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Research Report

SK-PC-B70M confers anti-oxidant activity and reduces Aβ levels in the brain of Tg2576 mice

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ABSTRACT

SK-PC-B70M is an oleanolic-glycoside saponin-enriched fraction derived from the root of *Pulsatilla koreana*. Recently, it was reported that hederacolchiside-E is an active ingredient of SK-PC-B70M that confers a neuroprotective effect against the cytotoxicity induced by Aβ(1–42) in SK-N-SH neuroblastoma cells. SK-PC-B70M improves scopolamine-induced impairments of spatial working memory in rats. In the present study, we investigated whether SK-PC-B70M has a beneficial effect on the Tg2576 murine model of Alzheimer's disease. ELISA analysis revealed that the levels of soluble and insoluble forms of Aβ(1–42) in Tg2576 mice fed SK-PC-B70M (2000 ppm) from 11 months to 16 months of age were reduced to, respectively, 66% and 79% of the control Tg2576 mice. Anti-Aβ antibody-stained brain sections of Tg2576 mice with SK-PC-B70M (2000 ppm) consistently showed a reduction in plaque formation in the brain. Western blot analyses showed altered expressions of various cellular factors, such as up-regulation of transthyretin, phospho-ERK, and phospho-CREB in the brain treated with SK-PC-B70M. SK-PC-B70M suppressed the neuronal toxicity induced by H_2O_2 in primary cortical culture. Moreover, biochemical and immunohistochemical analyses showed that the levels of malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), oxidized by-products of lipid peroxidation, were notably reduced in the hippocampus of Tg2576 mice treated with SK-PC-B70M compared with the Tg2576 control. These results suggest that SK-PC-B70M attenuates AD-like pathology in the brain of Tg2576 mice.

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by histopathologic hallmarks, including senile plaque deposition in the space outside neurons, neurofibrillary tangle formation within neurons, and neuronal loss. These pathologic processes are usually accompanied by marked changes in gene expression and biochemical states of various cellular factors. Because mutations in genes encoding

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APP, PS1 or PS2 are familial causes of AD and overproduction of Aβ(1–42) alone causes AD-like pathology, altered APP metabolism has been suggested to be a mechanism of AD (Selkoe and Schenk, 2003; Goedert and Spillantini, 2006). Therefore, intervening the metabolism of APP has been suggested to have therapeutic potential (Ghosh et al., 2002; Hills and Vacca, 2007; Imbimbo, 2008). However, most cases of AD occur sporadically, resulting from the influence of various non-genetic environmental factors. The mechanisms underlying AD appear to be diverse, and so are the potential therapeutic methods for treating AD.

Naturally occurring compounds from plants have been investigated for their therapeutic potential for AD. Curcumin and ginkgo biloba extract are such natural compounds that have been shown to be protective against the progression of AD pathology in AD murine models (Lim et al., 2001; Stackman et al., 2003). SK-PC-B70M is a naturally occurring oleanolic-glycoside saponin-enriched fraction from the root of *Pulsatilla koreana* (Ranunculaceae). *P. koreana* has had limited use in the treatment of amoebic dysentery, goiter under neck, scrofula, itchy and oozing boil after smallpox as a traditional herbal medicine in the Korean peninsula (Huh, 1610). Recently, it was reported that serial fractionations using solvent-partitioning followed by chromatographic separations has led to the identification of hederacolchiside-E, an oleanolic glycoside, as an active ingredient of SK-PC-B70M. Administration of hederacolchiside-E (30–60 mg/kg, P.O.) increased the step-through latency time in the passive avoidance test as efficiently as tacrine (30 mg/kg, P.O.) (Han et al., 2007a). Hederacolchiside-E inhibited the toxicity of Aβ(1–42) in SK-N-SH cells in a level comparable to that of catechin (Han et al., 2007a). Moreover, administration of SK-PC-B70M improved scopolamine-induced impairment of memory consolidation and spatial working memory in rats (Han et al., 2007b). As an extension of these results, we investigated whether SK-PC-B70M has a therapeutic potential for the brain of AD. To address this, we performed a set of experiments with a focus on the potential property of anti-beta-amyloid using a murine model Tg2576 of AD (Hsiao et al., 1996).

2. Results

Tg2576 mice were randomized into three groups at 10 months of age: control ($n=6$); low dose of SK-PC-B70M (500 ppm; $n=8$);

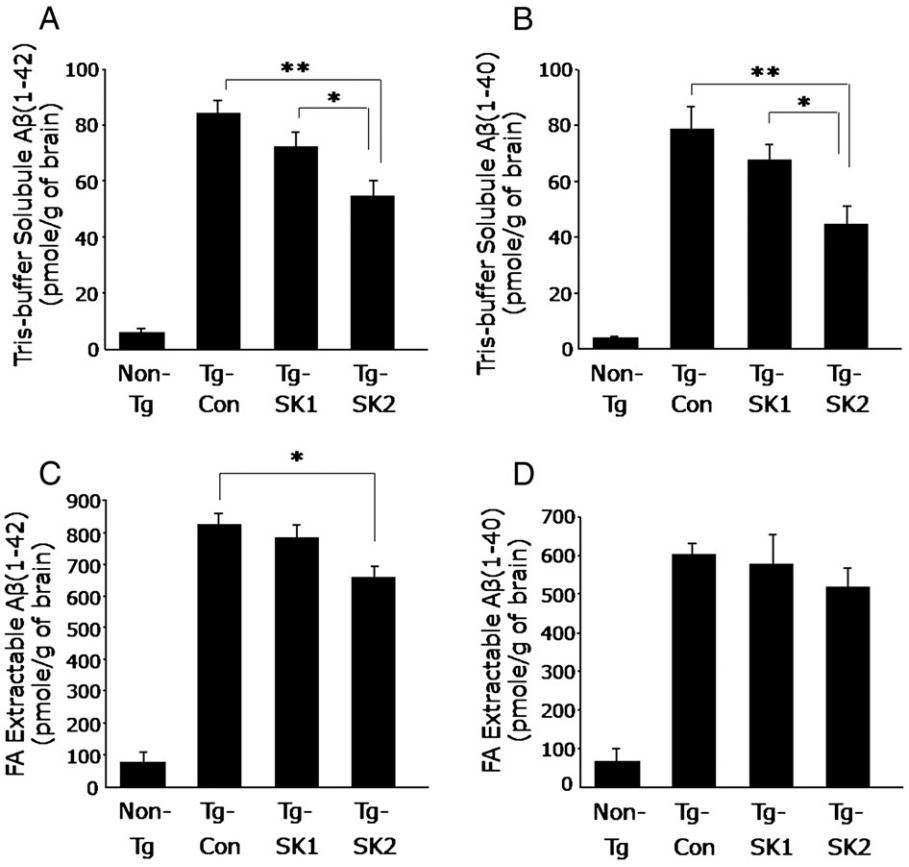

Fig. 1 – Administration of SK-PC-B70M reduced Aβ(1–42) levels in the brains of Tg2576 mice. (A–D) ELISA analysis showing the amounts of soluble (A, B) and insoluble (C, D) forms of Aβ(1–42) and Aβ(1–40) in the prefrontal cortex of Tg2576 mice at 16 months of age. ELISA analysis was performed for individual animals. Soluble and insoluble forms of Aβ were prepared as described in Experimental procedures. Data are presented as the means ± SEM. The numbers of animals examined for each group were 6–8. * denotes differences between Tg-con mice and Tg mice fed SK-PC-B70M at the $p<0.05$ level (one-way ANOVA, Newman–Keuls multiple comparison test). Non-Tg, non-transgenic control; Tg-Con, Tg2576 control; Tg-SK1 and Tg-SK2, Tg2576 mice treated with a low dose (500 ppm) or a high dose (2000 ppm) of SK-PC-B70M.