EFFECT OF PROLONGED L-ARGININE TREATMENT ON VASCULAR ACTIONS INDUCED BY LOSARTAN IN SHR.

We previously reported that nitric oxide (NO) participates in the antihypertensive effect of losartan in SHR. The administration of the precursor of NO, L-arginine, has shown beneficial effects on blood pressure and endothelial function in Dahl salt-sensitive rats. In the present study we have evaluated the effects of prolonged L-arginine administration on antihypertensive and vascular actions induced by losartan in SHR. Male SHR 20 weeks old received one of the following treatments in drinking water for 12 weeks: L-arginine (660 mg/Kg/day), losartan (10 mg/Kg/day) and L-arginine+ losartan. A control group with no treatment was run in parallel. Systolic blood pressure (SBP) and relaxing and contracting responses in aortic rings were evaluated in all groups. Chronic oral administration of losartan significantly reduced SBP (158 ± 3 vs 189 ± 4 mmHg; p<0.05) compared to controls. Doppler-related responses to acetylcholine (Ach; 10⁻⁶-10⁻⁴ mol/l) were enhanced by losartan administration (maximal response: 83 ± 8 vs 60 ± 3 % of precontraction to phenylephrine). However, responses to superoxide dismutase (SOD; 0.1-100 U/ml) and sodium nitroprusside (SNP; 10⁻⁶-10⁻⁴ mol/l) were not affected by losartan. L-arginine treatment, did not modify either SBP or vascular reactivity. By contrast, L-arginine attenuated the antihypertensive effect of losartan, as well as the enhanced relaxation to Ach induced by losartan. Maximal contractile responses to phenylephrine, endothelin-1 and the thromboxane A₂ analogue, U46619, were not affected by any of the treatments. In conclusion: 1) the antihypertensive effect of losartan is associated with an improvement of Ach-induced relaxation in aortic rings from SHR, 2) prolonged treatment with elevated doses of L-arginine exerts deleterious effects of the vascular actions of losartan in SHR.

Key Words: Nitric oxide, L-arginine, AT₁-antagonist, vascular function, blood pressure

EFFECT OF CHRONIC ET₁-SELECTIVE ENDOTHELIN RECEPTOR ANTAGONISM ON BLOOD PRESSURE IN EXPERIMENTAL AND GENETIC HYPERTENSION IN RATS. A Turgeon, ELS$Wh*, Clinical Research Institute, University of Montreal, Montreal, QC, Canada.

Treatment with an ET₁/ET₄ endothelin receptor antagonist reduced blood pressure in rat models of hypertension which overexpress endothelin-1 in the vascular wall, particularly in small arteries, but not in those models of hypertension which do not overexpress endothelin-1. Since failure to respond to the ET₁/ET₄ antagonist could be due in part to blockade of vasorelaxant endothelin ET₄ receptors, the effect of selective ET₁ antagonism (with A-127722.5 or LU135252) was investigated. Blood pressure of deoxycorticosterone acetate (DOCA)-salt hypertensive rats (which overexpress vascular endothelin-1 and respond with blood pressure lowering to ET₁/ET₄ antagonism), was lowered by a mean of 24 and of 27 mmHg (p<0.01) by A-127722.5 after 4 weeks of treatment, at two different oral doses (10 and 30 mg/kg per day), and by 18 mmHg by 50 mg/kg per day of LU135252. SHR (which do not overexpress endothelin-1 and do not respond with blood pressure lowering to ET₁/ET₄ antagonism), treated with A-127722.5 for 8 weeks exhibited the same rise in blood pressure as untreated SHR. Addition of the angiotensin converting enzyme inhibitor cilazapril (which might sensitize responses to endothelin antagonism) resulted in similar lowering of blood pressure in A-127722.5-treated and untreated SHR. One-kidney 1 clip Goldblatt (1-K 1C) hypertensive rats (which present mild overexpression of endothelin-1 but do not respond with blood pressure lowering to ET₁/ET₄ antagonism) treated with LU135252 at the dose which lowered blood pressure in DOCA-salt rats did not exhibit blood pressure reduction. Thus, treatment with either dose of A-127722.5 or with the dose used LU135252 results in blood pressure lowering similar to that obtained with an ET₁/ET₄ endothelin antagonist. Blood pressure was lowered only in hypertensive rats known to overexpress vascular endothelin-1 (DOCA-salt hypertensive rats) but not in those which do not (SHR) or only have mild vascular overexpression of endothelin-1 gene (1-K 1C hypertensive rats). Interruption of the renin-angiotensin system in SHR did not sensitize blood pressure to potential hypotensive effects of an ET₁-selective receptor antagonist.

Key Words: Endothelin receptor subtypes, antagonists, DOCA, renal and genetic hypertension, SHR, angiotensin converting enzyme inhibitor