RAPID COMMUNICATION

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

J. ZICHA[1], Z. DOBEŠOVÁ[1], V. ZÍDEK[1], J. ŠILHAVÝ[1], M. ŠIMÁKOVÁ[1], P. MLEJNEK[1], I. VANĚČKOVÁ[1], J. KUNEŠ[1], M. PRAVENEC[1]

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

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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

Corresponding author

M. Pravenec, Institute of Physiology Academy of Sciences of the Czech Republic, Vídeňská 1083, 142 20 Prague 4, Czech Republic. E-mail: pravenec@biomed.cas.cz

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 expresstion QTL (eQTL) for the *Ednrb* (endothelin receptor type B, ET_BR) 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).

Fax +420 241 062 164, e-mail: physres@biomed.cas.cz, www.biomed.cas.cz/physiolres

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 (ET_AR) and type B (ET_BR) that are coded for by *Endra* and *Ednrb* genes on rat chromosomes 19 and 15, respectively. While ET_AR mediates ET-1-induced vasoconstriction and has been implicated in the pathogensis of hypertension, the ET_BR 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). ET_BR 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 ET_BR 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 ET_BR.

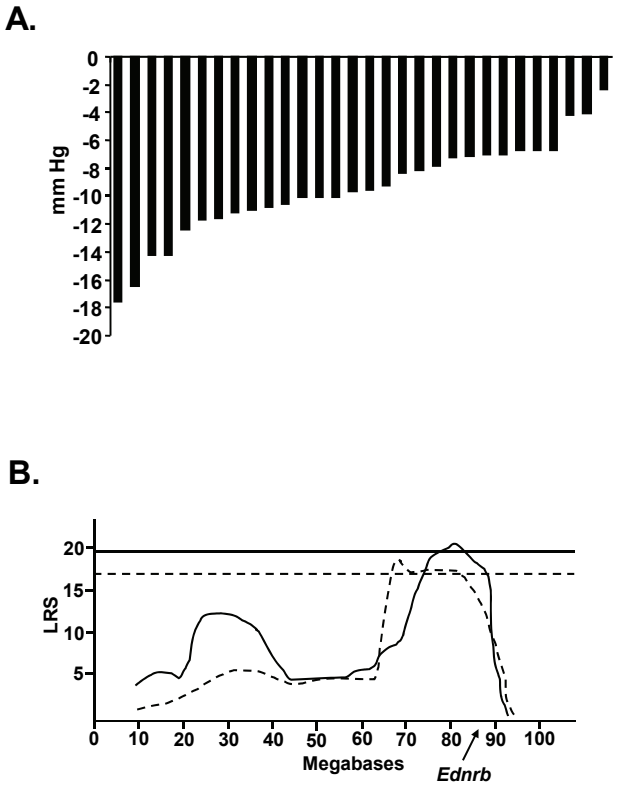

Fig. 1. Identification of genetic determinants of captopril-induced blood pressure effects in the BXH/HXB recombinant inbred (RI) strains. **A.** Distribution of captopril-induced BP effects among RI strains. Under light ether anesthesia, polyethylene catheters were inserted into the left carotid artery and jugular vein, and blood pressure was recorded in conscious animals after 24 h recovery. Basal mean arterial blood pressure values were monitored for 30 min. Thereafter, an intravenous bolus of captopril was injected. **B.** Interval mapping of QTL associated with captopril BP effects (dashed line) colocalized with cis-regulated eQTL for renal expression of the *Ednrb* gene (solid line). Genome wide statistical significance for both QTLs (horizontal dashed and solid lines) was estimated by the permutation tests using the WebQTL online software (www.genenetwork.org).

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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