A possible linkage between cholinergic and vascular endothelial growth factor (VEGF) systems in antidementia effects of traditional Chinese and Kampo medicines

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Chotosan (CTS) is a traditional Chinese and Kampo medicine which consists of 11 different crude drugs such as *Uncariae Uncis cum Ramulus*. CTS has long been used for the treatment of hypertension, headache, tinnitus, etc., and is believed to improve blood circulation deficits. Moreover, clinical studies demonstrated that CTS was beneficial for the treatment of patients with dementia. However, the mechanisms underlying the effects of CTS remain unclear. On the other hand, evidence indicates that vascular endogenous growth factor (VEGF) is involved in not only angiogenesis but also neuroprotection and neurogenesis in the brain. In order to have a better understanding the effects of CTS in patients with dementia, we investigated the effects of CTS on cognitive dysfunction in various animal models including diabetes mellitus and its action mechanisms including cholinergic and VEGF systems in the brain.

In our studies employing *db/db* (DB) and *m/m* mice as a model of type 2 diabetes and a non-diabetic control, respectively, CTS ameliorated diabetes-induced cognitive deficits via enhancing the function of central cholinergic and VEGF systems in a manner that was similar to tacrine (THA), an acetylcholinesterase inhibitor with anti-dementia activity. Furthermore, our neurochemical and histochemical studies revealed a diabetes-induced decrease in the number of cholinergic neurons in the medial septum as well as down-regulation of VEGF, VEGF receptor2 (VEGFR2), and p-Akt in the hippocampus. These changes were attenuated in the DB mice treated with CTS and THA, suggesting a linkage between cholinergic and systems in the anti-dementia effects of CTS and THA.

Interestingly, results from metabolomic experiments with a HPLC-FTMS system and from in vitro hippocampal slice culture system revealed that the repeated administration of CTS elevated the levels of glycereophosphocholine (GPC) in the blood and brains in DB mice and that GPC exerted a THA-like neuroprotective effects via being converted to acetylcholine (ACh) in the hippocampus.

Considering our recent findings that VEGF-VEGFR2 signaling systems play a role in the neuroprotective effects of THA in the hippocampal neurons and medial septum cholinergic neurons, a linkage between cholinergic and VEGF systems is likely to be implicated in the antidementia effects of CTS.