ACE INHIBITOR-INDUCED ANGIOGENESIS IN CORONARY ENDOTHELIUM IS MEDIATED BY FIBROBLAST GROWTH FACTOR-2

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Fibroblast growth factor-2 (FGF-2) is an angiogenic factor for the microvascular endothelium, which tonically promotes endothelial cell growth and survival through an autocrine/paracrine mechanism. Here we formulate the hypothesis that FGF-2 might contribute to the prosurvival/proangiogenic effect of ACEI. Zofenoprilat and lisinopril induced formation of pseudocapillaries in vessel fragments isolated from porcine coronary and human umbilical arteries. Angiogenesis was abolished by inhibitors of nitric oxide synthase (NOS) pathway and by anti-FGF-2 antibodies. Consistently, in cultured coronary endothelial cells (CVEC) ACEI up-regulated eNOS and FGF-2. The overexpression of eNOS/FGF-2 enhanced cell proliferation and migration, the latter effect being dose-dependent and maximal at 0,1 M zofenoprilat. FGF-2 silencing reduced ACEI-dependent endothelial cell growth and migration, and greatly affected the nuclear translocation of the FGFR-1, highlighting the autocrine mode of action of FGF-2. In conclusion we show that ACEI exert protective/proangiogenic effects in microvascular coronary endothelial cells by activating the endogenous FGF-2/FGFR-1 system.
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