Pharmacogenetic Analysis of Captopril Effects on Blood Pressure: Possible Role of the Ednrb (Endothelin Receptor Type B) Candidate Gene

J. ZICHA1, Z. DOBEŠOVÁ1, V. ZÍDEK1, J. ŠILHAVÝ1, M. ŠIMÁKOVÁ1, P. MLEJNEK1, I. VANĚČKOVÁ1, J. KUNEŠ1, M. PRAVENEC1

1Institute of Physiology Academy of Sciences of the Czech Republic, Prague, Czech Republic

Summary
The objective of the current study was to search for genetic determinants associated with antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitor captopril. Linkage and correlation analyses of captopril-induced effects on blood pressure (BP) with renal transcriptome were performed in the BXH/HXB recombinant inbred (RI) strains derived from spontaneously hypertensive rat (SHR) and Brown Norway (BN-Lx) progenitors. Variability of blood pressure lowering effects of captopril among RI strains was continuous suggesting a polygenic mode of inheritance. Linkage analysis of captopril-induced BP effects revealed a significant quantitative trait locus (QTL) on chromosome 15. This QTL colocalized with cis regulated expression QTL (eQTL) for the Ednrb (endothelin receptor type B) gene in the kidney (SHR allele was associated with increased renal expression) and renal expression of Ednrb correlated with captopril-induced BP effects. These results suggest that blood pressure lowering effects of ACE inhibitor captopril may be modulated by the variants at the Ednrb locus.

Key words
Captopril • Blood pressure • Genetics • Ednrb gene • Spontaneously hypertensive rat

Angiotensin-converting enzyme (ACE) inhibitors are widely used for the treatment of high blood pressure. ACE inhibitors do not lower blood pressure in all hypertensive patients (Dickerson et al. 1999, Struthers et al. 2001). Therefore it has been suggested that these differences in blood pressure lowering effects might be genetically determined. Identified responsible genetic determinants could serve as useful markers to predict the therapeutic efficacy of these drugs (Konoshita et al. 2011). The objective of the current study was to search for genetic determinants associated with antihypertensive effects of ACE inhibitor captopril in the BXH/HXB recombinant inbred (RI) strains derived from spontaneously hypertensive rat (SHR) and Brown Norway (BN-Lx) rat. Figure 1A shows continuous variability of blood pressure lowering effects of captopril among RI strains which suggests a polygenic mode of inheritance. Linkage analysis of captopril-induced BP effects revealed a significant quantitative trait locus (QTL) on chromosome 15 (Fig. 1B). RI strains with BN-Lx genotype at the peak of QTL linkage exhibited significantly smaller captopril-induced BP reduction when compared with RI strains with SHR genotype (−7.4±0.6 vs. −12.1±0.8 mm Hg, P=0.00003). This QTL is colocalized with cis regulated expression QTL (eQTL) for the Ednrb (endothelin receptor type B, ETBr) candidate gene in the kidney (SHR allele was associated with increased renal expression when compared with BN-Lx allele) (Fig. 1B). In addition, we observed a significant correlation between renal expression of Ednrb and captopril-induced BP effects (r=0.48, P=0.01).
Sequence analysis of the BN-Lx and SHR Ednrb alleles revealed several polymorphisms in the promoter region, however, promoter analysis using luciferase reporter gene assay showed no differences in transcriptional activity of the Ednrb promoter region of the SHR strain when compared with the Ednrb promoter region of the BN-Lx strain (data not shown). This result suggests that cis regulated renal expression of Ednrb gene is determined by variants outside the tested promoter region. The Ednrb is a promising candidate gene for blood pressure lowering effects of captopril. Endothelin 1 (ET-1), a major regulator of vascular function acts through endothelin receptors type A (ETAR) and type B (ETBR) that are coded for by Endra and Ednrb genes on rat chromosomes 19 and 15, respectively. While ETAR mediates ET-1-induced vasoconstriction and has been implicated in the pathogenesis of hypertension, the ETBR induces the release of vasodilatation factors including nitric oxide or prostacyclin and has been also implicated in the clearance of ET-1 (Mazzuca et al. 2012). ETBR plays an important role in sodium and water excretion in the kidney by reducing sodium reabsorption by inhibiting ET-1 action in the collecting ducts of the renal medulla (Kohan et al. 2011). The important role of ETBR in regulation of sodium balance is supported by the fact that rats with mutant Ednrb gene are salt-sensitive (Gariepy et al. 2000) and that mice with collecting duct-specific targeting of Ednrb gene are hypertensive (Ge et al. 2006). Finally, it has been demonstrated that ACE inhibition increases expression of Ednrb in kidneys (Moridaira et al. 2003).

In summary, our study identified Ednrb as a candidate gene for captopril-induced blood pressure effects: (1) cis-eQTL for renal expression of Ednrb is located at the peak of QTL linkage for captopril-induced BP effects, (2) reduced renal expression of Ednrb in RI strains with SHR allele is associated with significantly smaller BP changes after captopril when compared to RI strains with the BN-Lx Ednrb allele, and (3) renal Ednrb expression correlated with captopril-induced BP effects. Taken together, these results provide compelling evidence that captopril effects might be mediated via affecting renal expression of ETBR.

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