Angiotensin II Activates Signal Transducer and Activators of Transcription 3 via Rac1 in Atrial Myocytes and Fibroblasts

Implication for the Therapeutic Effect of Statin in Atrial Structural Remodeling

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Background—Recently, activation of the local renin-angiotensin system and mitogen-activated protein kinase pathways in atrial myocardium has been found to play an important role in atrial structural remodeling related to atrial fibrillation. Another important mediator of the angiotensin II (Ang II) effect is the Janus kinase/signal transducers and activators of transcription (STAT) pathway, which has never been characterized in the atrium.

Methods and Results—In cultured atrial myocytes and fibroblasts, Ang II induced tyrosine phosphorylation of STAT3 through a Rac1-dependent mechanism, which was inhibited by dominant-negative Rac1, losartan, and simvastatin. In atrial myocytes, activation of STAT3 by Rac1 was mediated by direct association of Rac1 with STAT3; however, in atrial fibroblasts, it was mediated by an indirect paracrine effect. Constitutively active STAT3 increased protein synthesis, and dominant-negative STAT3 abrogated Ang II–induced protein synthesis in atrial myocytes and fibroblasts. Rats infused long term with Ang II exhibited higher levels of activated Rac1, phospho-STAT3, collagen synthesis, and atrial fibrosis in the atria, all of which were attenuated by oral losartan and simvastatin. In human atrial tissues from patients with atrial fibrillation, Ang II and phospho-STAT3 levels were also elevated.

Conclusions—The Ang II/Rac1/STAT3 pathway is an important signaling pathway in the atrial myocardium to mediate atrial structural remodeling, and losartan and statin may be able to reverse Ang II–induced atrial structural remodeling in atrial fibrillation. (Circulation. 2008;117:344-355.)

Key Words: atrial fibrillation ■ angiotensin II ■ mitogen-activated protein kinase ■ signal transduction ■ small GTPases ■ Rac1 protein