学 位 論 文 の 要 旨

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学 位 論 文 名	A 1.8-Mbp Fragment on Chromosome 1 Affects Sympathetic Response to Stress: Evaluation in Reciprocal Congenic Strains Between Stroke-Prone Spontaneously Hypertensive Rat and Wistar-Kyoto Rat
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論 文 内 容 の 要 旨

INTRODUCTION

The sympathetic nervous system (SNS) is one of the most important systems that modulate blood pressure (BP) in response to various environmental stimuli. Both in humans and in rats, dysfunctions of SNS were reported to be a putative cause of hypertension. Genes influencing sympathetic activity are, therefore, important when considering the genetic susceptibility to hypertension, especially in the context of gene-environmental interaction. In the previous studies, we indicated that genes responsible for exaggerated sympathetic response to stressors were located in a chromosome 1 (chr-1) quantitative trait locus (QTL) for BP in stroke-prone spontaneously hypertensive rat (SHRSP). In the current study, we narrowed down the candidate region to a 1.8-Mbp fragment, and established reciprocal congenic strains for this region. We examined (1) urinary norepinephrine (NE) excretion under cold stress, (2)

cardiac autonomic response and (3) blood pressure change during restraint and cold stress in the congenic strains to confirm the effect of this region on the sympathetic responsiveness.

MATERIALS AND METHODS

Reciprocal congenic strains were established by introgressing the chromosomal segment from SHRSP/Izm into WKY/Izm (Wpch1.21) and vice versa (SPwch1.72). The urinary norepinephrine excretion (u-NE) was quantified with high-performance liquid chromatography in the urine collected under 6 h of cold stress (4°C). Electrocardiograph were recorded using the radiotelemetry under 3 h of restraint stress, and the relative sympathetic activity was evaluated using the low frequence/high frequence (LF/HF) ratio of heart rate variability by power spectral analysis. BP under the restraint and cold stresses was evaluated by the radiotelemetry system.

RESULTS AND DISCUSSION

The increases in the u-NE during the cold stress and in the LF/HF ratio under the restraint stress were significantly greater in Wpch1.21 when compared with Wistar-Kyoto (WKY) rat (Δu-NE: 342±47 vs 173±69 nmol, $P<0.05$; ΔLF/HF ratio: 1.9±0.9 vs 0.3±0.3, $P<0.05$). The stress-response in BP was significantly greater in Wpch1.21 than in WKY during restraint stress (ΔSBP: 13±5 vs 3±6 mmHg, $P<0.05$) and cold stress (ΔSBP:33±11 vs 17±8 mmHg, $P<0.05$). In the reciprocal congenic strain, SPwch1.72, the effects of the transferred fragment on the sympathetic stress responses were confirmed as the lower Δu-NE and ΔLF/HF ratio than those in SHRSP (Δu-NE: 389±128 vs 572±96 nmol, $P<0.05$; ΔLF/HF ratio: 1.9±1.1 vs 3.4±0.5, $P<0.05$). Further, BP response was significantly lower in SPwch1.72 than in SHRSP both under the restraint stress (ΔSBP: 2±4 vs 23±12 mmHg, $P<0.05$) and the cold stress (ΔSBP: 16±6 vs 35±4 mmHg, $P<0.05$). In this study, Wpch1.21, a congenic strain with a small SHRSP fragment in the WKY background was shown to have an exaggerated sympathetic response to the two

different stresses, cold and restraint stress. It was further confirmed in the reciprocal congenic strain that harbored the overlapped fragment of WKY in the SHRSP background. This reciprocal response in the pair of the congenic strains provided an important clue indicating that the gene(s) in this region influenced the stress responses of rats without any significant interactions with the genomic background.

CONCLUSION

We identified a 1.8-Mbp fragment on Chr 1 that influenced the sympathetic responsiveness to the stresses in SHRSP. As 29 known and putative genes are in this region in addition to 32 olfactory receptor genes, a comprehensive evaluation of these genes in congenic strains is essential to identify the responsible gene(s).