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Proof of the Mysterious Efficacy of Ginseng: Basic and Clinical Trials: Effects of Red Ginseng on Learning and Memory Deficits in an Animal Model of Amnesia

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Abstract. Ameliorating effects of red ginseng on learning and memory deficits due to hippocampal lesions and aging were reviewed; the performance of young rats with selective hippocampal lesions with or without red ginseng (p.o.), and aged rats with or without red ginseng (p.o.) in the spatial learning tasks was compared with that of sham-operated or intact young rats. Each rat was tested with 3 types of spatial learning tasks (distance movement task, DMT; random reward place search task, RRPST; and place learning task, PLT) in a circular open field using intracranial self-stimulation (ICSS) as reward. The results in the DMT and RRPST indicated that motivational and motor activity of young rats with hippocampal lesions with and without ginseng and aged rats with and without ginseng were not significantly different from that of control young rats. However, young rats with hippocampal lesions without ginseng and aged rats without ginseng displayed significant deficits in the PLT. Treatment with red ginseng significantly ameliorated place-navigation deficits in young rats with hippocampal lesions in the PLT. Similarly, red ginseng improved performance of aged rats in the PLT. The results, along with previous studies showing significant effects of red ginseng on the central nervous system, suggest that red ginseng ameliorates learning and memory deficits through effects on the central nervous system, partly through effects on the hippocampal formation. However, its mechanisms are still unclear, and further studies are required.

Keywords: Panax ginseng, aging, memory deficit, hippocampus, ischemia

Introduction

The medial temporal lobe including the hippocampal formation (HF) is most susceptible to senile dementia including Alzheimer's disease. Neuropsychological studies in both monkeys and humans reported that lesions in these regions were responsible for human amnesia (deficits in declarative memory) (1 – 3). Furthermore, our previous neurophysiological studies reported that HF neurons in both rats and monkeys responded during various spatial and non-spatial learning tasks (4 – 7). Therefore, prophylatic and therapeutic drugs for amnesia due to the senile dementia are expected to act on the medial temporal lobe including the HF.

The aim of the present review is to show effects of red ginseng on learning and memory functions of rats with HF lesions due to transient forebrain ischemia and aged rats. Numerous herbs have been used in traditional Oriental medicine for centuries to treat disorders associated with aging since these medicines have less side effects and consequently are safer. One of the most interesting sources is ginseng. Prescription of herbs including ginseng or ginseng extract alone have significant effects on neurological and psychiatric symptoms in aged humans (8) and psychomotor functions in healthy subjects (9). Although some pharmacological and behavioral studies in animals reported that ginseng contained chemical substances such as ginseno-

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sides (Rb_1, Rg_1, etc.) which had stimulating and/or suppressing effects on the central nervous system (10 – 14), its effects on cognitive functions are still unclear. On the other hand, ginseng extracts were reported to modulate long-term potentiation (LTP) in the dentate gyrus (12) and CA3 subfield of the HF (our unpublished observation). These results strongly suggest that ginseng has significant effects on the central nervous system, especially the HF to improve cognitive functions.

Behavioral paradigms

Recently, we developed a protocol for the study of the HF functions (7, 15). Each rat was anesthetized and implanted bilaterally with monopolar stimulating electrodes aimed at the medial forebrain bundle at the level of the lateral hypothalamic area (LHA). After 1 week of recovery, the rats were screened to self-stimulate (intracranial self-stimulation, ICSS) in an operant chamber equipped with a lever on one wall. Each lever press triggered the delivery of current for ICSS. The current intensity for ICSS was determined to produce 40 – 70 lever presses/min in the operant chamber. The rats were trained for ICSS for 8 days (30 min/day).

After ICSS training, the rats were tested in the 3 kinds of place tasks in a 150-cm-diameter circular open field with a 45-cm-high wall, painted black on the inside (Fig. 1A). The open field was enclosed by a black curtain. The ceiling of the enclosure contained 4 small speakers mounted near the circumference, 4 light bulbs individually mounted near the inner edge of each speaker, and a video camera at the center (Fig. 1A). A small light bulb was mounted on the head of the rat. The video camera tracked the 2-dimensional (horizontal) motion of the small bulb. A program delimited circular areas (reward places) in the open field and triggered the delivery of current for ICSS when the rat entered the reward place.

In each of the following 3 place tasks, each trial was terminated after 50 rewards had been delivered or

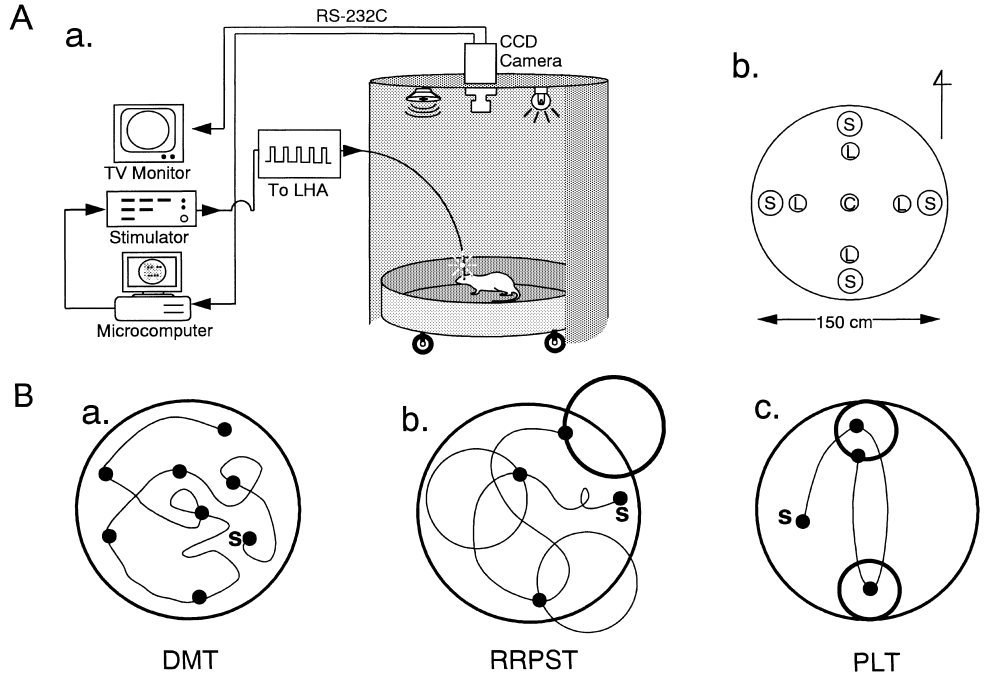

Fig. 1. Experimental setup and the paradigm for behavioral study. A: Experimental setup. a, Schematic illustration of the experimental set up. An open field (150-cm-diameter) containing a rat was viewed from top center by a video camera that signaled the rat's position in Cartesian coordinates. The microcomputer plotted the trail of the rat, and gated intracranial self-stimulation (ICSS) delivery as reward from a stimulator. b, Schematic diagram of top view of cues in an open field. Under usual conditions, an electric bulb at the 3 o'clock position and a speaker at the 9 o'clock position on the ceiling of the enclosure were turned on. B: Schema of the 3 behavioral paradigms. a, Distance moving task (DMT). A computer program computed distance traveled from a trail. A rat acquired ICSS rewards if it moved the fixed distance (i.e., 100, 120, 140, 160 cm). b, Random reward place search task (RRPST). A computer program delimited a circular reward place (thick line circle) at some randomly selected coordinate. A rat was rewarded with ICSS when it entered the reward place, which was then made inactive (changed to thin line circle). After a 5-s interval, the reward place was moved to a different location and reactivated. c, Place learning task (PLT). A rat received rewards in two target areas (thick line circles) when it returned to one reward place after a visit to the other reward place. (Reproduced from Ref. 16 with permission from Elsevier)

10 min had elapsed, whichever occurred first. Each session consisted of 3 trials, and the rats were given training of 1 session/day.

1) Distance movement task (DMT, Fig. 1Ba): Current for ICSS was delivered when the cumulative distance traveled by the rat reached a given distance. The initial distance was 100 cm, and this was increased progressively to 160 cm by 20-cm increments if the rat acquired 50 rewards in 10 min. The rats were trained until they could acquire 50 rewards within 10 min in a condition of 160-cm moving distance.

2) Random reward place search task (RRPST, Fig. 1Bb): In this protocol a reward place (90-cm diameter) was delimited; its center was chosen at random within a square circumscribed around the open field. The rat was rewarded with ICSS when it entered the reward place, which was then made inactive. After a 5-s interval, the reward place was moved to a different location and reactivated. The rats were trained until 3 sessions, which contained more than 2 trials with a total of moving distance more than 25 m/trial, were successively observed.

3) Place learning task (PLT, Fig. 1Bc): Two 40-cm diameter reward places were located diametrically opposite to one another in the open field. The rat was rewarded in both reward places, when it returned to one of them after a visit to the other one. The rats were trained for 30 days for the 1st experiment and 21 days for the 2nd experiment with this protocol.

Behavioral performance of the rats was analyzed using the following parameters: ICSS current intensity, spontaneous motor activity, performance in the DMT (number of sessions to reach the criteria), performance in the RRPST (number of sessions to reach the criteria, number of reward acquired and distance traveled per trail), and performance in the PLT (number of reward acquired and distance traveled per trail). Motivational level and motor activity of the rats were evaluated by ICSS current intensity, spontaneous motor activity, and performance in the DMT and RRPST in which only locomotion or lever press were required to acquire ICSS rewards except for spontaneous activity. The ability of place learning and memory were evaluated by the parameters in the PLT in which same locomotion was required to acquire same ICSS rewards as those in the DMT and RRPST, but the rats must learn the reward places and navigate according to their spatial memory.

Administration of red ginseng and surgery

Young male Fisher-344 (10 – 12-week-old) and aged male Fisher-344 (28 – 32-month-old) rats were used (15). First, effects of red ginseng on performance of young rats with HF lesions due to transient ischemia were investigated. In this 1st experiment, young rats were divided into 3 groups: Sham + water, Ischemia + water, and Ischemia + ginseng. These rats received ischemic or sham operation followed by implantation of ICSS electrodes in the LHA. Young rats for HF lesions were subjected to transient forebrain ischemia with the modified 4 vessel occlusion technique by Pulsinelli et al. (16) to produce selective lesions in the bilateral HF CA1 subfield. After recovery from these 2 operations, the rats were tested with the 3 spatial learning paradigms (see “Behavioral paradigms” in detail). Second, effects of red ginseng on performance of aged rats were investigated. In this 2nd experiment, young and aged rats were divided into 3 groups: Young + water, Aged + water, Aged + ginseng. After implantation of ICSS electrodes, the rats were similarly tested with the 3 spatial learning paradigms.

Suspension of red ginseng (Ginseng Radix rubura; Seikansho, Korea Tabacco & Ginseng Co., Ltd.) was administered daily (100 mg/kg per day, p.o.) 2 h before start of each session from the 4th day of ICSS training. Red ginseng was suspended in water (100 mg in 5 ml of water). Control rats received the same amount of water (5 ml/kg, p.o.).

Effects of red ginseng on young rats with HF lesions

In the ICSS training for the 1st experiment, there were no significant differences in the mean current intensity, nor in the mean number of bar pressings among these 3 groups of the rats. In the DMT, there were no differences in the training period to reach the criterion among the 3 groups. The results in the RRPST also indicated that there were no significant differences in the number of training sessions to pass the criteria among the 3 groups of the rats. Furthermore, when the rats passed the criteria of the RRPST in the last session, there were no significant differences in the number of rewards per trial nor in the distance traveled per trial among the 3 groups. All these evidence confirmed the finding that there were no significant differences in simple motor/motivational functions among the 3 groups of the rats.

These 3 groups of the rats were then tested with the PLT. The typical examples of trails of rats in the 3 groups on the 1st, 14th, and 28th day in the PLT are shown in Fig. 2. A Sham + water rat navigated randomly on the 1st day of training (Aa). Training improved navigation performance of the Sham + water rat; the rat showed constant trails connecting almost directly between 2 reward areas on the 14th (Ab) and 28th (Ac) day. Similarly, an Ischemia + water rat navigated randomly on the 1st day of training (Ba). However, the

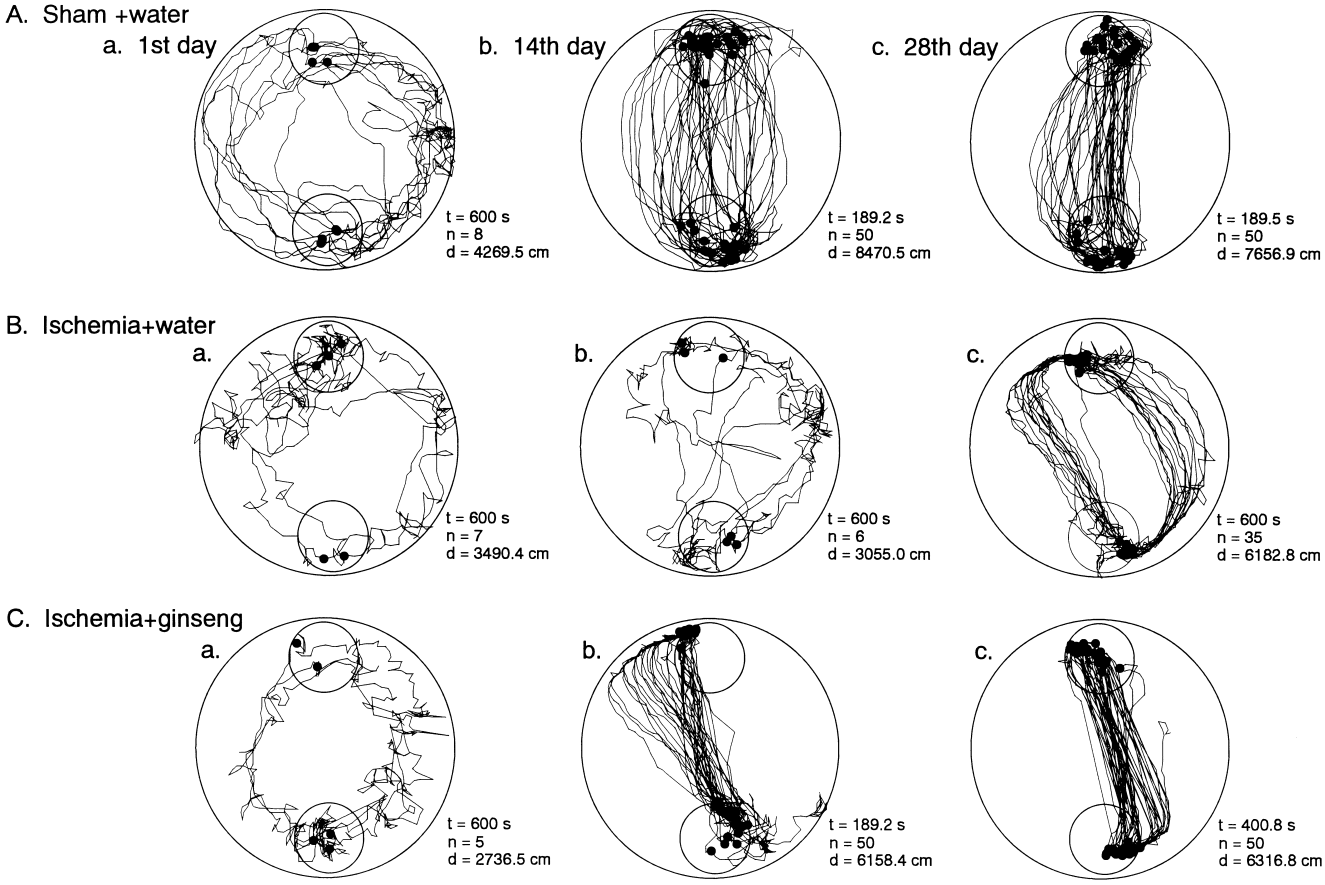

Fig. 2. Typical examples of trails of rats in the 3 groups in the PLT in the 1st experiment. A – C: Trails of Sham + water (A), Ischemia + water (B), and Ischemia + ginseng (C) rats on the 1st (a), 14th (b), and 28th (c) day. Note that a Sham + water rat in Ab and an Ischemia + ginseng rat in Cb navigated with shortcut trails between 2 reward areas, while an Ischemia + water rat in Bb navigated randomly in the open field on the 14th day. t: trial duration (s); n, number of rewards acquired; d, distance traveled (cm). (Reproduced from Ref. 16 with permission from Elsevier)

Ischemia + water rat still navigated randomly or along a wall in the open field on the 14th day (Bb). On the 28th day, the rat showed constant and stable trails (Bc). On the other hand, an Ischemia + ginseng rat showed a similar pattern of navigation to the Sham + water rat that navigated efficiently between the 2 reward areas on the 14th day (Cb).

Figure 3A shows the mean number of rewards per trial in each experimental day (session) acquired by each group of rats over 30-day navigation learning in the PLT. The number of rewards increased rapidly from 1st to 7th day and reached maximum on the 7th or 8th day, and then maintained the maximum value (i.e., 50 rewards/trial) in the Sham + water rats. On the other hand, the number of rewards increased gradually from 1st to 20th day in the both groups of the rats with HF lesions. Statistical analyses indicated that the mean number of rewards acquired by the Sham + water rats was significantly larger than that by the both groups of rats with HF lesions. Furthermore, the Ischemia + ginseng rats acquired more ICSS rewards than the Ischemia + water rats. When the mean number of rewards for each 3 successive days was compared, the mean number of rewards was larger in the Ischemia + ginseng rats than the Ischemia + water rats between the 4th to 6th, 10th to 18th, and 22nd to 24th day, but did not significantly differ in the initial and last stages of navigation learning (i.e., between the 1st to 3rd and the 25th to 30th day). This pattern of performance differences between the Ischemia + ginseng and Ischemia + water rats suggests that red ginseng significantly modulated learning in the rats with HF lesions, but not motor performance itself.

Figure 3B shows the mean distance traveled by each group rats in each experimental day (session) over 30-day navigation learning. The results were essentially similar to those shown in Fig. 3A. Briefly, distance increased rapidly from 1st to 7th day and then slightly

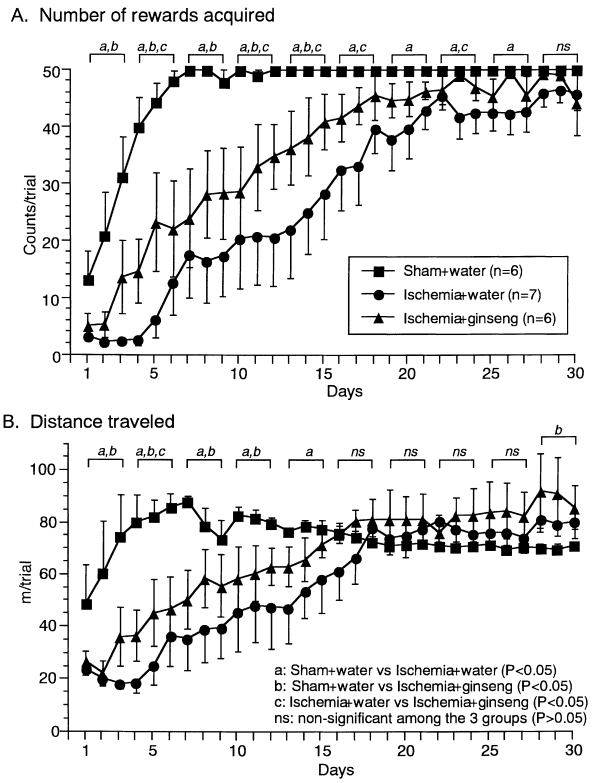

Fig. 3. Comparison of performance in the PLT among the 3 groups of rats in the 1st experiment. A: Mean number of rewards acquired per trial and B: Mean distance traveled per trial. Mean values of the 3 trials in each day (session) in each 3 groups are shown. Note that performance of both Ischemia + water and Ischemia + ginseng rats was significantly lower than that of Sham + water rats and that Ischemia + ginseng rats showed significantly higher performance than Ischemia + water rats (Newman-Keuls test after 2-way ANOVA, $P<0.05$). Filled squares, Sham + water; filled circles, Ischemia + water; filled triangles, Ischemia + ginseng; NS, non-significant difference among the 3 groups of the rats; a – c, significant difference by Newman-Keuls test after 2-way ANOVA ($P<0.05$). (Reproduced from Ref. 16 with permission from Elsevier)

decreased in the Sham + water rats. On the other hand, distance increased gradually from 1st to 17th day in the rats with HF lesions. Statistical analyses indicated that the distance traveled by the Sham + water rats was significantly longer than that by the Ischemia + ginseng rats and that distance traveled by Ischemia + ginseng rats was significantly longer than that by the Ischemia + water rats. However, when the distance for each 3 successive days was compared, distance was not significantly different between the Ischemia + ginseng and Ischemia + water rats during most of the experimental days except 4th to 6th day. This finding contrasted with that in the mean number of rewards shown in Fig. 3A.

Effects of red ginseng on aged rats

The 2nd behavioral experiment with the same protocol was performed using 3 groups of young and aged rats with and without treatment of red ginseng. Essentially similar results as those in rats with HF lesions were obtained, that is, 1) there were no significant differences in current intensity in ICSS bar-press behavior nor in the mean number of bar pressing among these 3 groups of the rats, 2) there were no significant differences in the mean number of training sessions among the 3 groups in the DMT and RRPST, and 3) there were no significant differences in the number of rewards nor in the distance traveled among the 3 groups of the rats in the last session when the rats passed the criteria of the RRPST. All these evidence further confirmed the finding that there were no significant differences among the 3 groups of rats in parameters correlated with simple motor/motivational functions.

Figure 4 illustrates typical examples of trails of rats in the 3 groups on the 1st, 7th, and 21st day in the PLT. A Young + water rat moved randomly on the 1st day (Aa). However, it navigated to display constant and straight trails connecting between the 2 reward areas on the 7th and 21st day (Ab,c). The trails of an Aged + water rat were similarly random on the 1st day (Ba). However, it did not show straight trails connecting between the 2 reward areas, but navigated along a wall of the open field on the 7th day (Bb). On the 21st day, the rat displayed shortcut trails connecting the 2 reward areas although the trails were not stable (Bc). On the other hand, the trails of an Aged + ginseng rat were similar to those of the Young + water rat on the 7th and 21st day except that the trails were not stable in the Aged + ginseng rat (Cb, c). Its trails were intermediate between those of Young + water and Aged + water rats.

Figure 5 shows the mean number of rewards acquired (A) and distance traveled (B) by the rats in each group over 21-day navigation learning. The Young + water rats displayed a similar learning pattern to that of Sham + water rats in the 1st experiment 1; the number of rewards and distance increased rapidly to the nearly maximum values from the 1st to 8th and from 1st to 4th day, respectively, and then maintained the values. On the other hand, the number of rewards and distance increased gradually with learning in aged rats regardless of treatment of ginseng, but more gradually in Aged + water rats. Statistical analyses indicated that there were significant differences in both the number of rewards and distance among the 3 groups; both the number of rewards and distance were significantly larger in Young + water than Aged + ginseng rats and significantly larger in Aged + ginseng than Aged + water rats.

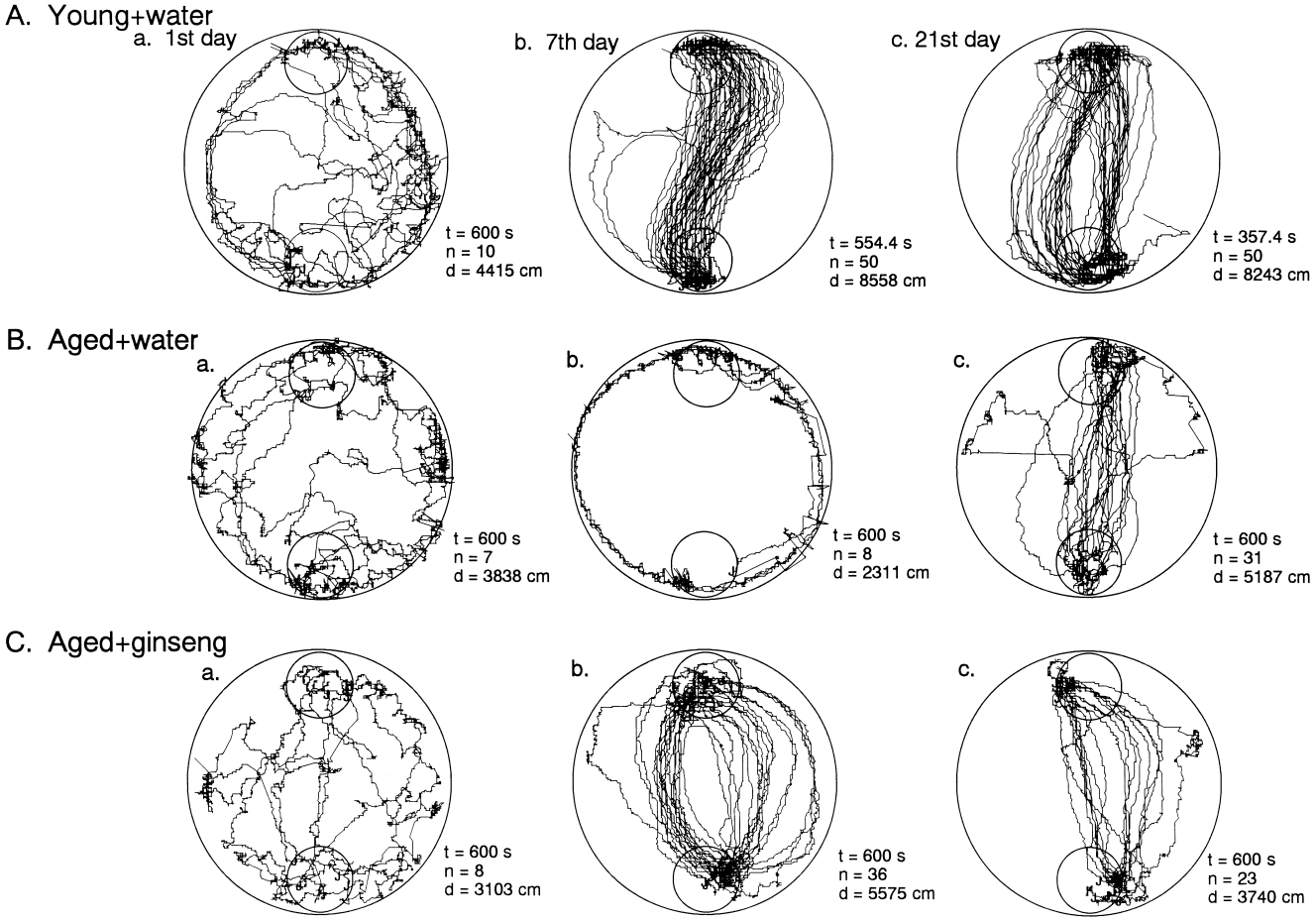

Fig. 4. Typical examples of trails of rats in the 3 groups in the PLT in the 2nd experiment. A – C: Trails of Young + water (A), Aged + water (B), and Aged + ginseng (C) rats on the 1st (a), 7th (b), and 21st (c) day. Note that a Young + water rat in Ab and an Aged + ginseng rat in Cb navigated with shortcut trails between the 2 reward areas, while an Aged + water rat in Bb navigated along a wall of the open field on the 7th day. t, trial duration (s); n, number of rewards acquired; d, distance traveled (cm). (Reproduced from Ref. 16 with permission from Elsevier)

When the data between Aged + water and Aged + ginseng rats were compared in each 3 successive days, both number of rewards and distance were significantly larger in Aged + ginseng rats than Aged + water rats except for on the initial and last 3 days. These findings suggested that treatment with red ginseng significantly modulated learning but not motor performance in the PLT in aged rats.

Effects of red ginseng on the central nervous system

It has been reported that red ginseng has several peripheral effects such as smooth muscle relaxation (17) or an increase in exercise endurance (18). Furthermore, it has been reported that ginseng extract had anti-fatigue effects in mice (19) and increased spontaneous motor activity during the dark period in aged rats (20). Therefore, these findings suggest that amelioration of performance decline in Ischemia + ginseng and Aged + ginseng rats might be attributed to elevated motor activity induced by ginseng, which seems to have both peripheral and central effects. However, this was not unlikely. First, there were no differences in spontaneous locomotor activity (data not shown) and performance in the DMT and RRPST between Ischemia + water and Ischemia + ginseng rats and between Aged + water and Aged + ginseng rats. Second, there were significant differences in the mean number of rewards in the PLT between Ischemia + water and Ischemia + ginseng rats from 10th to 18th day, although there were no significant differences in distance traveled in the same training period. These results strongly suggest that red ginseng ameliorated cognitive deficits in ischemic and aged rats. Consistently, previous behavioral studies reported that ginsenoside Rg_1 or crude ginseng extract ameliorated scopolamine-induced memory deficits (21) and

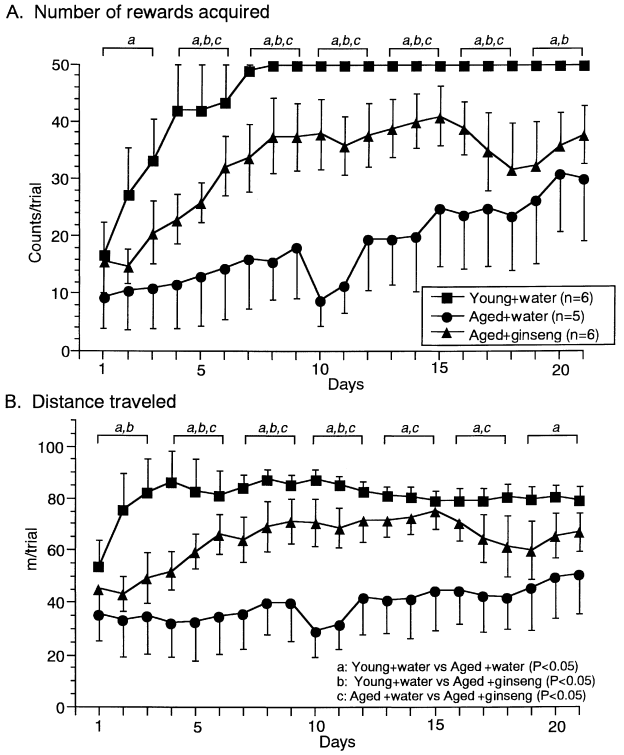

Fig. 5. Comparison of performance in the PLT among the 3 groups of the rats in the 2nd experiment. A: Mean number of rewards acquired per trial; B: Mean distance traveled per trial. Mean values of the 3 trials in each day (session) in each of the 3 groups are shown. Note that performance of both Aged + water and Aged + ginseng rats was significantly lower than that of Young + water rats and that Aged + ginseng rats showed significantly higher performance than Aged + water rats (Newman-Keuls test after 2-way ANOVA, $P<0.05$). Filled squares, Young + water; filled circles, Aged + water; filled triangles, Aged + ginseng; NS, non-significant difference among the 3 groups of the rats; a – c, significant difference by Newman-Keuls test after 2-way ANOVA ($P<0.05$). (Reproduced from Ref. 16 with permission from Elsevier)

learning deficits of rats with medial prefrontal cortical lesions (22).

Our recent study in vitro indicated that water extract of red ginseng significantly enhanced LTP in the CA3 subfield of the HF (unpublished observation). The present results along with this previous neurophysiological results strongly suggest that red ginseng improves learning and memory functions through its direct effects on the central nervous system, at least partly through effects on the HF. However, it is reported that the neural systems other than the HF such as the striatum (23, 24), the nucleus accumbens (25, 26), and the medial prefrontal cortex (27) are also involved in navigation and spatial learning. Consistently, intracerebroventricular infusion of ginsenoside Rc and Rg_1 modulated NMDA-receptor and $GABA_A$-receptor binding in the rat neocortex (28) and NMDA-receptor subunit mRNA in various areas of the rat brain (29). The present study does not deny effects of red ginseng on these systems. Finally, it should be emphasized that at least ginsenosides are poorly absorbed in the gastrointestinal tract, and resultant concentrations in the brain are lower than all other tissues (30). However, its metabolites produced by intestinal bacteria are well absorbed, and had significant pharmacological effects (31, 32). Further studies are required to elucidate sites of action of red ginseng and mechanisms of its effects on learning and memory.

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