Abstract of Doctoral Thesis

Title: The mechanism of functional recovery after focal cerebral ischemia

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Motor, sensory, and cognitive impairments are caused by cerebral ischemia. Exercise is prescribed in rehabilitation to improve the functional recovery after brain stroke. However, its mechanism is not clear because of the lack of reproducibility and low survival rate of conventional ischemic model animals. In this study, we assessed precisely the effects of exercise on functional recovery and pathophysiological remodeling in the ipsilateral hemisphere using highly reproducible model mouse of focal cerebral ischemia. Behavioral tests revealed the substantial effect of voluntary running exercise on functional recovery after cerebral ischemia. Exercise did not affect the volume of infarction or survived cortex, or the number of neurons in the peri-infarct cortex. In contrast, ischemia-induced dendritic spine loss was ameliorated by exercise in pyramidal neurons of motor cortex layer V on postoperative days (POD) 15. Neuronal morphology is affected by the perineuronal environment. Glial cells are important components of that environment, and their phenotypes may be modified by exercise after cerebral ischemia. We confirmed that voluntary running exercise increased the proportion of GFAP-positive astrocytes born between POD0 and 3 to all GFAP-positive astrocytes on POD15. Transcriptomic analysis revealed that 10 genes were upregulated, and 70 genes were downregulated in POD15 astrocytes by exercise. The Gene Ontology term “Cell morphogenesis involved in neuron differentiation” was significantly enriched in the gene set downregulated by exercise. Consistently, Lipocalin 2 expression was reduced in astrocytes on POD15 by exercise after ischemia. The results suggest that the effect of rehabilitation for brain stroke is derived from exercise-induced inhibition of dendritic spine loss. Exercise modifies the astrocytic phenotype, which contribute to the maintenance of dendritic spines in the ischemic brain.