Therapeutic potency of Kampo medicine against neurodegenerative diseases by multiple molecular mechanisms of enhancing neuronal polarity

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We aimed to clarify effects of Kampo medicine, “Kihi-to” on memory impairment in a mouse model of Alzheimer’s disease (i.c.v. injection of A) and the mechanism of Kihi-to. As a result, treatment with Kihi-to for 12 days (100 mg/kg B.W./day, p.o.) prevented A(25-35)-induced decreases in axons (marker: phosphorylated NF-H), dendrites (MAP2), synapses (synaptophysin) and myelins (MBP), and also restored A(25-35)-induced memory impairment in the brain of male ddY mice (7 weeks old).

Since our experiments using primary cultured cortical neurons suggested that Kihi-to might have a calpain inhibitor-like effect and a calpain inhibitor (MDL28170) also extended neurites similarly to Kihi-to, we compared effects of Kihi-to and MDL28170 on memory impairment in the AE i.c.v. model. Declined memory acquisition was completely recovered by comparatively short-term treatment with Kihi-to and MDL28170 (treatment for 3days). In contrast, impaired memory retention was recovered only by Kihi-to. In addition, loss of object recognition memory in the model was normalized only by Kihi-to. Immunohistochemistry of mouse brain slices showed that the expression level of calpain increased in A(25-35)-treated group, and was inhibited by treatment with Kihi-to and MDL28170. The expression level of calpastatin, an intracellular inhibitor of calpain, decreased in A(25-35)-treated group, and was increased by treatment with Kihi-to or MDL28170. Densities of axons in the cerebral cortex, radiatum region of the hippocampal CA1 and perirhinal cortex were increased by Kihi-to, but not MDL28170. Densities of dendrites in the cerebral cortex, and densities of myelins in the striatum and corpus callosum were also increased by Kihi-to, but not by MDL28170.

In conclusion, Kihi-to improves the A(25-35)-induced memory impairment by inhibition of the calpain system which brakes down several important proteins for the neuronal structure and function. In addition to this effect, Kihi-to increases axons, dendrites and myelins potentially and widely, resulting in the marked memory improvement.