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A NEW PEPTIDE. AC-SDKP WHICH INHIBITS COLLAGEN DEPOSITION IN THE HEART AND KIDNEY

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Left ventricular hypertrophy (LVH) is a cardiovascular risk factor and its regression has benefits independent of the decrease in BP (LIFE study). Thus it is important to develop novel pharmacological approaches that can prevent or regress the various components of LV remodeling (cardiomyocyte hypertrophy, reactive fibrosis, and inflammation). N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a tetrapeptide that is increased five-fold in plasma after administration of an ACE inhibitor. We found that *in vitro* this peptide inhibited fibroblast proliferation and collagen synthesis and also decreased p44/p42 mitogen-activated protein kinase (MAPK) and blocked phosphorylation and nuclear translocation of the Smad signaling system. This is important because Smads mediate TGF-β stimulation of collagen synthesis. *In vivo* we also tested the effect of Ac-SDKP on cardiac remodeling caused by hypertension or MI and found that it decreased 1) cell proliferation (fibroblasts?), 2) number of macrophages and TGF-β-positive cells, and 3) perivascular and interstitial collagen. Ac-SDKP did not decrease either BP or LVH; however, it depressed systolic cardiac function slightly while decreasing renal fibrosis and improving renal function. We concluded that Ac-SDKP decreases fibroblast proliferation and collagen synthesis, and this effect may be mediated by inhibiting p44/p42 MAPK and Smad activity and decreasing macrophage infiltration and expression of cytokines such as TGF-β. However, this decrease in fibrosis without changes in LVH was not accompanied by an improvement in cardiac function, suggesting that a coordinated decrease in cardiocyte hypertrophy and cardiac fibrosis is needed for improvement of cardiac function. On the other hand, decreasing renal fibrosis improves renal function.