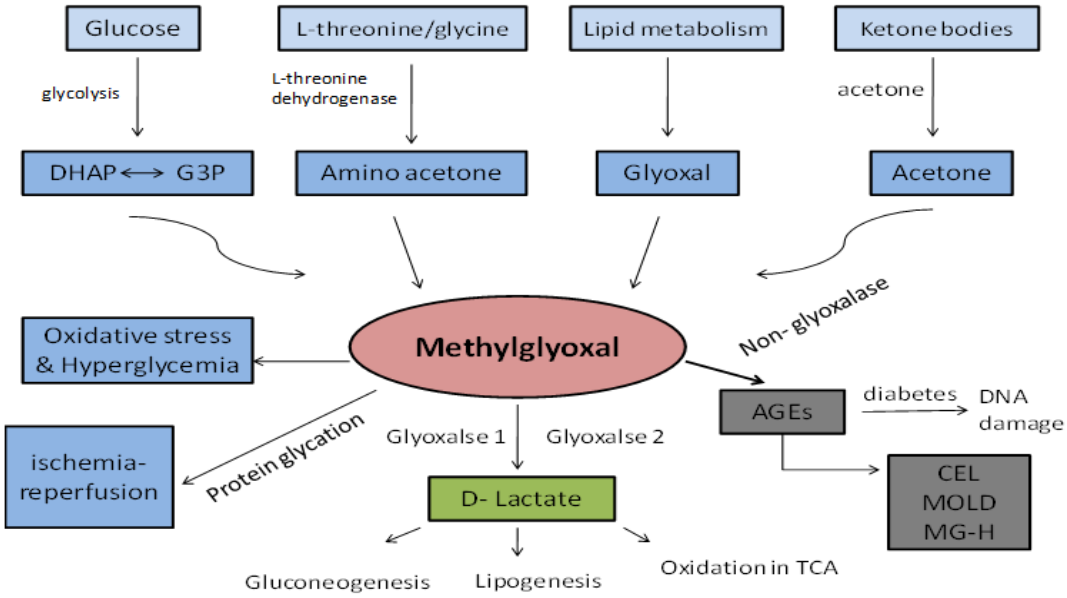

Figure 2
Metabolism of Methylglyoxal. Different sources of Methylglyoxal degrades in two ways 1) Glyoxalse system to non- toxic D-lactate 2) Non-glyoxalse system leading to CEL, MOLD and MG-H

MG AND HEART

Moreover, diabetic patients are at higher risk of developing serious complications including cardiomyopathy, characterized by myocellular hypertrophy and myocardial fibrosis. Emerging evidences suggest that fibrosis may play a role in mediating the association between diabetes and cardiovascular disease. [29] Myocardial fibrosis has direct relation with hyperglycemia, which is the initiating cause of cardiac tissue damage in diabetes that leads to diastolic dysfunction and decreased myocardial compliance with higher incidence and poor prognosis in heart failure cases. [30] Hyperglycemia promotes the development of cardiac fibrosis by causing excessive accumulation of collagen within the interstices of myocardium, and in extracellular matrix that impairs diastolic and systolic functions.[31] An 18-year follow-up study showed that high baseline serum levels of the MG-derived hydroimidazolone type of AGE-modified proteins were associated with cardiovascular disease mortality in non-diabetic women. [32] In Human cardiac fibroblasts cells, MG has been reported to affect cardiac fibroblasts function by promoting myofibroblast differentiation.[33] Previous investigations on MG-induced peritoneal fibrosis revealed thickening of peritoneum and ultrafiltration failure in MG treated rats. [34] MG is not only plays major role in diabetic complications but also in other age-related diseases such as obesity[35],

atherosclerosis[36], cancer [37] and neurodegenerative disorders[38].

MG AND CARDIAC DYSFUNCTION

Diabetes mellitus exerts pathophysiological effects on the heart, including impaired myocardial function. The concentration of MG is increased with duration of diabetes in IDDM (type1) patients at a rate of approximately 10% of the mean control/year. Studies showed that incubation with MG increases production of oxidative stress in vascular smooth muscle cells[39] and increases cardiomyocyte ischaemia-reperfusion injury (figure 3). MG induces cardiac dysfunction via C/EBP homologous protein (CHOP)-dependent myocyte apoptosis and inflammation. [40] It was shown that MG induced AGE is also found in atherosclerotic plaques and MG-H1 is found with rupture of the plaques. [41] MG-AGEs of mitochondrial protein induces the formation of reactive oxygen species (ROS), also effects the DNA in endothelial cells and also increases the oxidative stress in cardiomyocytes, modifies Ca^{2+} levels in augment fibrosis of extracellular matrix (ECM). [42] Gaku Oguri *et al* [43] recently suggest the findings of involvement of TRPA1 on MG-induced [Ca^{2+}] increase in cardiac fibroblasts of humans. After fibroblast proliferation, in the extracellular matrix they will get differentiate into myofibroblasts. One of the main cause and regulator for the heart attacks/death is differentiation between fibroblasts and myofibroblasts[44], which are supported by minor expression of α-SMA which increases as MGs dose increases. [45]

MG and Cardiac dysfunction

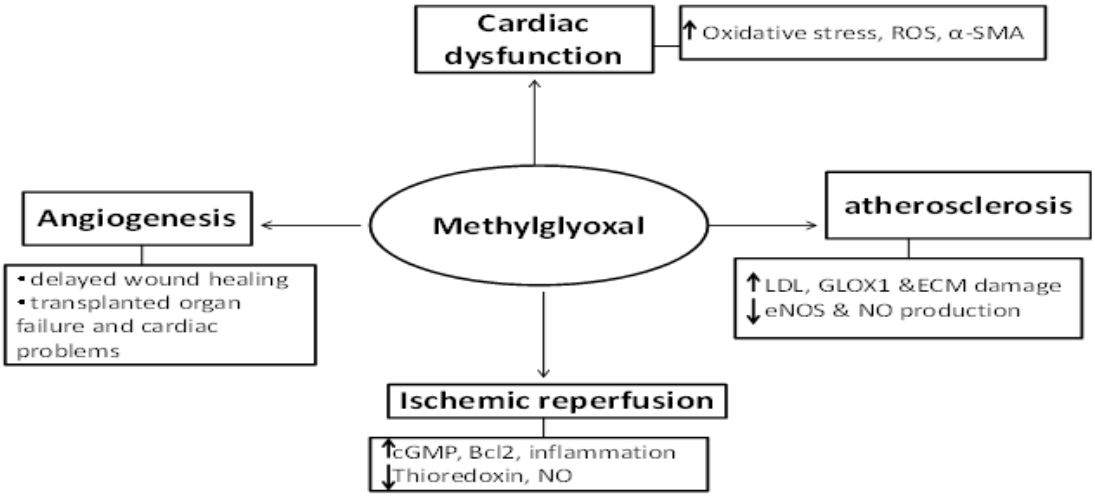

Figure 3
Various effects of methylglyoxal on different diseases state and the effects

MG AND ATHEROSCLEROSIS

MG targets lipids especially Low Density Lipoprotein (LDL), it is modified in atherosclerosis in terms of particle size, increased atherogenicity and reduced affinity for the LDL receptor molecules. [46] The initial stages of atherosclerosis on the walls of arteries includes the concentrated accumulation of small lipid droplets and vesicles in extracellular matrix ranging upto 400nm in diameter were binded to phosphoglycerides, the characteristic of this sdLDL, MG modified LDL had a very increased risk to form aggregates and increased binding affinity for phosphoglycerides present in arteries. [46] Vascular endothelial studies of zebra fish shows that MG modifies vascular intersomitic blood vessels, which acts by phosphorylating VEGF (Vascular endothelial growth factor) receptor 2 and akt/PKB and suggest the role of MG in hyperglycemia in inducing vascular damages and it also acts as a target site for pharmacological inhibitor. [47] Its proven that MG has direct effect on the development of atherosclerosis by either inducing increased detoxification by GLO1 (glycoxalse) or by impaired detoxification. [48] Diabetic patients receiving Metformin shows antiatherogenic effect which is likely due to a decrease of MG-modified LDL. [49] The modification of LDL by MG increases its arterial atherogenicity, partly by increasing its density and binding to proteoglycans in the arterial wall. [50] MG-induced modification of the platelet-derived growth factor receptor alters its mitogenic functions similar to that observed in atherosclerosis lesions of diabetic mice. [51] MG inhibits eNOS which is important for normal functioning of cardiac system through inhibiting the phosphorylation of serine 1177; thereby it inhibits NO production and vascular cells relaxation. [52] MG (100μM) triggers NO production and H_2O_2 generation in rat thoracic aortic smooth muscle cells (ASMC). These induced NO reacts with peroxides forming the most reactive oxidant peroxynitrite ($ONOO^-$), so that NO is bound and thereby making it physiologically non-functional. Moreover, $ONOO^-$ itself is considered as an essential atherosclerotic risk factor. [53] It has been reported that ONOO impairs the sarcoplasmic reticulum Ca^{2+} pump in pig coronary artery smooth muscle[54] and induces the apoptosis of cultured rat aortic smooth muscle cells. [55]

MG AND ANGIOGENESIS

Angiogenesis is growth of new blood vessels from the existing vasculature formed during embryo development. It occurs throughout life in both health and disease conditions, beginning in utero and continuing on through old age. Blood capillaries are needed in all the tissues and organs for diffusion exchange of nutrients, oxygen and other supplements.[56] It plays a vital role in human physiology during embryonic development, menstruation, wound healing, and tissue repair after surgery or trauma, inflammatory diseases, cardiac diseases and cancer. [57] Only few studies have specifically evaluated the importance and effects of diabetes on angiogenesis in ischemic vascular disease. The disability in the formation of angiogenesis in diabetic peripheral vasculature results in delayed wound healing, transplanted organ failure and cardiac problems. [58] Several data suggests that MG, the major inducer of AGEs formation and it's their receptor RAGE have role in the pathogenesis of diabetic vascular conditions. [59] AGE formation has also been shown to affect the proteolysis of the glycated proteins[60] and finally they may affect the angiogenic reactions in the body. It has been shown that restriction of AGE formation or accumulation improves wound healing by angiogenesis in a diabetic animal model. [61] The direct relevance of AGE- altered angiogenesis can be seen in MG connected gastric ulcer healing. [62] Vascular endothelial growth factor blockades acts as antiangiogenic agents[63], in zebra fish during high glucose level, MG acts on endothelial cells and blood vessels by augmenting phosphorylation of VEGF and prevents it from acting as antiangiogenic.[64] MG can activate various signaling pathways such as NF-κB, JNK (c-Jun N-terminal kinase) and p38 MAPK (mitogen-activated protein kinase) pathways in ECs and leucocytes. [65] MG induces leucocyte recruitment to the microvasculature by increasing EC adhesion molecule expression, leading to increased inflammation. [65]

MG AND ISCHEMIC REPERFUSION

Ischemic injury occurs when the blood supply to an area of tissue is cut off. The incidences of ischemic injury are myocardial infarction, stroke, and other thrombotic events affect more than millions of people all over world. Ischemic injury also occurs during surgery when blood vessels are cross-clamped, and in organs for transplant. [66] Ischemic reperfusion injuries are caused by number of interacting factors. Oya et al[67] showed that MG and other MG modified sugars play a vital role in acute arterial injury due to ischemia reperfusion. Recent studies of AGE receptor of RAGE shows that MG binding leads to the generation of free radicals, iNOS, nitrite and nitrate, and increased cGMP in the cardiac muscles are the reasons for ischemia reperfusion.[68,69] Thioredoxin (trx), is small protein which is housekeeping gene normally expressed in all living cells acts as a regulator of cell proliferation, apoptosis & mainly for ischemia reperfusion injury, which is inhibited by MG via glycation,[70] and demonstrated that MG increases the cultured cardiomyocyte ischemia reperfusion in a post translation modification of thioredoxin. MG by increasing inflammation and decreasing NO bioavailability stimulates pathogenesis of atherosclerosis and develops macrovascular diabetic complications.[35] In addition, MG led to increased apoptotic markers during ischemia and may contribute to a poor outcome after ischemia. [71] MG accumulation in the heart tissues leads to an impaired ability to increase Bcl-2 levels during ischemia, through decreased Akt activation.[72] Modification of hypoxia-inducible factor 1α (HIF1α) or its co-activator p300, by MG, and the reduced binding to promoters of genes required for neovascularisation leads to defective new vessel formation in diabetes. [73] MG also induces macrovascular damage by reduction of sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA2a), which normally translocates Ca^{2+} from the cytoplasm to the lumen of the sarco(endo)plasmic reticulum during cardiac relaxation, resulting in diastolic dysfunction of the heart. [74]

CONCLUSION

Diabetes mellitus (DM) is a pandemic metabolic disease characterized by hyperglycemia a resulting from insulin deficiency or insulin resistance or both. Studies demonstrated a strong link between diabetes and cardiovascular morbidity and mortality. MG is a highly reactive electrophilic α,β-dicarbonyl compound derived from metabolic intermediates of carbohydrates, proteins and fatty acids. However, the increased blood concentrations of MG have been observed in diabetes which was associated with cardiovascular disease mortality in humans. Studies in this review showed that MG plays a vital role in cardiac dysfunction during diabetes and it might be identified as therapeutic targets for treating cardiovascular diseases in diabetic conditions.

CONFLICT OF INTEREST

Conflict of interest declared none.

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