Effect of a Nutritive-Tonic Drink on Scopolamine-Induced Memory Impairment in Mice

Yasuko SAKATA, a Rie CHIDA, a Kumiko ISHIGE, a Yoshikuni EDAGAWA, a Takeshi TADANO, b and Yoshihisa ITO* a

a Department of Pharmacology, College of Pharmacy, Nihon University; 7–7–1 Narashinodai, Funabashi, Chiba 274–8555, Japan; and b Department of Pharmacology, Tohoku College of Pharmacy; 4–4–1 Komatsushima, Aoba-ku, Sendai 981–8538, Japan. Received June 21, 2005; accepted July 7, 2005

The effects of a liquid nutritive and tonic drug (NTD) selected from a modification of the “Kai-xin-shou-yu-shen-qi-wan” prescription, on scopolamine-induced amnesia in mice were investigated using the passive avoidance and water-maze tasks. A popular NTD in Japan that contains 17 crude (natural) drug extracts together with synthetic drugs such as taurine, caffeine, various vitamins and ethanol, and the natural drug extracts is based on a prescription of “Kampo" origin in Chinese medicine. Scopolamine (0.4 mg/kg, i.p.) reduces the step-through latency of the passive avoidance test and fear reaction behavior at 24 and 48 h after treatment. A single oral administration of the NTD (10 ml/kg) increased the step-through latency and the fear reaction behavior score in scopolamine-treated mice. Administration of the natural drug extracts found in the NTD tended to extend the step-through latency in the retention test at 48 h, but not 24 h after the initial scopolamine trial. However, administration of the synthetic drugs found in the NTD did not improve either the step-through latency or the behavioral score. The NTD and the natural drug extracts also improved the scopolamine-induced spatial memory impairment as assessed using the Morris water-maze test. In contrast, the synthetic drugs did not affect the escape latencies. Both NTD and the synthetic drugs increased the locomotor activity in scopolamine-treated mice, whereas the natural drug extracts did not. These results suggest that NTD improves scopolamine-induced amnesia, and that this action is attributable to the natural drug extracts in the NTD.

Key words: natural drug extract; passive avoidance test; Morris water-maze test; nutritive-tonic drink; scopolamine; learning and memory

Crude drugs obtained from plants, animals, or minerals have long been used widely in many cultures as folk remedies. A number of nutritive-tonic drinks are over-the-counter drugs that have been licensed officially by the Minister of Welfare in Japan. The formulae of the nutritive and tonic drug (NTD) used in this study is based on the “Kampo” prescription (a traditional Japanese medicine that originates in Chinese medicine). It contains 17 crude natural drug extracts together with taurine, caffeine, and various vitamins. The natural drugs used in the NTD were selected from a modification of the “Kai-xin-shou-yu-shen-qi-wan” prescription, which itself originates from the “Fan-wang prescription”. The Fan-wang prescription was used in ancient China for disorders deriving from fatigue, such as decline in physical activity, lax muscles, lassitude, oversensitivity to cold, blurred vision, loss of sexual drive, loss of appetite, dyspepsia, palpitations, insomnia, mild depression, and forgetfulness. The Fan-wang prescription has not been preserved in its original form in China, but the prescription was recorded in “Ishinpo”, which is the oldest Japanese medical text in existence. The Ishinpo manuscript was based on about 200 Chinese medial texts by Yasuyori Tamba, and dedicated to the Japanese Emperor in the year 984 A.D. Ever since, the Ishinpo has been used by medical students, and it was designated a national treasure in 1984.

Recently, pharmacological studies revealed evidence indicating that a series of NTDs exerts positive effects on physical and mental fatigue. Tadano et al. reported that administration of ZENA F-I, F-II and F-III, when given to mice after forced swimming, markedly increased the duration of the subsequent swimming bout, and decreased the duration of immobility during this session. They observed similar antifatigue effects of the mixture when it was given to tetra-benazine-treated mice, although imipramine, a typical antidepressant, exerted no such antifatigue effects in their experimental system. Interestingly, ZENA F-III, when given to mice under electric-shock-induced conditioned immobility (or freezing), induced enhanced locomotor activity. Hanawa et al. showed that administration of this NTD attenuates the exercise-induced calcium elevations in the serum and brain, and increases the level of dopamine in the brain. We reported recently the serum glucocorticoid levels of mice under conditions of “restraint with gnawing (R’G’+)” and “restraint without gnawing (R’G’−)”; R’ G− induced a higher serum glucocorticoid level than R’ G+. This NTD reduced the glucocorticoid elevation observed in R’ G+, but not that observed in R’ G−. Therefore, we concluded that this NTD reduced the severity of mental or emotional fatigue, or increased the level of motivation in stressful situations. Although it is likely that both ZENA F-III and ZENA King will have effects on conditions other than fatigue, until now no further investigations have been performed.

In dementia, a typical “forgetfulness” disease, patients appear to have a dysfunctional central cholinergic system. Indeed, cholinesterase inhibitors have been reported to be effective in the treatment of Alzheimer’s disease. Scopolamine, a nonselective muscarinic receptor antagonist, has been used as a pharmacological tool to evaluate the effects of nootropic drugs on memory deficits in experimental animals. The purpose of the study presented here was to investigate the effects of oral administration of a NTD (ZENA King), which includes crude natural drug extracts, on scopolamine-induced amnesia in mice, using the passive avoidance and water-maze tasks. We also investigated the ef-
ffect of the NTD, the natural drug extracts and the synthetic drugs contained in the NTD on the locomotor activity of control and scopolamine-treated mice.

MATERIALS AND METHODS

Animals  Male, 5-week-old ddY mice were used in the passive avoidance task and to investigate locomotor activity, and 5-week-old ICR mice were used in the Morris water-maze task. All of the animals were provided by Japan SLC (Shizuoka, Japan). The mice were housed in groups of 5—6 in plastic cages, which were maintained at room temperature (23 ± 1 °C) and a relative humidity of 50 ± 10%, for 1 week under a 12 h : 12 h light : dark cycle (lights on between 8:00 and 20:00). They were allowed food and water ad libitum before the commencement of the experiments. All procedures used in this study were performed in accordance with the guidelines established by the College of Pharmacy at Nihon University for the care and use of laboratory animals.

Drugs  The constituents of the NTD are listed in Table 1. It contains extracts of 17 natural drugs, and synthetic drugs such as taurine, caffeine, various vitamins, and ethanol, and is packed into light-shielded 50-ml bottles. This NTD was manufactured in the factory of Taisho Pharmaceutical Co., Ltd., Tokyo, Japan, which conforms to “The medical supplies GMP standard in Japan”. The natural drug extracts were also provided by Taisho Pharmaceutical Co., Ltd. Scopolamine hydrobromide (Wako Pure Chemical Industries Ltd., Osaka, Japan) was dissolved in 0.9% physiological saline.

Passive Avoidance Response  Apparatus: The apparatus for the step-through passive inhibitory avoidance test (O’Hara & Co., Ltd., Tokyo, Japan) consists of an illuminated (base side; 13.5 × 4.5 cm, floor side; 13.5 × 10 cm, height 8.5 cm) and a dark (base side; 15.5 × 4.5 cm, floor side; 15.5 × 10 cm, height 8.5 cm) compartment. These two compartments are divided by a wall that has either a guillotine door or a hole (2.5 cm in diameter) connecting them. The dark compartment has a removable cover made of the same material. A lamp (20 W, positioned 20 cm above the apparatus) is used to illuminate the side of the light compartment.

Procedure: The test was conducted on 3 consecutive days. On the 1st day, in the acquisition trial, the mice were gently placed into the illuminated compartment, facing away from the dark compartment. The door to the dark compartment was then opened and the mouse was allowed to step with all four paws into the dark compartment, after which the door was immediately closed. Three seconds later an electric shock (0.6 mA, 5 s duration) was delivered through the grid floor of the dark compartment. The latency to step-through was recorded, and the responses to the electric shock were observed for 5 s, as follows: 0, no response; 1, flinch (movement of any part of the body); 2, run (running or jumping) or 3, run and vocalization. Only those mice that entered the dark compartment within 40 s in the acquisition trial were used in subsequent experiments. Retention tests were performed 24 and 48 h after the acquisition trial. The mice were again placed in the illuminated compartment and allowed to step into the dark compartment; the latency of step-through was recorded. The maximum cut-off time for the step-through latency was 300 s. The behavior of the mice (i.e., number of evacuations, frequency with which they looked through to the dark compartment, and pilomotor, shaking, grooming, and freezing scores) was recorded from when it was introduced into the illuminated room until it moved into the dark compartment.

Scopolamine-induced amnesia was effected by injecting scopolamine (0.4 mg/kg, administered intraperitoneally, i.p.) 30 min before the acquisition trial. Control mice received 0.9% physiological saline. The NTD, the natural drug extracts, and the synthetic drugs were administered orally (10 ml/kg body weight) 60 min before the scopolamine treatment, and tap water was used as a control. Experiments were carried out between 10:00 and 16:00.

Morris Water-Maze Test  Apparatus: The apparatus for the Morris water-maze with a video tracking system was purchased from Muromachi kikai Co., Ltd. (Tokyo, Japan). The water-maze test, performed according to the method of Morris, was carried out in a circular pool (diameter: 120 cm, height: 30 cm) that was filled to a depth of 24 cm with water (20—21 °C). The pool was divided into four quadrants of equal area. A clear platform (diameter: 10 cm) was centered in one of the four quadrants of the pool and submerged approximately 1 cm below the surface of the water. The mice could escape from the water onto the platform. The time taken for the mouse to escape from the water onto the platform was measured.

Procedure: In this experiment, ICR mice were used since the mice have been shown to be the most preferable to the Morris water-maze test among four different strains of mice tested. During the experimental period, each mouse was trained two times each day. Each mouse was placed in the

<table>
<thead>
<tr>
<th>Table 1. Constituents of NTD</th>
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<tr>
<td><strong>Drugs</strong></td>
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<tr>
<td>Source of natural drugs</td>
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<tr>
<td>Muira puama (muira puama)</td>
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<tr>
<td>Ginseng radix (ninjin)</td>
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<tr>
<td>Epimedi herba (inouyakaku)</td>
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<tr>
<td>Rehmanniae radix (jigou)</td>
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<tr>
<td>Cistanchis herba (nikujyubou)</td>
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<tr>
<td>Cnidii monnieri fructus (jasyoushi)</td>
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<tr>
<td>Cuscutae semen (toshishi)</td>
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<tr>
<td>Poria (bukuryou)</td>
</tr>
<tr>
<td>Phloae testis et penis (kaikujin)</td>
</tr>
<tr>
<td>Glycyrrhiza radix (kanzou)</td>
</tr>
<tr>
<td>Corni fructus fluid (sansyu-u)</td>
</tr>
<tr>
<td>Dioscoreae rhizoma fluid (sanyaku)</td>
</tr>
<tr>
<td>Eucommiae cortex liquid (toyu-u)</td>
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<tr>
<td>Schizandrae fructus fluid (gomishi)</td>
</tr>
<tr>
<td>Cervi parvum coru (tojou)</td>
</tr>
<tr>
<td>Asigirodon japonia (hanpi)</td>
</tr>
<tr>
<td>Cordyceps (tougakusou)</td>
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</table>

a Each value represents the original weight of natural drugs in a bottle. It comes from extracting of natural drugs by ethyl alcohol mixed with water.
water facing away from the wall from one of four starting sites in a random sequence; each site was used only once each day. The time taken for the mouse to find the escape platform was measured by the video tracking system. The mouse was allowed to rest on the platform for 15 s. If after 120 s the mouse had failed to find the platform, it was taken by the experimenter and placed onto the platform for 15 s. The experimenter always sat at the same position.

As for the passive-avoidance response test, amnesia was induced by injecting scopolamine (0.4 mg/kg, i.p.) 30 min before the trial, and control mice received 0.9% physiological saline. The NTD, the natural drug extracts, and the synthetic drugs were administered orally (10 ml/kg body weight) 30 min before the scopolamine treatment, and tap water was used as a control. Experiments were carried out between 10:00 and 16:00.

**Locomotor Activity** Apparatus: The apparatus for the locomotor activity test (O’Hara & Co., Ltd., Tokyo, Japan) was a tilting-type round activity cage (18 cm in diameter and 18 cm in height).

Procedure: The mice were administered the NTD, the natural drug extracts, or the synthetic drugs orally (10 ml/kg body weight), followed 60 min later by scopolamine (0.4 mg/kg, i.p.). They were then placed into the locomotor activity cages. Locomotor activity counts/10 min were measured for 2 h.

**Data Analysis** Experimental values are given as the mean±standard error of the mean (S.E.M.). The step-through latency and the electric-shock-induced response behavior scores were evaluated using the Kruskal-Wallis H-test followed by the Mann-Whitney U-test with Bonferroni’s correction. The timing of the electric-shock-induced response behavior, the total locomotor counts, and the escape latency from the Morris water-maze were evaluated by one-way analysis of variance (ANOVA) followed by Bonferroni’s correction.

**RESULTS**

**Effects of NTD, Natural Drug Extracts, and Synthetic Drugs on Scopolamine-Induced Memory Impairment: the Passive Avoidance Task** Figure 1 shows effects of a single oral administration of the NTD, natural drug extracts, and synthetic drugs on passive avoidance responses in scopolamine-treated mice. When administered water, NTD, natural drug extracts, and synthetic drugs with scopolamine did not affect the latencies of the acquisition trial compared to control mice (administered water with saline) (Fig. 1A). Scopolamine (0.4 mg/kg, i.p.) significantly reduced the step-through latencies at both 24 and 48 h after treatment as compared with control mice at the same time points (Figs. 1B, C; p<0.01 for both). The NTD partially, but significantly extended the latency in the retention test at both 24 and 48 h after the acquisition trial in scopolamine-treated mice. Administration of natural drug extracts tended to extend the latency in the retention test at both 24 and 48 h after the acquisition trial. Administration of synthetic drugs had no effect on the latency at either 24 or 48 h after the acquisition trial. Neither the NTD, natural drug extracts, nor synthetic drugs affected the electric-shock-induced response scores achieved during the acquisition trial (Table 2).

Table 2. Effects of NTD, Natural Drug Extracts, and Synthetic Drugs on the Electric Shock Behavior on the Acquisition Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Score±S.E.M.</th>
<th>n</th>
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<tr>
<td>Water +saline</td>
<td>2.4±0.18</td>
<td>13</td>
</tr>
<tr>
<td>Water +scopolamine (0.4 mg/kg, i.p.)</td>
<td>1.7±0.20</td>
<td>15</td>
</tr>
<tr>
<td>NTD +scopolamine (0.4 mg/kg, i.p.)</td>
<td>1.8±0.18</td>
<td>15</td>
</tr>
<tr>
<td>Natural drug extracts +scopolamine (0.4 mg/kg, i.p.)</td>
<td>1.4±0.12</td>
<td>16</td>
</tr>
<tr>
<td>Synthetic drugs +scopolamine (0.4 mg/kg, i.p.)</td>
<td>1.9±0.12</td>
<td>15</td>
</tr>
</tbody>
</table>

Water, NTD (ZENA King), natural drug extracts, and synthetic drugs were administered (p.o., each dose was 10 mg/kg body weight). Scopolamine (0.4 mg/kg) or saline was administered intraperitoneally 60 min before the acquisition trial. Results are expressed as the mean±S.E.M. of 13—16 mice. 

* p<0.05, ** p<0.01 as compared with W (Sal.), †† p<0.01 as compared with W (Scop.).
frequency with which the mice looked through to the dark compartment in the retention test 24 h and 48 h after the trial, these effects were not significant as compared to water- or synthetic drugs-administered mice. Natural drug extracts mimicked the effects of the NTD with respect to the total behavior score; however, the effect was weaker than that observed with the NTD. Synthetic drugs had almost no effect on any type of behavior in scopolamine-treated mice.

**Effects of NTD, Natural Drug Extracts, and Synthetic Drugs on Scopolamine-Induced Memory Impairment: the Morris Water-Maze Task** Figure 3 shows effects of the NTD, natural drug extracts, and synthetic drugs on the escape latency achieved in the Morris water-maze task in saline- and scopolamine-treated mice. Saline-treated mice rapidly acquired the spatial task, as indicated by a gradual, session-dependent decrease in escape latency. When administered water (i.e., in control mice), the NTD, natural drug extracts, and synthetic drugs did not affect the escape latencies (Fig. 3A). Although the escape latencies of scopolamine-treated mice were significantly longer than those of saline-treated mice from days 3 to 5, the NTD tended to reduce the escape latencies achieved on days 3 and 4, and significantly reduced the latency achieved on day 5 (Figs. 3A, B). The effects of the natural drug extracts tended to be stronger than those of the NTD in this task, and it significantly reduced the escape latencies achieved on days 3—5. In contrast, the synthetic drugs had no effect on the escape latencies. The NTD, the natural drug extracts, and the synthetic drugs had no effect on swimming speed in either the saline- or scopolamine-treated mice (data not shown).

**Effects of NTD, Natural Drug Extracts, and Synthetic Drugs on Locomotor Activity** Figure 4 shows the locomotor activities in normal and scopolamine-treated mice treated with the NTD, natural drug extracts, and synthetic drugs. In normal mice (i.e., not treated with scopolamine), treatment with the NTD or synthetic drugs increased locomotor activity by 77% and 78%, respectively, compared with water-treated mice. Treatment with scopolamine alone increased locomotor activity by up to 96% compared with normal mice. In scopolamine-treated mice, the NTD significantly increased locomotor activity by up to 111% and 133% compared to that observed for water-treated mice and those treated with natural drug extracts, respectively (p < 0.01 for both). Remarkable increases in locomotor activity were observed during 60—90 min after the treatment with the NTD. Although synthetic drugs also increased the locomotor activity, their effects were 54% less potent than those of the NTD. In contrast, natural drug extracts had no effect on locomotor activity.
this difference in sensitivity between the two tests remains to scores achieved in the water-maze task. The reason behind original natural drug extracts; however, the natural drug induced amnesia in the passive avoidance task than were the feine and taurine. found in the NTD, but not to the synthetic drugs, such as caf-
are attributable, at least in part, to the natural drug extracts and the water-maze task, and that these antiamnesic effects lamine-induced amnesia in both the passive avoidance task. Although the natural drug extracts alone did not affect the step-through latency 24 h after the acquisition trial, it tended to extend the step-through latency 48 h after the trial. The mixture of synthetic drugs affected neither the latency nor the response behavior in scopolamine-treated mice, however, it might modulate the action of NTD in combination with natural drug extracts. The NTD at the same dose also improved spatial memory impairment in the scopolamine-induced amnesia mice using the passive avoidance task. Although the natural drug extracts alone did not affect the step-through latency 24 h after the acquisition trial, it tended to extend the step-through latency 48 h after the trial. The mixture of synthetic drugs affected neither the latency nor the response behavior in scopolamine-treated mice, however, it might modulate the action of NTD in combination with natural drug extracts. The NTD at the same dose also improved spatial memory impairment in the scopolamine-induced amnesic mice in the Morris water-maze test, but had no effect on the escape latencies of the control mice. Moreover, natural drug extracts also significantly reduced the escape latency at days 3—5 in the scopolamine-induced amnesic mice. Taken together, these results suggest that orally administered NTD partially but significantly improves scopolamine-induced amnesia in both the passive avoidance task and the water-maze task, and that these anti-amnesic effects are attributable, at least in part, to the natural drug extracts found in the NTD, but not to the synthetic drugs, such as caffeine and taurine.

The NTD was more effective in improving scopolamine-induced amnesia in the passive avoidance task than were the original natural drug extracts; however, the natural drug extracts were more effective than the NTD in improving the scores achieved in the water-maze task. The reason behind this difference in sensitivity between the two tests remains to be elucidated. One explanation may be the different strains of mouse used for the two tasks (male ddY mice in the passive avoidance task and male ICR mice in the Morris water-maze task).

Although the active ingredient(s) of the natural drug extracts in the NTD have yet to be examined, one of them, Ginseng radix, has been shown to affect negatively reinforced tasks such as passive avoidance and conditioned avoidance tasks in rats. Furthermore, red ginseng saponins have been shown to improve scopolamine-induced amnesia in mice in both the passive avoidance and Morris water-maze tasks. Hsieh et al. also reported that ginseng administered orally for 1 week improved scopolamine-induced amnesia in rats, as assessed using the passive avoidance task. It appears, therefore, that some of the ginseng ingredients in the NTD may play a role in improving scopolamine-induced amnesia. In addition, Poria, which is also a constituent of the natural drug extracts in the NTD, has been shown to increase the frequency of correct choices in the eight-armed radial maze task.

The results presented here also demonstrate that both the NTD and the synthetic drugs increase locomotor activity in normal mice (in this study by 77% and 78%, respectively). Treatment of the mice with scopolamine alone significantly increased locomotor activity, as has been reported previously, and the NTD dramatically potentiated this activity. Unlike the normal mice, the effects of the NTD on locomotor activity were stronger than those of the synthetic drugs in scopolamine-treated mice. Remarkable increases in locomotor activity were observed during 60—90 min after the treatment with the NTD, suggesting that the NTD might exhibit delayed effect on locomotor activity in scopolamine-treated mice.

The dose of caffeine in the NTD and in the synthetic drugs used in these experiments was 10 mg/kg (p.o.), a dose that has been shown previously to increase locomotor activity in mice. Therefore, it appears that caffeine plays a pivotal role in increasing locomotor activity. In contrast, the natural drug extracts affected the locomotor activity of neither normal nor scopolamine-treated mice, suggesting that none of the ingredients in the natural drug extracts have locomotor-increasing activity at the doses used in this experiment. We have reported previously that a prototype of this NTD which differs only in that it lacks two of the natural drug extracts present in

**DISCUSSION**

The data presented here demonstrate that a single oral administration of a NTD which is selected from a modification of the “Kai-xin-shou-yu-shen-qi-wan” prescription a dose of 10 ml/kg body weight improves scopolamine-induced amnesia at both 24 and 48 h after the acquisition trial in mice without affecting the electric-shock-induced behavior score. It extended the step-through latency in the passive avoidance test at both 24 and 48 h after the acquisition trial, and increased the passive avoidance response behavior score (pilo-
motor, shaking, grooming, and freezing) 24 h after the acquisition trial as compared to the controls.

Since the NTD used in this study contains extracts of 17 crude natural drugs together with taurine, caffeine, and various vitamins, we investigated the effects of those natural drug extracts and a mixture of synthetic drugs independently on scopolamine-induced amnesia using the passive avoidance task. Although the natural drug extracts alone did not affect the step-through latency 24 h after the acquisition trial, it tended to extend the step-through latency 48 h after the trial.

Unlike the normal mice, the effects of the NTD on locomotor activity were stronger than those of the synthetic drugs in scopolamine-treated mice. Remarkable increases in locomotor activity, as has been reported previously, and the NTD dramatically potentiated this activity. Unlike the normal mice, the effects of the NTD on locomotor activity were stronger than those of the synthetic drugs in scopolamine-treated mice.

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the NTD (Cordyceps and Gycyrrhizae radix), reduces the elevation in glucocorticoid induced during restraint-gnawing stress, and reduces the severity of mental or emotional fatigue and increases motivation in stressful situations in which mice are allowed to look after themselves. The application of foot shocks during passive avoidance training has been shown to significantly increase plasma corticosterone levels in mice. Since there is clearly a relationship between stress, glucocorticoid levels, and memory impairment, further study is necessary to elucidate the mechanism of action of the NTD. The application of foot shocks during passive avoidance training has been shown to significantly increase plasma corticosterone levels in mice. Since there is clearly a relationship between stress, glucocorticoid levels, and memory impairment, further study is necessary to elucidate the mechanism of action of the NTD. NTDs called as “Drink-Zai” (drinking drugs), are widely used in Japan, and a number of NTDs are classified as an over-the-counter drug. Many users claim that the NTD used in this experiment is useful in the recovery from physical and psychological fatigue, for improving a weak constitution, and as a nutritive supplement. We have shown here that the NTD based on the “Kai-xin-shou-yu-shen-qi-wan” prescription (ZENA King) might also be effective in improving amnesia under certain conditions.

Acknowledgments We thank Taisho Pharmaceutical Co., Ltd., Japan for providing ZENA King and the natural drug extracts used in our experiments.

REFERENCES