S22-4 Preventive action of nobiletin, a component of AURANTII NOBILIS PERICARPIUM with anti-dementia activity, against amyloid-beta peptide-induced neurotoxicity expression and memory impairment

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Alzheimer's disease (AD) has become a major health burden to society. However, no fundamentally therapeutic drugs for AD have been developed. Increasing evidence suggests that the elevation of β-amyloid (Aβ) peptides in brain is central to the pathogenesis of AD. Recently, in the course of our survey of substances having anti-dementia activity from natural resources, we have successfully found nobiletin, a polymethoxylated flavone included in AURANTII NOBILIS PERICARPIUM which is a component of traditional Chinese medicines. In this study, we examined the effects of nobiletin on trafficking of AMPA receptor (GluR1), CRE-mediated transcription and intracellular signaling required for LTP, which have been reported to be inhibited by a sublethal concentration of Aβ in cultured hippocampal neurons. Nobiletin induced trafficking of GluR1 which was abolished by a PKA inhibitor, H89, and a CaMK inhibitor, KN62, in cultured hippocampal neurons. This natural compound also increased CREB phosphorylation and CRE-mediated transcription in cultured hippocampal neurons. Furthermore, a sublethal concentration of Aβ impaired glutamate-induced trafficking of GluR1 and CRE-mediated transcription in the cultured neurons, whereas the Aβ-induced impairment of such biochemical processes was reversed by nobiletin in a concentration-dependent manner. Notably, this natural compound also improved the memory deficit in fear conditioning in a transgenic mouse model introduced human "Swedish" and "London" mutant amyloid precursor protein (APP-SL 7-5 Tg mice). These findings suggest that nobiletin prevents Aβ-induced suppression of the intracellular events involved in LTP induction, and shows the protective effect on Aβ-induced impairment of learning ability in APP-SL 7-5 Tg mice. This natural compound with such a unique anti-AD action has thus potential to become a novel drug for fundamental treatment of AD. **References:** *Biochemistry* **44**, 13683-91, 2005; *Neurosci. Lett.* **400**, 230-34, 2006; *J. Pharmacol. Exp. Ther.* **321**, 784-90, 2007; *Eur. J. Pharmacol.* **578**, 194-200, 2008; *J. Pharmacol. Exp. Ther.* **326**, 739-44, 2008.