Salt-Sensitive Hypertension and Cerebral Circulation in Gene-Mutant Mouse and Genetically Stroke Rat

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Summary

Recently, the availability of transgenic mice has enabled us to examine the involvement of specific gene products in various pathological and physiological conditions. Furthermore, we used gene-targeting technology to generate M5 muscarinic acetylcholine receptor-deficient mice ($M5R^{-/-}$ mice). In the present study, we made a measurement system for blood pressure and cerebral hemodynamics (cerebral blood flow; CBF, vessel diameter; VD) in pial microcirculation in mouse. Using this system, we measured cerebral hemodynamics in gene mutant mice and genetically stroke model rat (stroke-prone spontaneously hypertensive rats; SHRSP) under physiological and pathological condition.

We first measured CBF and the diameter of cerebral arterioles using intravital microscopy through a cranial window in male $M5R^{-/-}$ and wild-type ($M5R^{+/+}$) mice. All mice showed normal peripheral blood pressure (tail-cuff method) ($M5R^{+/+}$, 111.6 + 4.6 mmHg; $M5R^{-/-}$, 111.8 + 3.6 mm Hg; means + s.e.m.; n = 8 for each group of 3 month-old mice). The branches of the middle cerebral arterioles (MCA) were defined in the order from A1 to A3. Under resting conditions, male $M5R^{-/-}$ mice showed a small but significant reduction ($P < 0.05$ in one-way ANOVA) in MCA diameter, as compared with $M5R^{+/+}$ mice. Laser-Doppler flowmeter measurements showed that male $M5R^{-/-}$ mice showed significantly lower ($P < 0.001$ in one-way ANOVA) CBF at the A1 branch of the MCA in the resting state. Male $M5R^{-/-}$ and $M5R^{+/+}$ mice did not differ in the levels of blood gases and pH (see Supplementary Methods).

We quantitated regional CBF in male $M5R^{-/-}$ and $M5R^{+/+}$ mice by using ^{14}C-labeled iodoantipyrine autoradiography. $M5R^{-/-}$ mice displayed significantly reduced CBF ($P < 0.05$) in all cortical, hippocampal, and thalamic regions studied. CBF was not significantly reduced in different regions of the midbrain.

These data strongly suggest that M5 receptor dysfunction leads to impaired CBF in higher brain regions.