学 位 論 文 の 要 旨

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学 位 論 文 名	Genetic Effects of Blood Pressure Quantitative Trait Loci on Hypertension-Related Organ Damage: Evaluation Using Multiple Congenic Strains
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論 文 内 容 の 要 旨

Introduction

The stroke-prone spontaneously hypertensive rat (SHRSP) is a genetic model for hypertension and hypertension-related disorders (e.g. cerebral stroke and renal failure). We identified a potent quantitative trait locus (QTL) for blood pressure on rat chromosome (Chr) 1 by a genetic analysis using SHRSP and Wistar-Kyoto (WKY) rats , which was confirmed in congenic strains. In addition, several QTLs regulating the susceptibility to renal damage as well as to cerebral stroke were found on Chr 1 of different hypertensive rat strains, some of which were claimed to be independent of high blood pressure.

In this study, we therefore employed five congenic strains harboring different fragments of the Chr1 QTL to examine whether any genes in the QTL affect the susceptibility to renal damage or to cerebral stroke independently of hypertension

Methods

Animals

We used five congenic strains harboring different chromosomal fragments from the Chr-1 QTL; they were SHRSP. WKY(D1Wox29-D1Arb21)/Izm (abbreviated as SHRSPwch1.0), SHRSP.WKY(D1Rat44-D1Arb21)/Izm (SHRSPwch1.5), SHRSP.WKY(Apbb1-D1Arb21)/Izm (SHRSPwch1.8), SHRSP.WKY(D1Mgh5-D1Rat44)/Izm (SHRSPwch1.9), and SHRSP.WKY(D1Mgh5-D1Wox29)/Izm (SHRSPwch1.11). Male rats at 12 weeks of age were employed in the experiments.

Evaluation of Phenotypes

At 12 weeks of age, drinking water was changed to 1% sodium chloride solution until the end of the experiments. Blood pressure was measured by the tail-cuff method before and after 2 weeks of salt-loading.

During salt-loading, symptoms of cerebral stroke were assessed in individual rats every day. After rats were diagnosed as cerebral stroke, rats were sacrificed and the brain was quickly removed to confirm the infarcted regions.

In the study of the renal damage, rats were sacrificed after 4 weeks of salt loading. Fifty to 70 glomeruli from the bilateral kidneys were evaluated in each rat by the light microscopy. The severity of glomerulosclerosis was classified into three categories, mild (<10%), moderate (10 to 70%) and severe(>70%) in each glomerulus. Percentages of glomeruli with the moderate to severe sclerosis were used in the analysis.

Results and Discussion

Blood pressure

The "basal" blood pressure before the salt-loading was significantly lower in all congenic strains, except in SHRSPwch1.8, than in SHRSP. The significant increase in blood pressure by the salt-loading was observed in the four congenic strains with the exception of SHRSPwch1.5.

These results indicated 1) that a chromosomal region represented by SHRSPwch1.8 did not harbor a major gene responsible for hypertension, and 2) that SHRSPwch1.5 was the only strain that did not show salt-sensitivity.

In addition, SHRSPwch1.9 and 1.11 showed the lowest blood pressure, when compared with SHRSPwch1.0, which implied that additional genes responsible for hypertension were located in the region represented by these two congenic strains.

Cerebral stroke and blood pressure

Four congenic strains excluding SHRSPwch1.8 showed significantly greater stroke latencies than SHRSP. Incidence of the stroke showed significant correlation with the basal blood pressure among the five congenic strains, which implied that blood pressure was the major factor controlling the susceptibility to stroke among the congenic strains, and that no major susceptibility genes to the stroke were in this region.

Glomerulosclerosis and blood pressure

SHRSPwch1.0, and 1.8 were susceptible to glomerulosclerosis when compared with other congenic strains. It was of interest that SHRSPwch1.0 showed a severe renal damage in spite of its modest hypertension. This result suggested that genes controlling the susceptibility to glomerulosclerosis might be located in the region represented by this congenic strain.

Conclusion

The present study implied that this chromosomal fragment included not the genes for the susceptibility to cerebral stroke but to glomerulosclerosis. Further analysis using another series of congenic strains is essential to identify the susceptibility genes.