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THE ROLE OF EPLERENONE ON ACTIVITY OF MATRIX METALLOPROTEINASE-2 STIMULATED BY HIGH GLUCOSE AND INTERLEUKIN-1 β IN HUMAN CARDIAC FIBROBLASTS

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Objectives Recent studies have demonstrated an important role of high glucose for collagen deposition in fibroblasts. However, little is known about the interaction of hyperglycaemia and inflammatory cytokines on matrix metalloproteinase (MMP) regulation in human cardiac fibroblasts. In this article, we determined the influence of high glucose and interleukin (IL)-1 β on human cardiac fibroblasts functions and the effects of eplerenone in these responses.

Methods Human cardiac fibroblasts were cultured in normal or high glucose median the absence or presence of IL-1 β and/or eplerenone. We have determined their MMP-2 activities by using in-gel zymography. In addition, the mRNA expression of MMP-2 and tissue inhibitor of metalloproteinase-2 (TIMP-2) were evaluated by the means of reverse transcription-PCR. Results show that high glucose stimulates the activity of MMP-2 and accelerates MMP-2 mRNA synthesis. When Equimolar mannitol was used as an osmotic control, the activity enhancement of MMP-2 were also observed, however, it is not as strong as that by using high glucose. We have also found that MMP-2 activity and mRNA expression were improved significantly ($\sim 2\times$) by using the combination of high glucose and IL-1 β as compared with using high glucose or IL-1 β alone. Increase of MMP-2 activity and mRNA expression were blocked by eplerenone, that is, neither high glucose nor IL-1 β has impacted TIMP-2 mRNA expression in the experiments.

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Conclusions High glucose increases the activity of MMP-2 by means of regulating MMP-2 mRNA expression in human cardiac fibroblasts through osmotic and non-osmotic pathways. Combining IL-1 β with high glucose was found to increase significantly the MMP-2 activity and mRNA expression in human cardiac fibroblasts as compared with using IL-1 β or high glucose in dividedly. However, such induced effects can be readily normalised by the use of Eplerenone.