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ORIGINAL ARTICLE

Enhancement of Matrix Metalloproteinase 2 and 9 Inhibitory Action of Minocycline by Aspirin: An Approach to Attenuate Outcome of Acute Myocardial Infarction in Diabetes

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Background and Aims. Diabetes is a risk factor for exacerbated outcome after acute myocardial infarction (AMI) and doubles the risk of mortality after MI. Increased levels of MMP-2 and MMP-9 in diabetes cause vascular remodelling, which leads to cardiovascular complications of diabetes. We hypothesized that inhibition of MMP-2 and MMP-9 can reduce worsening of myocardial ischemia in diabetic patients. Further, we hypothesized that minocycline induced MMP-2 and MMP-9 inhibition will be potentiated by aspirin and the combination of both drugs will prevent worsening of MI in diabetic patients. In the present study, efficacy of combination of minocycline and aspirin to attenuate exacerbation of myocardial ischemia/reperfusion (I/R) injury in diabetic rats was evaluated.

Methods. Diabetes was induced in male Wistar rats by streptozotocin (55 mg/kg i.p.). Three weeks after diabetes induction, rats were treated with minocycline (50 mg/kg, p.o.), aspirin (50 mg/kg, p.o.), or minocycline (50 mg/kg, p.o.) plus aspirin (50 mg/kg, p.o.) for a period of 3 weeks. At the end of week 6, I/R injury was induced by ligating the left anterior descending coronary artery for 30 min followed by 2 h reperfusion.

Results. Percentage infarct volume, arrhythmias, mortality, collagen level and MMP-2 and MMP-9 level were significantly increased in vehicle-treated diabetic group when compared with normoglycemic rats. Treatment with a combination of minocycline and aspirin decreased percentage infarct volume, arrhythmias, mortality and collagen level when compared with vehicle-treated diabetic controls and showed reduced levels of MMP-2 and MMP-9.

Conclusions. Results of the present study suggest that the combination of minocycline and aspirin prevent worsening of AMI in diabetic rats. © 2014 IMSS. Published by Elsevier Inc.

Key Words: Myocardial ischemia/reperfusion, Matrix metalloproteinase 2, Matrix metalloproteinase 9, Extracellular matrix.

Introduction

One of the major risk factors for cardiovascular disease is diabetes mellitus (DM). It accounts largely for the higher mortality and morbidity of diabetic populations (1). A complex interplay of various factors is the underlying pathophysiology. One of the chronic complications of DM is coronary artery disease (CAD) leading to myocardial infarction (MI) and accounts for >75% of hospitalizations in diabetic patients (2–4). Also, MI accounts for nearly 50% of all deaths in patients with DM (5). The mortality rate of diabetic patients after acute MI resulting from ischemia/reperfusion (I/R) injury is approximately twice that of nondiabetic patients. Myocardial I/R injury results in greater damage in the diabetic (*db/db*) mouse hearts than in nondiabetic controls. A group of enzymes that hydrolyze

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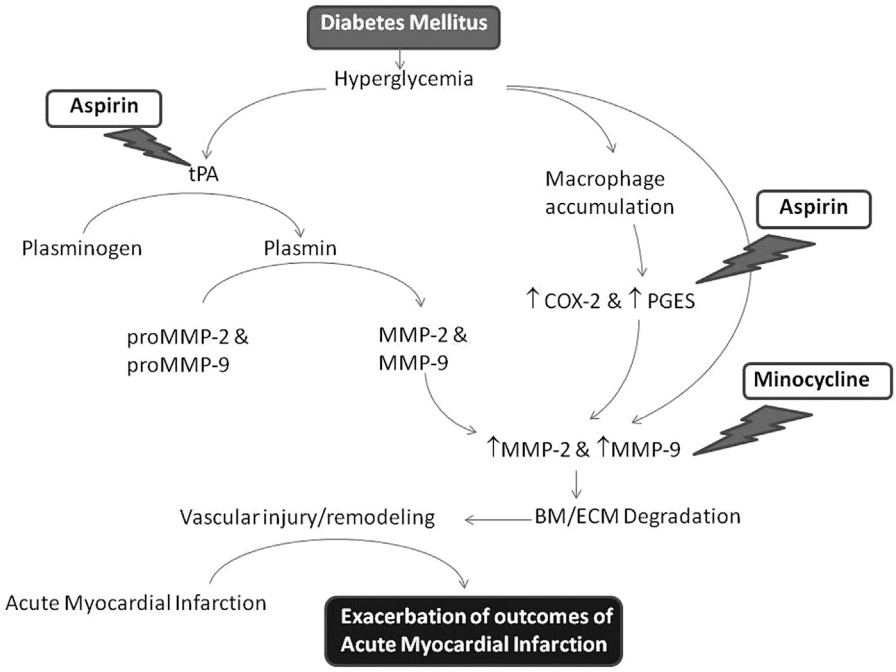

Figure 1. Proposed hypothesis: Enhanced Inhibition of MMP-2 and MMP-9 by combination of minocycline and aspirin for attenuation of outcome of acute myocardial infarction in diabetes.

protein components of the extracellular matrix (ECM) is known as matrix metalloproteinases (MMPs) (6). The subgroup of MMPs, specifically gelatinase A (MMP-2) and gelatinase B (MMP-9), digests collagen, denatured collagens (i.e., gelatins), laminin, elastin and fibronectin among other substrates (7) and have been implicated in the pathological processes that contribute to fibrotic diseases, tumor progression and inflammation (8–10). In the cardiovascular system, MMPs may become deleterious because of the dysregulation and can result in tissue injury and inflammation (11). It has been observed in earlier experimental studies that increased MMP activity contributes to cardiac and vascular complications.

Regulation of MMPs in DM has been widely investigated. It has been shown that hyperglycemia increased activity and expression of MMP-2 and MMP-9 in rat aortic smooth muscle cells and mouse vascular tissue and plasma (12). We hypothesized that inhibition of MMP-2 and MMP-9 can reduce worsening of myocardial ischemia in diabetic patients. Further, we hypothesized that aspirin will enhance inhibitory action of a MMP-2 and MMP-9 inhibitor and a combination of both drugs will prevent worsening of MI in diabetics. Minocycline is a known inhibitor of MMP-2 and MMP-9 and was selected to evaluate the hypothesis. It was thought that aspirin may potentiate MMP inhibitory action of minocycline by COX-2 (Figure 1) and tissue plasminogen activator (tPA) inhibitory action (Figure 2). COX-2 and tPA can induce expression of MMP-2 and MMP-9 by different pathways. Earlier we reported attenuation of cardiovascular dysfunction by this combination in rats (13). In the present study, efficacy of minocycline plus aspirin to attenuate exacerbation of myocardial I/R injury was evaluated.

Materials and Methods

Animals

Male Wistar rats (210–250 g) were purchased from the Haffkine Institue, Mumbai, India and were housed at a temperature of 25 ± 1°C and relative humidity of 45–55% in a clean environment under 12:12 h light and dark cycle. The animals had free access to food pellets and filtered water.

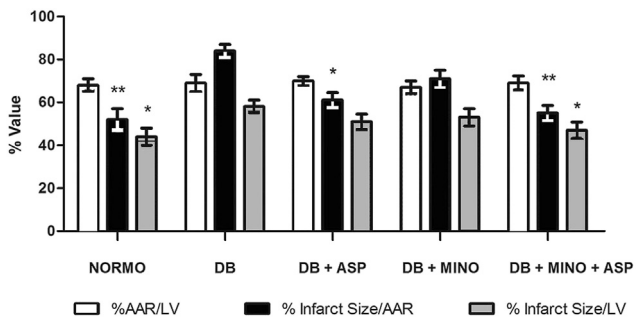

Figure 2. Effects of three week treatment with MINO *per se*, ASP *per se* and MINO plus ASP on % infarct size/AAR and % infarct size/LV after 30 min of left anterior descending coronary artery occlusion and 2 h reperfusion. The mean areas at risk (% AAR/LV) were not found significantly different, indicating that the degree of the ischemic insult was similar with all animals. *p <0.05 vs. DB, **p <0.01 vs. DB.