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学位論文の内容の要旨

専攻	機能構築医学	部　門	神経構造学
学籍番号	11D709	氏　名	劉　亜南
論文題目	Ameliorative effects of yokukansan on behavioral deficits in a gerbil model of global cerebral ischemia.		

(論文要旨)

Cerebral ischemia is a subtype stroke which common happens worldwide and can lead to death. It can lead to severe cerebral damage in selectively vulnerable brain areas, such as hippocampal CA1 region and result in subsequent dysfunction, including motor and sensory symptoms, impaired spatial orientation and memory impairment. Yokukansan, one of the Kampo prescriptions, is composed of seven herbaceous plants and was developed in China as a cure for restlessness and agitation in children. Recently, yokukansan has been reported in the treatment of behavioral and psychological symptoms of dementia (BPSD) such as aggression, anxiety and depression in patients with Alzheimer's disease, cerebrovascular dementia and other forms of senile dementia. However, relatively little is known of the effect of yokukansan on behavioral deficits induced by transient forebrain ischemia.

The present study investigated the effect of yokukansan on behavioral deficits and hippocampal neuronal damage in a gerbil model of transient forebrain ischemia and examined the mechanisms underlying those effects.

Male Mongolian gerbils were treated with yokukansan by oral for a period of 30 days once per day until the day before induction of ischemia, which was induced by occluding the bilateral common carotid artery for 5min. Distilled water was administered to the control groups at the same time points. The effects of yokukansan were examined by measuring neuronal damage with a dose-dependent manner (50 mg/kg; 100 mg/kg; 300 mg/kg) and behavioral deficits (locomotor activity, 8-arm radial maze task). The anti-inflammatory and anti-oxidant properties of yokukansan were also detected for mechanism investigation.

Administration of yokukansan with the dosage at 300 mg/kg significantly reduced hippocampal neuronal death after brain ischemia, neither 50 mg/kg nor 100 mg/kg yokukansan provided neuroprotection. Yokukansan at 300 mg/kg significantly decreased the number of Iba1 (microglia marker) positive cells, the level of 8-OHdG (DNA oxidation marker) and also reduced the locomotor activity 72h after transient forebrain ischemia and the number of errors in 8-arm radial maze task. These findings suggest that yokukansan treatment can inhibit the inflammatory reaction, the oxidative damage and subsequent neuronal death induced by cerebral ischemia reperfusion injury, and also can contribute to the improvement of neurological deficits following such injury.

In conclusion, the present study suggests that yokukansan treatment may be beneficial for global cerebral ischemia by suppressing neuronal damage in the hippocampus and ameliorating behavioral dysfunction.

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