Effects of combined AT1 receptor antagonist/NEP inhibitor on vascular remodeling and cardiac fibrosis in SHRSP.

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Abstract

BACKGROUND:

The association of an angiotensin-converting enzyme inhibitor (ACEI) with a neutral endopeptidase inhibitor (NEPI) has potent blood pressure (BP) lowering action, but is associated with side-effects. We evaluated the effects of combining an angiotensin II type 1 (AT1) receptor blocker (ARB, valsartan) and a NEPI (CGS 25354) in comparison with a dual ACEI/NEPI (CGS 30440) in stroke-prone spontaneously hypertensive rats (SHRSP).

METHODS AND RESULTS:

Ten-week-old SHRSP were treated with valsartan (10 mg/kg per day), valsartan + CGS 25354 (100 mg/kg per day), CGS 25354, CGS 30440 (10 mg/kg per day) or hydralazine (25 mg/kg per day) for 10 weeks. Mesenteric resistance arteries were studied on a pressurized myograph, whereas cardiac effects were assessed by histology and immunohistochemistry. BP of SHRSP was lowered by combined valsartan/NEPI and ACEI/NEPI slightly more than valsartan, whereas NEPI was ineffective. Valsartan, valsartan/NEPI and ACEI/NEPI normalized resistance artery relaxation responses to acetylcholine, and significantly decreased media/lumen ratio and collagen deposition. All treatments decreased vascular NAD(P)H oxidase-mediated superoxide production. Valsartan/NEPI and ACEI/NEPI decreased media/lumen ratio of intramyocardial coronary arteries, while valsartan alone had no effect. Valsartan/NEPI and ACEI/NEPI increased vascular matrix metalloproteinase-2 activity, and decreased tissue inhibitors of metalloproteinase-2 activity and macrophage infiltration.

CONCLUSION:

Combined valsartan/NEPI was almost as effective as a dual ACEI/NEPI in lowering BP and improving vascular remodeling in SHRSP. These findings suggest the potential therapeutic value of combining ARB and NEPI in the treatment of hypertension.