EFFECTS OF GLUCOSE ON ANG II INDUCED JAK2/STAT3 TYR-PHOSPHORYLATION IN CARDIAC FIBROBLASTS

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Background: Cardiac fibroblasts significantly contribute to diabetes-induced structural and functional changes. Angiotensin (Ang) II activates Janus kinase signal transducers and activators of transcription (JAK-STAT) pathway. The activation of STAT3 during cardiac hypertrophy was recently reported to induce collagen synthesis. The objective of the present study was to determine the effects of glucose on Ang II induced JAK2/STAT3 Tyr-phosphorylation in cardiac fibroblasts.

Methods: Rat ventricular fibroblasts were passaged three times to yield almost pure cultures (>99% purity). Cells were changed to serum free for 24 h, exposed to media containing glucose 5nM (NG) or 25 mM (HG) for 2h, and finally stimulated with angiotensin II (100 nM) or buffer. JAK2 and STAT3 phosphorylation were then investigated in lysed cells with Western blot analysis using specific antibodies. Generation of reactive oxygen (ROS) species was investigated using DCF-DA probe.

Results: Ang II enhances JAK2 and STAT3 phosphorylation (60% and 90% vs buffer, respectively) after 60 minutes, in fibroblasts preincubated in LG. Conversely, in fibroblasts preincubated with HG, JAK2 and STAT3 phosphorylation were already significantly enhanced before Ang II stimulation (50%, and 110% respectively, p<0.05 for both). Ang II ROS generation was significantly enhanced in HG vs LG (+50%, p<0.05). However no further increase in JAK2 and STAT3 phosphorylation was observed.

Conclusions: Present findings indicates that HG concentration which can be reached in vivo, can enhance in cardiac fibroblasts the phosphorylation of JAK2 and STAT3, both implicated in cardiac hypertrophy and collagen deposition. Although Ang II stimulation cannot further enhance JAK2 and STAT3 phosphorylation, the participation of HG induced intracellular ANG II synthesis in cardiac fibroblasts cannot be excluded.