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PROTECTIVE EFFECTS OF MANIDIPINE/DELAPRIL COMBINATION ON MYOCARDIAL HYPERTROPHY AND ENDOTHELIAL DYSFUNCTION IN SHR-RATS

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Aim of the present study was to investigate the protective effects of manidipine/delapril combination (CHF 1521) and an approximately equi-hypotensive dose of manidipine towards the hypertension-induced organ damages in spontaneously hypertensive rats (SHRs).
Twelve-week old SHRs received orally vehicle, manidipine/delapril combination (1+3 mg/kg/day) and manidipine (2 mg/kg/day) for 12 weeks. A group of age-matched WKY rats was used as normotensive control group. Blood pressure, heart rate and renal function were evaluated once a week in conscious animals. Endothelial function has been assessed at the end of treatment period both, in vivo, by evaluating systemic vascular tone of anaesthetised animals after either inhibition or activation of the nitric oxide (NO) pathway by N^G-nitro-L-arginine-methyl-ester (L-NAME) or L-arginine, respectively, and, in vitro, by measuring ec and iNOS protein expression and activities in the aorta. Left ventricle and kidneys were also post mortem dissected for hypertrophy evaluation.
Both CHF 1521 and manidipine decreased blood pressure in a highly significant way. Manidipine was slightly but significantly more effective in reducing systolic blood pressure (SBP). Heart rate was not affected by the combination, while it was increased by manidipine. The increase in mean arterial pressure (MAP) induced by L-NAME ranged around 35% in WKY-, manidipine- and CHF 1521-treated groups, without any statistically significant difference between them, while it was significantly smaller in the vehicle-treated SHRs (25.3±2.5%). When L-arginine (0.5 g/kg iv) was added, recovery to baseline values was complete in WKY and vehicle-treated groups, but partial (about 50%) in CHF 1521 group and absent in the manidipine one. ecNOS but not iNOS protein expression and activity were higher in the SHR rats ($p<0.05$ vs WKY). The treatment with CHF 1521 or manidipine did not normalise the ecNOS expression and activity. Left ventricle hypertrophy, evaluated both as left ventricle weight to body weight ratio and as left ventricle wall thickness measurement by histology examination, evidenced that only the combination was able to regress cardiac hypertrophy in a statistically significant way ($P<0.05$). Neither manidipine or CHF 1521 affected renal function, in terms of urine output, urinary electrolytes and protein excretion and kidneys hypertrophy.
We conclude that manidipine/delapril combination attenuates myocardial hypertrophy and endothelial dysfunction caused by hypertension.