Psychopharmacology (1990) 101:486–488

Psychopharmacology

Panax ginseng extract modulates sleep in unrestrained rats

Young Ho Rhee[1], Sung Pil Lee[2], Kazuki Honda[2], and Shojiro Inoué[2]

[1] Department of Neuropsychiatry, College of Medicine, Chungbuk National University, Chungju, Korea
[2] Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Kanda-Surugadai 2–3–10, Chiyoda-ku, Tokyo 101, Japan

Received October 23, 1989 / Final version February 19, 1990

Abstract. The amount of wakefulness and slow wave sleep (SWS) during the 12-h light period slightly but significantly decreased and increased, respectively, in freely behaving rats after continued 1-week intake of Panax ginseng extract through drinking water (15 mg/day). Paradoxical sleep was little affected. No sleep parameters were modulated by the treatment during the dark period. The diurnal SWS enhancement disappeared and recovered to the baseline level after 2 weeks of continued treatment. It is speculated that the well known health-improving effect of the ginseng may be, at least in part, related to an enhancement of sleep.

Key words: Circadian rhythm – Ginseng extract – Panax ginseng – Rat – Slow wave sleep (SWS)

The preparation of *Panax ginseng,* as a herbal medicine, has long enjoyed fame because of its remarkable health-promoting properties (for reviews, see Li and Li 1973; Hu 1977; Yamamura et al. 1989). Its medicinal applications cover a wide variety of diseases, including insomnia. The ginseng root contains a number of physiologically important constituents such as ginseng saponins, ginseng oils and phytosterol, carbohydrates and sugars, organic acids, nitrogenous substances, amino acids and peptides, vitamins and minerals, and certain enzymes (Hou 1977). In rats, it is reported that ginseng extract produces a decrease in blood pressure (Takagi et al. 1972a; Saito et al. 1973), suppression of conditioned avoidance response (Takagi et al. 1972b; Nabata et al. 1973; Saito et al. 1973, 1977) and sound discrimination (Saito et al. 1977), inhibition of gastric ulceration (Chang and Kim 1974), facilitation of sexual behavior (Lim and Kim 1982), and an increase in essential fatty acids (Kim and Kim 1984) and several essential amino acids (Lee and Kim 1984) in serum.

Offprint requests to: S. Inoué

One may hypothesize that the health-improving effect of the ginseng might be, at least in part, related to an enhancement of sleep or vice versa. However, no literature deals with a systematic analysis of this hypothesis on the basis of modern experimentation. We previously detected an electroencephalographic (EEG) sleep-promoting activity of the bracket fungus, *Fomes japonicus* or *Ganoderma lucidum,* in freely behaving rats (Honda and Inoué 1988; Honda et al. 1988). Using the same technique, the present study was conducted to evidence the sleep-modulatory effect of ginseng, if any, in animal experiments, using sophisticated methods. A preliminary report has appeared elsewhere in abstract form (Lee et al. 1989).

Materials and methods

Adult male rats of the Sprague-Dawley strain raised in our closed colony were used. They were kept on a 12-h light and 12-h dark schedule (light period: 08.00–20.00 hours) under a constant air-conditioned environment of $25 \pm 1°$ C and $60 \pm 6\%$ relative humidity with free access to rat chow and tap water. At the age of 60–70 days, animals weighing 300–400 g were anesthetized with pentobarbital sodium (50 mg/kg IP), placed on a stereotaxic apparatus and implanted with three cortical electrodes for EEG recording, two nuchal electrodes for electromyographic (EMG) recording, and a thermistor electrode for brain temperature (T_b) recording. The technique of surgery was the same as described in a previous paper (Honda and Inoué 1978). The electrodes were chronically fixed with dental acrylic resin over the skull. Following the operation, each animal received in total 40000 U penicillin G potassium (Meiji) around the incision and under the dorsal skin.

The animals were individually housed in a special cage which enabled continuous monitoring of EEG, EMG and T_b. Lead wires of the electrodes were connected to a polygraph (Nihon-Kohden EEG-4317) via a slip ring (Airflyte Electronics Co. CAY-675) fixed above the cage. Thus free movement of the rats was guaranteed. Each cage was placed in a sound-proof, electromagnetically shielded chamber under the same environmental conditions as above.

One week was allowed for recovery from surgery. After observing the establishment of circadian rhythms in sleep-waking behavior, the rats were subjected to experiments. For the purpose of obtaining baseline data, the first 24-h polygraphic recording was started at the onset of the light period. Immediately after the

Table 1. Changes in sleep-waking parameters before and after the intake of Panax ginseng extract through drinking water (15 mg/31 ml per day) in freely behaving rats ($N=8$)

Parameter	Baseline		Week 1		Week 2	
	L	D	L	D	L	D
Wakefulness						
Total time (min)	206.1±4.7[a]	461.7±12.1	180.6±3.1[a,d]	452.4±10.6	205.1±5.7[a]	460.6±10.0
Episode frequency	116.6±4.7	76.8±4.5	113.9±5.6	75.5±2.4	115.1±2.9	76.4±4.0
Episode duration (min)	1.9±0.1	6.2±0.5	1.6±0.1	6.1±0.4	1.8±0.1	6.2±0.4
Slow wave sleep						
Total time (min)	441.3±3.0[b]	231.5±11.3	460.5±8.6[b,c]	238.5±8.6	440.0±6.0[b]	229.0±7.6
Episode frequency	120.4±4.0	78.8±4.8	120.6±5.5	76.1±2.4	121.9±3.4	78.1±3.7
Episode duration (min)	3.7±0.1	3.0±0.1	3.9±0.2	3.1±0.1	3.7±0.1	2.9±0.1
Paradoxical sleep						
Total time (min)	72.7±4.2	26.6±2.8	78.9±3.9	28.8±2.6	74.9±1.5	30.0±3.0
Episode frequency	38.8±2.3	19.4±2.1	42.6±2.7	21.9±1.9	43.3±2.4	23.5±2.1
Episode duration (min)	1.9±0.1	1.4±0.1	1.9±0.1	1.3±0.1	1.8±0.1	1.3±0.1

L and D stand for the light and dark period, respectively
[a] $P<0.005$ (ANOVA, $F_{2,21}=6.888$)
[b] $P<0.05$ (ANOVA, $F_{2,21}=4.692$)
[c] $P<0.05$, [d] $P<0.01$ as compared to the corresponding baseline (Student's t-test)

baseline recording, tap water was replaced by ginseng water for 2 weeks. The daily dose of Panax ginseng extract (Korean Red Ginseng Extract, Korea Monopoly Corporation) was adjusted to 15 mg, dissolved in 31 ml tap water. This is based on the finding that the daily intake of drinking water was 31 ml in our young adult male rats (Honda and Inoué 1988). The second and third 24-h polygraphic recordings were done, respectively, 1 and 2 weeks after the treatment.

During the recording periods, EEG (bipolarly registered between two combinations of the three electrodes) and EMG were polygraphically recorded at a paper speed of 0.5 mm/s. By means of high-cut and low-cut band filters, EEG wave ranges were selected from 0.3 to 120 Hz. Sleep-waking states were visually classified on a large scale digitizer as slow wave sleep (SWS), paradoxical sleep (PS) and wakefulness (W). Each state was characterized as follows. SWS: a high-amplitude and low-frequency EEG and a low-amplitude EMG. PS: a low-amplitude and high-frequency EEG, almost no trace of EMG except for occasional muscle twitches, also succeeding to SWS. W: a low-amplitude and high-frequency EEG and a high-amplitude EMG. The minimal scoring interval was 12 s, and any episode less than 12 s was added to the preceding state. The successive episodes of each state were fed into a computer (microNOVA) directly from the digitizer, and further numerically processed (Honda and Inoué 1981). Intragroup differences between the data of the baseline, week 1 and week 2 were statistically analyzed by repeated measures analysis of variance (ANOVA) and Student's t-test.

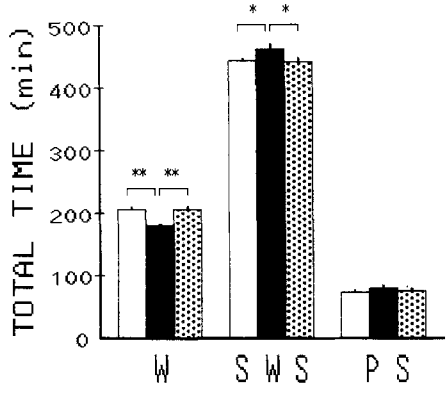

Fig. 1. Changes in the diurnal amount of wakefulness (W), slow wave sleep (SWS) and paradoxical sleep (PS) before treatment (baseline), 1 week and 2 weeks after the intake of Panax ginseng extract through drinking water (15 mg/day) in freely behaving rats ($N=8$). *Vertical lines* indicate standard error of mean. * $P<0.05$, $P<0.01$ (compared to the baseline by Student's t-test). □ Baseline; ■ week-1; ▩ week-2

Results

The amounts of W and SWS during the 12-h light period significantly changed in the course of experiments (Table 1). After 1 week's continuous intake of the ginseng water, the total amount of diurnal W decreased by 25.5 min ($P<0.01$, t-test), whereas that of diurnal SWS increased by 19.2 min ($P<0.05$) as compared to the baseline (Fig. 1). The changes were rather small, since the ratio was 11.9% below the baseline for W and 4.4% above for SWS. The total amount of diurnal PS also slightly increased but the difference was not statistically significant. The amount of W, SWS and PS during the dark period was little affected by the treatment. Changes in the number and duration of episodes of W, SWS and PS were so little that no statistical significance was detected (Table 1), indicating that sleep-waking cylces were maintained in a physiologically normal state. The feeding and drinking activities of rats were also quite normal as revealed by daily inspection.

The amounts of W and SWS during the light period recovered to baseline level after 2 weeks of the continued ginseng water treatment. All the other sleep parameters recorded at this period showed no difference from those of the baseline (Table 1). No remarkable change was observed in brain temperature during the experimental period.

Discussion

For the first time, we detected a sleep-modulatory effect of Panax ginseng extract in rats. The daily dosage of Panax ginseng extract was 15 mg in the present experiment for oral intake. This seems to be adequate, since 15 mg administered to rats weighing 300–400 g is comparable to 3 g recommended for humans of 60–80 kg in body weight as an effective dose (i.e., 38–50 mg/kg).

The sleep modulation caused by the extract was neither dramatic nor long-lasting. It was dependent on the environmental light-dark rhythm, because the ginseng extract significantly changed the amount of diurnal but not nocturnal W and SWS, as revealed 1 week after the ginseng treatment. Since rats are nocturnal animals and they sleep twice as much in the light period, the ginseng intake amplified the tendency towards sleeping during their resting phase.

However, this tendency was no more observable after 2 weeks' treatment. The reason was not clear but it must be considered that all the recipient rats were kept under normal healthy conditions without a physiological need for excessive sleep. Hence, it seems likely that the change was due to a transient, perhaps pharmacological activity of the ginseng. In this connection, there are several reports on its central nervous system depressant activities, such as prolonging the duration of hexobarbital-induced "sleep" in mice (Takagi et al. 1972b), suppressing conditioned avoidance response in rats (Takagi et al. 1972b; Nabata et al. 1973; Saito et al. 1973, 1977), and inhibiting sound discrimination in rats (Saito et al. 1977). It has also been suggested that Panax ginseng extract contains at least three sedative compounds (Saito et al. 1977).

On the other hand, we have recently found that Panax ginseng extract can virtually normalize the disturbances of sleep-waking states caused by food deprivation in rats (Lee et al. 1990). Such normalizing activity of ginseng is often referred to an "adaptogen"-like property (Brekhman and Dardymov 1969). In the case of the present study, it is possible to speculate that the supranormally elevated amount of sleep after 1 week's intake of the ginseng, due to the above mechanism, might be cancelled by this adaptogen-like stabilizing activity. Thus, the amount of sleep eventually returned to the baseline level.

In conclusion, it is speculated that the well known health-improving activity of Panax ginseng may be, at least in part, related to its sleep-modulatory, both sleep-enhancing and sleep-stabilizing, activity.

Acknowledgement. This research was partially supported by a research fund from the Scientific Research Foundation of Chungbuk National University under the supervision of the Ministry of Education of Korea to Y.H.R.

References

Brekhman II, Dardymov IV (1969) New substances of plant origin which increase nospecific resistance. Ann Rev Pharmacol 9:419–430

Chang WA, Kim C (1974) Influence of Panax ginseng upon gastric ulceration produced by restraint. J Cath Med Coll 27:249–255

Honda K, Inoué S (1978) Establishment of a bioassay method for the sleep-promoting substance. Rep Inst Med Dent Eng 12:81–85

Honda K, Inoué S (1981) Effects of sleep-promoting substance on sleep-waking patterns of male rats. Rep Inst Med Dent Eng 15:115–123

Honda K, Inoué S (1988) Sleep-promoting effects of a bracket fungus, Fomes japonicus. In: Koella WP, Obál F, Schulz H, Visser P (eds) Sleep '86. G. Fischer, Stuttgart, pp 338–339

Honda K, Komoda Y, Inoué S (1988) Sleep-promoting effects of *Ganoderma* extracts in rats: comparison between long-term and acute administrations. Rep Inst Med Dent Eng 22:77–82

Hou JP (1977) The chemical constituents of ginseng plants. Comp Med East West 5:123–145

Hu SY (1977) A contribution to our knowledge of ginseng. Am J Chin Med 5:1–23

Kim AE, Kim CC (1984) Effect of ginseng on the serum fatty acid composition in the rats. J Cath Med Coll 37:55–61

Lee BK, Kim CC (1984) Change of the serum composition in the rats receiving ginseng. J Cath Med Coll 37:47–53

Lee SP, Honda K, Rhee YH, Inoué S (1990) Chronic intake of *Panax ginseng* extract stabilizes sleep and wakefulness in food-deprived rats. Neurosci Lett 111:217–221

Lee SP, Rhee YH, Honda K, Inoué S (1989) Effect of the ginseng extract on sleep in unrestrained rats. Jpn J Psychiatry Neurol 43:776

Li CP, Li RC (1973) An introductory note to ginseng. Am J Chin Med 1:249–261

Lim SY, Kim CC (1982) Influence upon male rats' sexual behavior of ginseng administered before and after mature state. J Cath Med Coll 35:9–14

Nabata H, Saito H, Takagi, K (1973) Pharmacological studies of neutral saponins (GNS) of Panax ginseng root. Jpn J Pharmacol 23:29–41

Saito H, Morita M, Takagi, K (1973) Pharmacological studies of Panax ginseng leaves. Jpn J Pharmacol 23:43–56

Saito H, Tsuchiya M, Naka S, Takagi, K (1977) Effects of Panax ginseng root on conditioned response in rats. Jpn J Pharmacol 27:509–516

Takagi, K, Saito H, Nabata H (1972a) Pharmacological studies of Panax ginseng root: estimation of pharmacological actions of Panax ginseng root. Jpn J Pharmacol 22:245–259

Takagi, K, Saito H, Tsuchiya M (1972b) Pharmacological studies of Panax ginseng root: pharmacological properties of a crude saponin fraction. Jpn J Pharmacol 22:339–346

Yamamura Y, Kumagai A, Oura H, Okuda T, Morisawa S, Yamamoto M (eds) (1989) Medicinal ginseng: progress in its basic and clinical studies. Kyoritsu Shuppan, Tokyo