234 The Journal of Toxicological Sciences,
Vol.23, Supplement II, 234—236, 1998

Proccedings of the 1st ASIATOX Conference, June 29-July 2, 1997, Yokohama, Japan

PROTECTIVE EFFECT OF A TRADITIONAL MEDICINE, SHI-MOTSU-TO, ON BRAIN LESION IN RATS

Hiroshi WATANABE

Department of Pharmacology, Research Institute for Wakan-Yaku,
Toyama Medical and Pharmaceutical University, Toyama, 930-01, Japan

INTRODUCTION

Shimotsu-to (SMT) is a basic prescription of traditional Chinese medicine, which is consisted of four herbs: Japanese angelica root, cnidium rhizome, peony root and rehmannia root. It has been clinically used to treat menstrual problems and autonomic imbalance of women for several centuries in China and Japan (Table 1). Recently SMT was shown to be useful for the treatment of dementia in aged people (Table 2) [1].

There are so many papers which have been investigated the effects of SMT on rheology of the blood and on circulation. The CNS pharmacological actions of SMT and of the component herb, however, have not been studied in the past.

Thus, we have investigated psychopharmacological effects of SMT and its component herbs on emotional stress and on spatial cognitive deficit induced by chronic brain ischemia in experimental animals.

Effect of SMT on emotional stress in mice

Repeated exposure of mice to forced shaking under the low temperature for 4 days (totally 7 times) significantly reduced pentobaribital-sleeping time[4]. SMT (1 g dried herbs/kg, p.o.) significantly reversed the pentobarbital-sleeping time to the control level. When each component herb was examined, it produced no significant effect on pentobarbital sleeping time.

Chronically isolated housing of mice caused a significant increase in locomotor activity, prominent shortening of pentobarbital sleeping time and an induction of aggressive behavior. A single administration of SMT (1 g/kg, p.o.) inhibited locomotor activation induced by long-term isolation without affecting it in group-housed control mice. SMT also inhibited the aggressive behavior in isolated mice. The component herbs, angelica root and cnidium rhizome, also suppressed the aggressive behavior.

SMT did not affect the pentobarbital sleeping time in isolated mice. The component herbs, angelica root and cnidium rhizome, however, recovered the shortened pentobarbital sleep to the control level. Other components, paeony and rehmannia roots, did not affect the pentobarbital-induced sleep.

Table 1. Component of Shimotsu-to (四物湯) and its indications.

1. Components: Angelica root 3g, Paeony root 3g, Cnidium rhizome 3g, Rehmannia root 3g
2. Indications: Feeling of cold, dysmenorrhea, menopause-syndrome, dysfunction of autonomic nervous system, infertility, exhaustion after parturition, hypertension, pigment in old people
3. Target group: Relatively weak, pale face, dried skin, trophic disturbance of the skin, reduced abdominal tension, palpitation of the abdominal aorta
4. Traditional applications: Yin-disease 1 stage, Yin-excess, OKETSYU-syndrome, Ki-deficience

(Terasawa, K.; Kampo, p216, K K Standard McIntyre, Tokyo, 1993)

Correspondence : Hiroshi WATANABE

The Journal of Toxicological Sciences,
Vol.23, Supplement II, 234—236, 1998

Proccedings of the 1st ASIATOX Conference, June 29-July 2, 1997, Yokohama, Japan

Effect of Shimotsu-to on spatial cognitive deficits induced by chronic brain ischemia in the rat

We investigated the effect of SMT on the working memory performance impaired by scopolamine and reported that SMT improved the working memory deficit, which is attributed mainly to the effect of the component of peony and angelica roots, and their constituents, paeoniflorin and tetramethylpyrazine, respectively[5, 6]. Therefore, we further studied the effect of SMT on a model of the spatial cognitive deficit following permanent occlusion of the bilateral common carotid arteries of the rat.

The permanent occlusion of the bilateral common carotid arteries (2VO) of the rat produced a chronic ischemia of the brain, i.e. 30 to 50% reduction of the cerebral blood flow in the cerebral cortex and the striatum. Various degree of the brain lesion was induced by a chronic brain ischemia[7]. The ratios of animals with infarction in the cerebral cortex 1 and 4 months after permanent 2VO were 28.6 and 14.3%, respectively, whereas those in the striatum 1 and 4 months after 2VO were both 42.9%. Infarction in the hippocampus and hypothalamus was not observed by 1 month after 2VO. On the other hand, the rarefaction in the white matter was observed in 14.3 and 71.4% of the animals when examined 1 and 4 months after the 2VO, respectively. The number of CA1 neurons in the hippocampus significantly decreased 1 month after the 2VO, while the number of neuronal cells in the CA2 and 3 areas did not significantly decrease at the same time period. The ACh content in the striatum significantly decreased 1 month after the 2VO by 14.9%, whereas those in other regions did not change significantly[8]. These results indicate that the brain lesions after 2VO is quite similar to the leukoencephalo-pathy in human.

The chronic ischemia of the brain produced a gradual development of the spatial cognitive deficit in the radial maze performance. The rat, that had not been pretrained, failed to learn the radial maze performance after the permanent 2VO. The number of errors in such rats did not decrease even after the repeated training. The rats, that had been well pretrained, exhibited only slight impairment in the retention of radial maze performance 3-7 days after 2VO, but their errors gradually recovered to the level of the control group with trials.

Subchronic administration of SMT (0.3 and 1.0 g/kg, p.o.) did not improve the spatial cognitive deficit induced by the permanent 2VO. SMT did not change the induction rate of the infarction in the cerebral cortex, striatum and thalamus, and of the rarefaction in the white matter. However, the development of infarction of the parenchyma and enlargement of the cerebral ventricle were significantly inhibited by SMT (0.3 g/kg, p.o.) at two months after the 2VO. The enlargement of the cerebral ventricle was also inhibited by SMT (1 g/kg, p.o.) at 4 months after the 2VO.

Repeated administration of aminotetrahydroacridine (tacrine; 0.1 and 0.3 mg/kg, i.p.), a reference drug, from one month after the 2VO improved the spatial cognitive deficit in the radial maze task.

CONCLUSION

The present results suggest that a basic prescription of the traditional medicine, SMT, prevents the development of brain infarction and rarefaction induced by chronic brain ischemia in the rat. If we could clarify the active constituent(s) and action

Table 2. Traditional medicines which have therapeutic effects on senile dementia in human.

Name of Prescription	Component herbs
Ouren-gedoku-to 黄連解毒湯	Coptis, Scutellaria, Phellodendron, Gardenia
Chouto-san 釣藤散	Uncaria, Citrus, Pinellia, Ophiopogon, Poria, Ginseng, Chrysanthemum, Ledebouriella, Gypsum, Glycyrrhiza, Zingiber
	combined with Shigyaku-san (Bupleurum, Paeonia, Glycyrrhiza, Citrus) 四逆散
	with Shimotsu-to (Cnidium, Angelica, Paeonia, Rehmannia) 四物湯

Proccedings of the 1st ASIATOX Conference, June 29-July 2, 1997, Yokohama, Japan

mechanism of SWT, it is possible to find much more effective cognitive enhancers.

ACKNOWLEDGEMENTS

This work was done in collaboration with Matsumoto K., Ohta H., Ni J-W., Ojima K., Kohno S., Sakai T., and Tanaka M.

REFERENCES

H Narita (1991): Kampo medicine and brain desease. In Vascular deseases in aged people and Kampo medicine. edited by G Araki, 16-24, Iyaku Journal Co., Tokyo.

K Ojima, K Matsumoto, M Tohda and H Watanabe (1995): Hyperactivity of central noradrenergic and CRF systems is involved in social isolation-induced decrease in pentobarbital sleep in mice. Brain Res. **684**, 87-94.

K Matsumoto, K Ojima, H Watanabe (1996): Neurosteroidal modulation of social isolation-induced decrerase in pentobarbital sleep in mice. Brain Res. **708**, 1-6.

K Matsumoto, T Satoh, H-B Li, H Ohta and H Watanabe (1991): Effects of forced shaking stress at low temperature on pentobarbital-induced sleeping in mice. Gen. Pharmacol. **22**, 729-733.

H Watanabe, J-W Ni, H Ohta, X-H Ni and K Matsumoto (1991): A Kampo prescription, Shimotsu-to, improves scopolamine-induced spatial cognitive deficits in rats. Jpn. J. Psychopharmacol. **11**, 215-222.

H Ohta, J-W Ni, K Matsumoto, H Watanabe and M Shimizu (1993): Peopny and its major constituent, paeoniflorin, improve radial maze performance impaired by scopolamine in rats. Pharmacol. Biochem Behav. **45**, 719-723.

J-W Ni, H Ohta, K Matsumoto and H Watanabe (1994): Progressive cognitive impairment following chronic cerebral hypoperfusion induced by permanent occlusion of bilateral carotid arteries in rats. Brain Res. **653**, 231-236.

J-W Ni, K Matsumoto, H-B Li, Y Murakami and H Watanabe (1995): Neuronal damage and decrease of central acetylcholine level following permanent occlusion of bilateral common carotid arteries in rats. Brain Res. **673**, 290-296.