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Antihypertensive effects of endothelin receptor antagonists on a diabetic nephropathy-induced SDT fatty rat with hypertension

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Objectives : The Spontaneously Diabetic Torii (SDT) fatty rat, an animal model for type 2 diabetes and obesity, causes early onset of hypertension and diabetic nephropathy by loading salt. In our previous study, an angiotensin-converting enzyme inhibitor showed no antihypertensive effects in the salt-loaded SDT fatty. The aim in this study is to identify the mechanism of hypertension and effective medicine for SDT fatty.
Methods : Firstly, male SDT fatty and Sprague Dawley (SD) rats underwent drinking water without (Cont) or with 0.3% NaCl (Salt) from 10 to 20 weeks of age and were measured systolic blood pressure (SBP) at 19 weeks of age. The expression of blood pressure-related genes in kidneys from the 20-week-old rats was analyzed using quantitative RT-PCR. Secondly, two endothelin receptor (ER) antagonists, Ambrisentan [AMB (type A-selective); 5 mg/kg/day] and Bosentan [BOS (Non-selective); 100 mg/kg/day] were administered to the salt-loaded SDT fatty males from 10 to 16 weeks of age. SBP was measured on every two weeks. Urine liver-type fatty acid binding protein-to-creatinine ratio (uL-FABPCR), a marker of tubular damage, was measured on 13 weeks.
Results : SBP in the salt-loaded SDT fatty was higher than the unloaded SDT fatty and SD. The expressions of renin and kallikreins were significantly lower in SDT fatty than SD. The expression of endothelin as a vasoconstrictor was significantly higher in salt-loaded SDT fatty rats than unloaded SDT fatty and SD rats. AMB showed significantly antihypertensive effects in SBP on 12 and 16 weeks, although it was not shown in BOS. Additionally, uL-FABPCR increased in salt-loaded SDT fatty at 13 weeks was significantly suppressed by AMB. These results suggest AMB is an optimal antihypertensive drug in rodent SDT fatty model.
Conclusions : High expressed-endothelin in salt loaded-SDT fatty is a factor for hypertension. An ER type A-selective antagonist shows higher antihypertensive effect than non-selective that in SDT fatty.