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Stimulation of Growth Hormone Gene Expression in the Pituitary and Brain by *Panax ginseng* C. A. *MEYER*

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THE neuronal or neuroendocrine action of GH on the central nervous system (CNS) has attracted increasing interest [1], although the source of GH, peripheral or central, acting on CNS is still unclear [2, 3]. We have recently reported that GH mRNA is expressed in the lateral hypothalamus, and that its expression is regulated by GHRH and restraint stress [4]. Other investigations have also suggested the involvement of GH in the regulation of emotion, memory, behavior and the quality of life in man [5, 6]. On the other hand, *Panax ginseng C. A. Meyer* (Ginseng) has been used as nourishment, tonics or euphoriant acting on the CNS. Ginseng has been reported to have stimulatory or inhibitory effects on memory, learning, behavior, immune functions and stress resistance [7], but the effects of Ginseng on neuroendocrine functions, particularly on the hypothalamo-pituitary-somatomedin axis, have not yet been clarified. In this study we examined the effects of Ginseng on the levels of peripheral GH and the GH gene expressions in the pituitary and brain.

Materials and Methods

Adult male Sprague-Dawley rats (10 weeks old) were purchased from SLC (Shizuoka, Japan) and were housed and handled for two weeks before the experiments. Ginseng extracts (500 mg/kg/ml/day) were orally administered for two weeks. Ginseng is extracted from crude powders with hot water, and dissolved in distilled water. Five hundreds mg of the extracts corresponds to 1.67 g crude powder. After 2 weeks of Ginseng extracts administration, rats were sacrificed by decapitation and the trunk blood was collected. The cerebrum, cerebellum and pituitary gland were promptly removed and quickly frozen in liquid nitrogen until used. Total RNA was extracted from the pituitary or cerebrum by the guanidium isothiocyanate-phenol-chloroform method. Serum GH concentrations was determined in duplicate by a double antibody radioimmunoassay (RIA). Standard hormones and antibodies were kindly supplied by the NIDDK Hormone Distribution Program. GH and β-actin mRNA expressions in the pituitary were analyzed by Northern blot hybridization, and brain GH and β-actin mRNA expressions were analyzed by RT-PCR/Southern blot hybridization as described previously [4]. Radioactivities of the Northern and Southern blot hybridization signals on the membranes were determined by a bioimage analyzer (BAS2000, Fuji Film, Japan). The data were analyzed for statistical significance by using the Macintosh SuperANOVA program and expressed as means ± SE. The significance of differences between the values was analyzed by Scheffe's post hoc test, and $P<0.05$ was considered significant.

Results

The serum GH concentration was significantly increased by orally administered Ginseng extracts

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Key words: GH, Gene expression, Ginseng, Brain, Pituitary

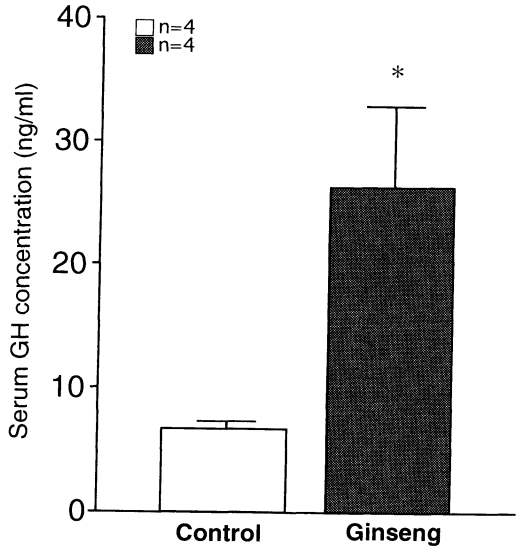

Fig. 1. Increase in serum GH concentration caused by Ginseng administration. Rats were orally administered Ginseng extracts dissolved in water (500 mg/kg/ml/day) or water alone every day for 2 weeks. Values are the means ± SEM. *; $P<0.01$ *vs.* the control.

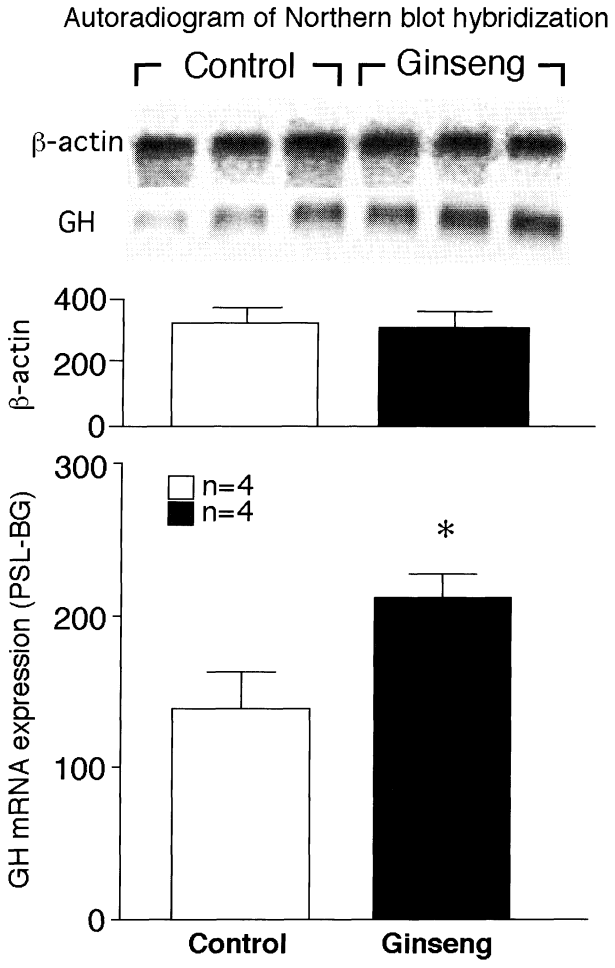

Fig. 2. Enhanced expression of GH mRNA in rat pituitary caused by Ginseng administration for 2 weeks. Lanes 1–3; treated with water alone, lanes 4–6; treated with Ginseng extracts (500 mg/kg/ml/day). GH and β-actin mRNA expressions in the pituitary were detected by Northern blot hybridization. Autoradiograms are shown in the upper panels, and the radioactivities determined by a BAS2000 bioimage analyzer (Fuji Film) are expressed as the photo-stimulated luminescence value (PSL) minus background (PSL-BG) in the lower panels. Values are the means ± SEM. *; $P<0.01$ *vs.* the control.

as compared to H_2O treatment (26.4 ± 6.58 *vs.* 5.76 ± 0.71 ng/ml, respectively, $P<0.01$, Fig. 1). Concomitantly, the GH mRNA expression level in the pituitary detected by Northern blot hybridization was significantly increased by orally administered Ginseng extracts (1.53 fold, $P<0.01$, Fig. 2). The brain GH mRNA expression level determined by RT-PCR was more strongly stimulated by Ginseng extracts (2.74 fold, $P<0.01$, Fig. 3), but the levels of β-actin mRNA expression in the brain and pituitary were not altered significantly by these treatments (Figs. 2 and 3).

Discussion

Previous studies suggest that the major active elements in Ginseng are ginsenoides (glycosides), derivatives of the tritepene dammarane compound [8]. The mechanisms of ginseng actions still remain unclear, but an extensive literature describes the effects of Ginseng on CNS affecting memory and behavior [1–3], as well as its actions as the stimulant and nourishment [9, 10]. In this study we have shown that the serum GH level and GH mRNA expression in the pituitary and brain were increased by oral administration of Ginseng extracts. These increases in GH expression may be mediated by hypothalamic GHRH rather than by the Ginseng's direct action on the pituitary or brain. Other GH secretagogues, such as arginine, L-dopa, α-adrenergic agonist (clonidine), opioid peptides or dopaminergic and serotonergic system, also

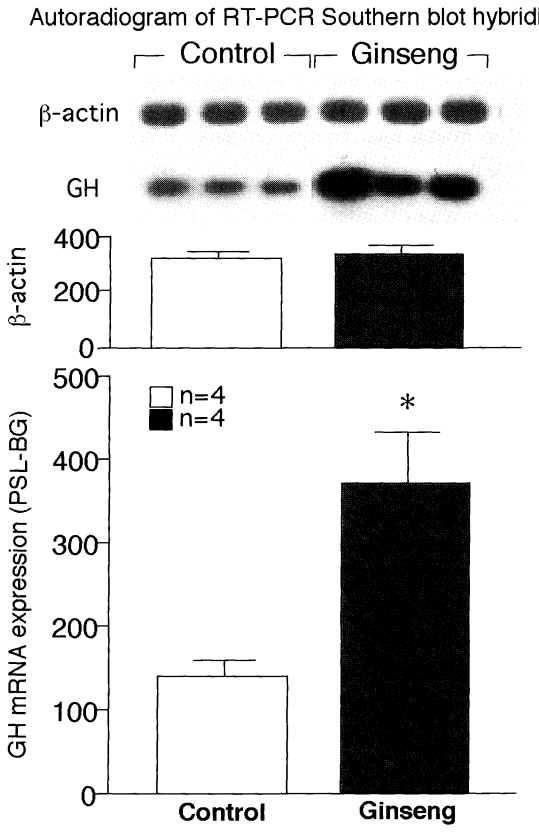

Fig. 3. Enhanced GH mRNA expression in rat brain caused by Ginseng administration for 2 weeks. Lanes 1–3; treated with water alone, lanes 4–6; treated with Ginseng extracts (500 mg/kg/ml/day). GH and β-actin mRNA expressions in the brain were detected by RT-PCR/Southern blot hybridization. Autoradiograms and radioactivities determined are shown as described in the legend to Fig. 2.

stimulate GH secretion from the pituitary by means of hypothalamic GHRH release [11]. In a previous study, we showed that the icv injection of GHRH stimulates the GH gene expression in the brain [4]. Moreover, it has been reported that oral administration of Ginseng extracts or its major component, ginsenoides, induces an increase in brainstem dopamine, norepinephrine or cortex serotonin in rats [12], but further studies are needed to elucidate whether the action of Ginseng on the GH gene expression in the pituitary and brain is mediated by GHRH or not.

The results of the present study also suggest that some of the Ginseng-induced effects of well-being or nourishment may be due to the GH molecules synthesized in the brain acting directly on CNS.

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