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## **NEUROENDOCRINE AND KAMPO MEDICINE -From Here to Molecular Biology**

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The question of whether or not the brain is involved in the action of kampo medicine has been our concern for a long time. One of these oriental recipes, Toki-Shakuyaku-San(Dang Gui Shao Yao San) has been known to treat ovarian disorders in women for long time in Japan and China. Therefore, our first endeavor is to investigate the effect of Toki-Shakuyaku-San on the hypothalamic-controlled pituitary and ovarian function in female rats. Treatment with Toki-Shakuyaku-San(500mg/kg bwt) through drinking water stimulates synthesis and release of hypothalamic LHRH and pituitary LH which in turn, activates immature ovary and uterus to initiate ovarian estrogen output and cyclicity. Furthermore, treatment with Toki-Shakuyaku-San in menopausal female rats which demonstrate cessation of ovarian cyclicity restores their ovarian estrogen output and ovarian cyclicity. It is confirmed the clinical evidence that Toki-Shakuyaku-San has a therapeutic efficacy for treatment for ovarian disorders in adult and menopausal women, and further, the results suggest the involvement of brain cells in the action of Toki-Shakuyaku-San. Our second endeavor, therefore, is to investigate the effect of Toki-Shakuyaku-San on the activity of neurotransmitters and receptors in the brain: It is revealed that Toki-Shakuyaku-San(500mg/kg bwt) through drinking water stimulates synthesis and release of acetylcholine, dopamine, norepinephrine and serotonin, and further, it increases the activity of nicotine acetylcholine receptors in the brain. These results prompt us to investigate a therapeutic efficacy of Toki-Shakuyaku-San for treatment for age related declining of memory in mice, because such neurological disorders as dementia of Alzheimer type

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patients demonstrate a decrease of synthesis and release of above neurotransmitters and receptor in the brain. Indeed, it is that treatment with Toki-Shakuyaku-San(500mg/kg bwt) through drinking water reverses age related declining of memory in male mice. Perhaps Toki-Shakuyaku-San acts not only on menopausal women to restore the quality of daily life, but it acts also on men. Brain cell death is the major pathological change in dementia in aging and in dementia of Alzheimer type. Our in vivo study provides the evidence of neuroprotective effect of Toki-Shakuyaku-San previously; however, a recent in vitro study provides further evidence of involvement of gene expression in the action of Toki-Shakuyaku-San(0.05mg/ml) in brain cells. These results support the clinical trials of Toki-Shakuyaku-San in dementia of Alzheimer type. Indeed, it is that treatment with Toki-Shakuyaku-San improves the recognition of space and time(psychometric tests) and it provides the quality of daily life of patients in dementia of Alzheimer type. Recently, we have established therapeutic efficacy of estrone for treatment of dementia of Alzheimer type; therefore, the modulation of neuroendocrine activity in menopausal women with treatment of Toki-Shakuyaku-San could be associated with direct action of Toki-Shakuyaku-San on the brain cells to bring the quality of daily life in aging in women.

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