

### III-3. Ameliorative effects of Yokukansan on behavioral deficits following ischemic dementia in gerbils

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#### 【Objective】

The traditional herbal medicine yokukansan (YKS) has been used for the treatment of behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease and other forms of senile dementia. The present study investigated the effect of YKS on behavioral deficits and hippocampal neuronal damage in a gerbil model of transient forebrain ischemia and examined the mechanisms underlying those effects.

#### 【Methods】

Gerbils were treated with YKS by oral gavage for 30 days, once per day, until the day before induction of ischemia, which was induced by occluding the bilateral common carotid artery for 5min. The effects of YKS (50, 100 and 300 mg/kg) were examined by measuring neuronal damage and behavioral deficits (locomotor activity, 8-arm radial maze task). The anti-inflammatory and anti-oxidant properties of YKS were also examined.

#### 【Results】

YKS reduced hippocampal neuronal death after cerebral ischemia with a dose-dependent manner ( $p < 0.05$ ). Administration of YKS at 300 mg/kg significantly reduced ischemia-induced locomotor hyperactivity and improved memory impairment ( $p < 0.05$ ), also inhibited the ischemia-induced inflammatory response and DNA oxidative damage ( $p < 0.05$ ).

#### 【Discussion】

Recently, YKS has been used to treat BPSD in patients with some types of senile dementia. Vascular dementia is the second most common form of dementia, accounting for up to 40 percent of cases in older adults. It usually results from a series of strokes, particularly ischemic stroke<sup>1)</sup>. This study demonstrates that YKS improves behavioral deficits induced following transient forebrain ischemia in gerbils by a dose-dependent attenuation of neuronal injury.

Kampo medicine is Japan's traditional medicine, which is mainly based on traditional Chinese medicine (TCM). Over millennia, TCM has accumulated extensive clinical experience in treating stroke with indigenous herbal materials<sup>2)</sup>. The compounds of YKS, such as *Uncaria rhynchophylla* and *Angelica acutiloba* have been reported to affect the serotonergic system, further explaining the improvement of YKS on BPSD<sup>3,4)</sup>. Moreover, *Cnidium officinale*, *Angelica acutiloba*, *Poria cocos*, are most frequently used for ischemic stroke. Some studies have reported that the compounds of YKS have ameliorative effects on cognitive impairment<sup>5,6)</sup>, inflammatory activity<sup>7)</sup> without adverse effects.

Sensorimotor deficits and spatial memory impairment are associated with cerebral ischemia/reperfusion injury. We performed locomotor activity and 8-arm radial maze task to examine the effect of YKS (300 mg/kg) on such dysfunction after transient brain ischemia. Our results revealed that YKS decreased

ischemia-induced hyperactivity, and improved learning and memory impairment after ischemia. This may be attributed to reduced hippocampal neuronal damage.

### **【Conclusion】**

The present study suggests that YKS treatment ameliorates behavioral dysfunction after transient forebrain ischemia by suppressing neuronal damage. This beneficial effect of YKS may have potential for ischemic stroke.

### **【References】**

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### **[Discussion]**

**OKADA:** Thank you for your excellent experiments and studies concerning ischemic stroke to prevent the deterioration of cognitive function and motor function. Are there any comments or questions? It was clearly demonstrated and you suggested the effects of Yokukansan on the hippocampus cells damaged by ischemia. What do you think is the most important factor of Yokukansan to prevent ischemic stroke?

**LIU:** The behavioral deficit induced by ischemia is also related to neuronal death. In this study, we just focused on the effects of Yokukansan to see whether it has or not.

**OKADA:** This gerbil model is the delayed neuronal death model suggested by Prof. Taka Kirino, so I imagine that the radical-scavenging effect of Yokukansan is the most important factor in this study. The anti-oxidative effects you describe in this paper, I think are important. I hope that you progress this study. Thank you very much.

**LIU:** Thank you very much.