Effects of eplerenone on the activation of matrix metalloproteinase-2 stimulated by high glucose and interleukin-1β in human cardiac fibroblasts

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ABSTRACT. The aim of this study was to determine the influence of high glucose (HG) and interleukin (IL)-1β on human cardiac fibroblast (HCF) functions, and to evaluate the effects of eplerenone in these responses. HCFs were cultured in normal or HG media in the absence or presence of IL-1β and/or eplerenone. We assessed matrix metalloproteinase-2 (MMP-2) activity in the supernatant by in-gel zymography, and determined mRNA expression levels of MMP-2 and tissue inhibitor of metalloproteinase-2 (TIMP-2) by reverse transcription-polymerase chain reaction. Equimolar D-mannitol was used as an osmotic control. HG stimulated MMP-2 activity and promoted MMP-2 mRNA synthesis. Increased effects were also observed in equimolar D-mannitol treatments, but these effects were weaker compared to those of glucose. The combination of HG and
IL-1β resulted in a 2-fold increase in MMP-2 activity and mRNA expression compared with HG or IL-1β alone. Increases in HG- or IL-1β-induced MMP-2 activity and mRNA expression were blocked by eplerenone. Neither HG nor IL-1β affected TIMP-2 mRNA expression. HG increased MMP-2 activity by regulation of MMP-2 mRNA expression in HCFs through osmotic and non-osmotic pathways. Synergistic effects of IL-1β added to HG media on MMP-2 activity and mRNA expression were observed in HCFs. Eplerenone normalized the effect of MMP-2 activity and HG- or IL-1β-induced expression in HCFs.

Key words: Fibroblasts; High glucose; Matrix metalloproteinase-2; Interleukin-1β; Mineralocorticoid receptor antagonists