Extract from Acanthopanax senticosus Harms (Siberian Ginseng) Activates NTS and SON/PVN in the Rat Brain

Hideaki SOYA,1 Custer C. DEOCARIS,1 Kaoru YAMAGUCHI,1 Nao OHIWA,2 Tsuyoshi SATO,3 Takeshi NISHIMA,1 Morimasa KATO,4 Masaru TATEOKA,1 Takashi MATSUI,1 Masahiro OKAMOTO,1 and Takahiko FUJIKAWA5

1Laboratory of Exercise Biochemistry, University of Tsukuba Graduate School of Comprehensive Human Sciences, 1-1-1 Tennoudai, Tsukuba 305-8574, Japan
2Department of Sports Sciences, Japan Institute of Sports Sciences, Tokyo 115-0056, Japan
3Department of Psychology in Social Welfare, Faculty of Social Welfare, Shizuoka University of Welfare, Yaizu 425-8611, Japan
4Yonezawa Women’s Junior College of Yamagata Prefecture, Yonezawa 992-0025, Japan
5Biochemistry and Proteomics, Mie University School of Medicine, Tsu 514-8507, Japan

Received April 2, 2008; Accepted June 21, 2008; Online Publication, September 7, 2008
[doi:10.1271/bbb.80209]

The extract of the stem bark of Siberian ginseng, Acanthopanax senticosus Harms (ASH), is believed to play a body-coping role in stress through a brain noradrenergic mechanism. The present study was carried out to investigate the effect of ASH on the neuronal activation patterns of c-Fos expression in the rat brain. With ASH administration, c-Fos accumulated in both the supraoptic nuclei (SON) and paraventricular nuclei (PVN), which regulate stress response. Only the caudal regions in the nucleus of the solitary tract (NTS), a locus innervating both the SON and PVN, were activated. Such a neuro-anatomical pattern associated with ASH suggests the possible involvement of these stress-related brain loci.

Key words: Siberian ginseng (Acanthopanax senticosus Harms); neuronal activation; hypothalamus; medulla oblongata; anti-stress effects

Siberian ginseng, Acanthopanax senticosus (Rupr. et Maxim) Harms, ASH, a relative of Asian ginseng (Panax ginseng), grows abundantly in the taigas of South-East Russia, in North-East China, Korea, South-East Asia, and on the island of Hokkaido in Japan.1) Considered a classical adaptogenic agent, ASH has been found to stimulate the CNS by modulating its stress-response system leading to a sense of euphoria and increasing mental alertness and concentration (Panossian and Wagner, 2005).3) Further, the anti-stress effects of ASH have also been found to mediate some of the substances, syringaresinol di-o-b-D-glucoside (SYG), by dampening of gastric ulceration in rats induced by water-restraint stress.3) The mechanisms of stress-induced gastric ulceration implicate, among other things, brain-driven mechanisms such as changes in levels of biogenic monoamines, i.e., noradrenaline (NA), dopamine (DA), and serotonin, in discrete brain regions.6,7) On a similar note, ASH activates GABA-ergic6) and monoaminergic neurons triggering the release and turnover of dopamine, noradrenaline (NA), and serotonin in the cortex and anterior hypothalamus.7,8) The possible roles of these brain loci, responsible for the anti-stress activity of ASH, remain to be determined. To address this, we delineated the responsive brain loci after oral administration of ASH by examining c-Fos expression, a marker of neuronal activation. We focused on the hypothalamus and the brain stem, regions associated with NA metabolism.

Stem bark of ASH harvested in the eastern part of Hokkaido was extracted successively with 100% ethanol, 50% ethanol, and hot water. After the extracts were pooled, ASH extract was authenticated by reverse-phase HPLC (apparatus, ERC-8710 (EMA); column, ERC-ODS, 3 m, 6 mm × 100 mm, eluent; CH3CN–H2O–HCOOH, 15:85:1, flow rate; 1 ml/min; detection; UV at 270, 275, and 345 nm; room temperature). Our results identified the following components in mg/100 g: isofraxidin, 55; syringaresinol di-o-β-D-glucoside, 1,156; syringin, 454; chlorogenic acid, 1,473; isofraxidin-7-o-β-D-glucose, 109; sesamin, 10.6.9) Animal experiments were carried-out according to the 1996 NIH guidelines for animal care as approved by Tsukuba University. Nine-week-old male Sprague-
Dawley rats (250–300 g) were group-housed (three per cage) and acclimatized under laboratory conditions (temperature, 22–24 °C; humidity, 60 ± 10%; fixed light-dark cycle, lights on 0800 to 2000 H) for 10 d prior to the feeding experiment. Food (MF, Oriental Yeast Company, Tokyo) and water were given ad libitum. ASH (100 mg/kg b.w.) was administered with a feeding tube to seven randomly chosen animals. The dosage used was sufficient to increase the levels of catecholamines in the rat hypothalamus,10) our previous findings a reduction in plasma ACTH response to restraint stress (RS) in eight rats per treatment: ASH alone (0), water alone (0), water + RS (56.25 ± 3.82), and ASH + RS (23.75 ± 3.84). The significant difference (p < 0.01) in GEIs between stressed rats given ASH or vehicle validates our initial report on the protective effects of ASH against gastric erosion. This is supported by previous findings that NA inhibits ulceration (Szabo, 1979),23) as well as gastric acid secretion (Glavin et al., 1991).6) Considering our data, it is likely that drinking ASH extracts acts on neural pathways that are common to those triggered by aversive and emotional stresses. If so, would previous exposure to milder stress help an organism to deal with the future onslaught of stress-induced physiological disturbances, e.g., stress-induced gastric ulcers? For rats that underwent intraventricular administration of prolactin-releasing peptide (PrRP), at low doses alone insufficient to induce ACTH, we previously found a reduction in plasma ACTH response associated with moderate running stress (Ohiwa et al., 2007).13) Taking this into account, we hypothesized that...
prior mild stimulus exposure due to ASH ingestion, as revealed by the brain pathways that recapitulate emotional stress, can lead to a hormetic-like reduction in restraint stress-induced gastric ulcerations.

Collectively, evidence for the cytoprotective effects of ASH via modulation of brain functions is probably associated with activation of the NTS and SON/PVN, two of the most important loci in regulating stress response via the NA system (Pacak, 2001), although it is still a matter of debate how these responsive loci are involved in the development of cytoprotective effects.

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**Fig. 1.** c-Fos-Activation in the Hypothalamus, Pons, and Medulla Oblongata Due to ASH Extract.

Representative bright field photomicrographs show distribution of c-Fos(+) neurons in (A, left) the pPVN, SON, VLM, and NTS 3 h after the rats drank the ASH decoction. Nuclei immunoreactive for c-Fos protein appeared with intense black staining. Scale bar, 100 μm. (A, right) Bar graphs show the average number of c-Fos(+) nuclei from each nucleus in each brain locus. Each bar represents the mean ± S.E. for each group of rats; statistical significance is indicated at p < 0.05. (B) The number of c-Fos(+) nuclei from caudal to rostral positions was determined for the NTS and VLM regions. The x-axis indicates distance of the level of the coronal sections from the obex. In the NTS region, there was a significant difference only in the caudal regions in the percentage of c-Fos immunoreactive cells with ASH as compared to the control.
Acknowledgments

This study was supported in part by the 21st Century Center of Excellence program from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. TN is a COE postdoctoral fellow, and CCD is a post-doctoral research fellow of the Japan Society for the Promotion of Science (JSPS).

References


