Effects of Kampo-medicines on spatial memory impairment induced by repeated cerebral ischemia in rats

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Cerebral ischemia causes irreversible neuronal degeneration with necrosis and apoptosis in hippocampal CA1 neurons. We developed transient repeated cerebral ischemia model with 10 min occlusion x 2 times at 1 h intervals. This model produced spatial memory impairment in the 8-arm radial maze at 7 days after the occlusion and the impairment was associated with apoptosis and a decrease in GluR2mRNA, one subunit of the AMPA receptor, in hippocampal CA1 pyramidal cells (Brain Res 995, 131-139, 2004). These results suggest that the excess glutamate release/AMPA receptor/Ca^{2+} influx/NO signaling pathway is important to the induction of hippocampal neuronal injury and a reduction in acetylcholine release is related to the impairment of spatial memory in rats subjected to repeated cerebral ischemia. We examined effects of Kampo-medicines on spatial memory impairment induced by repeated cerebral ischemia in rats. The 21-day regimen with Kangen-karyu (14-day pre-ischemic and 7-day post-ischemic administration) ameliorated not only spatial memory impairment in the 8-arm radial maze, but also necrosis and TUNEL-positive cells in the hippocampal CA1 area subjected to repeated cerebral ischemia. On the other hand, 7-day post-ischemic treatment with Toki-shakuyaku-san ameliorated spatial memory impairment in the 8-arm radial maze, TUNEL-positive cells and a decrease in GluR2 mRNA in the hippocampal CA1 area (Am J Chin Med 33, 475-489, 2005). Moreover, single treatment with Toki-shakuyaku-san prior to the test, improved spatial memory impairment with an increase in acetylcholine release in the hippocampus using microdialysis without affecting hippocampal neuronal injury. Thus, Kangen-karyu and Toki-shakuyaku-san may be useful for treating cerebrovascular disease, although adequate attention must be given to the injection timing of each Kampo-medicine.