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Cardioprotective Effects of Angiotensin-Converting Enzyme 2 in Apolipoprotein E-Deficient Mice in Response to Angiotensin II

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Objectives: Objective of the renin-angiotensin system (RAS) has lead to important pharmacological tools to treat atherosclerosis and other cardiovascular diseases. Angiotensin-converting enzyme 2 (ACE2) has emerged as a central negative regulator of RAS by degrading angiotensin (Ang) II to generate Ang-(1-7). We hypothesized that ACE2 would exert beneficial effects on myocardial injury in apolipoprotein E- knockout (apoEKO, Akre;2; 2 mg/kg/d). We characterized the functional, structural and molecular changes in mice hearts.

Methods: In this work, we used 3-month-old wild-type, apoEKO, and ACE2/ApoE double-KO mice. We implanted subcutaneously mini-osmotic pumps with Ang II (1.5 mg/kg/d) or saline for 2 weeks in the ApoE2 mice which were then treated with recombinant human ACE2 (hrACE2; 2 mg/kg/d). We measured HR, HRV, and arterial systolic blood pressure.

Results: Compared with the ApoE2 mice, ACE2 deficiency triggered greater increases in cardiac expression of CTGF and phosphorylated level of pERK1/2 in the ACE2/ApoE double-KO mice (n=5-6; P<0.01, respectively). These changes were associated with exacerbation of myocardial ultrastructure injury and greater activation of inflammatory factors including CCL2, fractalkine (FKN), interleukin 1 (IL1), IL17, and ICAM1 in the ApoE2 mice with activation of the CTGF and ERK signaling (n=5-6; P<0.05 or P<0.01, respectively). Consistent with induction of inflammation, Ang II infusion led to elevation of superoxide production and severe ultrastructure injury in hearts of the ApoE2 mice with increased cardiac NADPH oxidase activity and elevated circulating Ang II levels. Notably, treatment with hrACE2 strikingly alleviated oxidative stress and attenuated ultrastructure injury in the hearts of Ang II-treated ApoE2 mice linked with reduction of NADPH oxidase activity and abolishment of expression of CTGF, P-ERK1/2, CCL2, ICAM1, FKN, IL17, IL17, and ICAM1 in the ApoE2 mice with activation of the CTGF and ERK signaling (n=5-6; P<0.05 or P<0.01, respectively). However, there were no changes in p38-MAPK and COXCR1 levels among groups (n=4-6; P>0.05, respectively).

Conclusions: Absence of ACE2 triggers greater increases in myocardial inflammation and oxidative stress in the ACE2/ApoE double-mutant mice with exacerbation of myocardial ultrastructure injury. Conversely, ACE2 overexpression alleviates Ang II-mediated inflammation and ultrastructure injury in hearts of the ApoE-deficient mice with suppression of superoxide generation and the CTGF-ERK signaling activation. Strategies aimed at enhancing ACE2 action may have important therapeutic potential for cardiac disorders.

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Different Doses of Angiotensin Receptor Blocker Therapy for Early Diastolic Heart Failure on Myocardial Diastolic Stiffness: a Preliminary Diabetic Study

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Objectives: To investigate the effects of Angiotensin-(1-7) (Ang-(1-7)) signaling pathway on atrial electrophysiological remodeling in rapid atrial pacing canine model and the possible role of atrial natriuretic peptide (ANP).

Methods: Thirty-five dogs were assigned to seven groups randomly. There are sham group, paced control group, paced + Ang-(1-7) group, paced + Ang-(1-7) + A-779 group, paced + Ang-(1-7) + L-NAME group, 5 dogs in each group. Rapid atrial pacing at 600 bpm was maintained for 2 hours except the animals from the sham group. During the pacing, Ang-(1-7) (0.66 mg/kg (b)-1, A-779 (Mas inhibitor, 5.83 kg (h)-1); API-2 (Akt inhibitor, 2.14 kg (h)-1); L-NAME (NO synthase inhibitor, 180 kg (h)-1) were given intravenously, respectively. Electrophysiological parameters including atrial effective refractory periods (ERP), inducibility and duration of atrial fibrillation (AF) under different basic pacing cycle length (300, 250, and 200 ms) were measured. Following electrophysiological study, ANP concentration of the left atrium was detected.

Results: All the diabetic rabbits were identified by electron microscopy, HE staining method. Immunohistochemical method, and Quantitative histomorphometry. Cardiac total titin and titin N2B/N2BA ratio were measured by gel electrophoresis, and total titin mRNA level expression was assessed by Quantitative real-time PCR.

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