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Effects of red ginseng saponins and nootropic drugs on impaired acquisition of ethanol-treated rats in passive avoidance performance

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Abstract

Effects of single and repeated administration of red ginseng total saponins (ROTS) and nootropic drugs were examined on impairment of acquisition induced by single oral administration of 3 g/kg ethanol (EtOH) in a step through test. The inhibitory effect of EtOH on acquisition was significantly reduced following single or repeated RGTS administration. The nootropic drugs, piracetam and *N*-methyl-D-glucamine, given orally significantly reduced impairment of acquisition induced by EtOH. On the other hand, the inhibitory effect of repeated RGTS on the EtOH-induced amnesia was blocked by the pretreatment of α-methyl-ρ-tyrosine (α-MT), an inhibitor of catecholamine synthesis, in a dose-dependent manner but not ρ-chlorophenylalanine (PCPA), an inhibitor of serotonin synthesis, whereas the inhibitory effect of repeated *N*-methyl-D-glucamine on the EtOH-induced amnesia was blocked neither by α-MT nor PCPA. These results suggest that repeated RGTS and *N*-methyl-D-glucamine ameliorate the impairing effect of EtOH on acquisition, and the effect of RGTS on EtOH-induced amnesia is dependent on the catecholaminergic but not serotonergic neuronal activity, while RGTS and *N*-methyl-D-glucamine seem to have a different mechanism on EtOH-induced amnesia.

Keywords: Acquisition; Ethanol; α-Methyl-ρ-tyrosine; Nootropic drug; Red ginseng total saponin; Repeated administration

1. Introduction

Korean red ginseng, well known as a herbal medicine, has been used for treatment and prevention of many diseases for thousands of years (Park et al., 1984). In recent years, numerous studies have been done on saponins isolated from Korean red ginseng. These studies have demonstrated that Korean red ginseng saponins possess various effects on the spatial memory (Buresova and Bures, 1982; Jaenicke et al., 1991; Park et al., 1994), electric shock (Oh et al., 1969) and intoxication (Kim et al., 1996). Studies from our laboratory have demonstrated the effects of ginseng saponins on catecholaminergic neuronal activity

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in modulation of motor activity by studying the spontaneous locomotor activity (Kim et al., 1992) and apomorphine-induced stereotyped behavior (Lee et al., 1995a,b) in normal rat or in 6-hydroxydopamine (6-OHDA)-treated rats (Lee et al., 1993). The study of Benishim (1992) reported the effects of red ginseng saponins on the spatial memory and suggested the involvement of the cholinergic system. The studies on the effect of red ginseng saponins on the catecholaminergic system in modulation of memory are lacking.

Nootropic drugs, including piracetam, *N*-methyl-D-glucamine, centrofenoxine and pyritinol, enhance learning ability and memory consolidation (Mouravieff-Lesuisse and Giurger, 1968; Wolthuis, 1971), increase the resistance of brain cells to hypoxia and intoxication (Sara and Lefever, 1972; Giurgen, 1973). Many studies have been directed toward the development of drugs for the treatment of dementia and for the understanding of the neurological basis of nootropic drugs (Schmidt, 1990; Yamamoto et al., 1990). Although the mechanism is not yet clear, some reports have suggested that the ameliorating effects of nootropic drugs on amnesia experimentally induced by administration of scopolamine and by lesion of the dorsal hippocampus is mediated by cholinergic activation, but that on amnesia produced by ischemia is not solely related to the cholinergic system (Kabuta et al., 1982; Yamamoto et al., 1990). There are few studies indicating the ameliorating effects of nootropic drugs on ethanol-induced amnesia relating to the central catecholaminergic system modulating learning and memory (Corrodi et al., 1966; Wise, 1978; Tabakoff and Hoffman, 1979).

The purpose of this study is to investigate the effects of single or repeated administration of the RGTS and nootropic drugs on impairment of acquisition induced by single oral administration of ethanol (EtOH). Furthermore, functional difference between RGTS and nootropic drugs on central catecholaminergic processes in the modulation of EtOH amnesia was also examined.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats, 6–8 weeks of age were used throughout the study. All animals were housed in cages having four rats in a case and under temperature- and humidity-controlled (22 ± 1°C, 55 ± 2%) conditions with a 12-h dark/light cycle (light at 07:00 h), and were allowed free access to food and water.

2.2. Drug preparation and administration

Ethanol (EtOH, Ducsan Pharmaceutical), *N*-methyl-D-glucamine (Sigma), piracetam (Sigma), α-methyl-ρ-tyrosine (α-MT, Sigma), ρ-chlorophenylalanine (PCPA, Sigma), and red ginseng total saponin (RGTS, characterized the saponin mixture quantitatively containing at least 11 glycosides; Rb1 (18.26%), Rb2 (9.07%), Rc (9.65%), Rd (8.24%), Re (9.28%), Rf (3.48%), Rg1 (6.42%), Rg2 (3.62%), Rg3 (4.70%), Ro (3.82%), Ra (2.91%) and other minor ginsenosides and components (20.55%), from Panax ginseng, extracted and purified by Namba et al. (1974) method and supplied by Korea Ginseng and Tobacco Research Institute, Taejon, Korea).

EtOH was given to the rats in a single oral administration at a dose of 3.0 g/kg body weight as a 50% (w/v) solution in physiological saline. *N*-Methyl-D-glucamine, piracetam and RGTS were dissolved in physiological saline and were administered orally either singly or in repeated doses on 7 consecutive days (0.1 ml/100 g body weight). α-MT and PCPA were dissolved in 0.5% carboxymethylcellulose (CMC) solution and were injected intraperitoneally.

2.3. Passive avoidance performance test; step through test

The step through test was performed according to the modified method of Casamenti et al. (1993). The apparatus (PACS-30, Columbus, OH, USA; $54.5 \times 33.0 \times 48.3$ cm) consisted of two compartments separated by a wall with a

hole in the lower middle part. One of the two chambers was illuminated and the other was dark. The test was conducted on 2 consecutive days at the same time of day. On the first day (learning trial), each rat was placed in the illuminated compartment of the apparatus. After 30 s the guillotine door was raised, allowing access to the dark chamber. Rats preferred the dark compartment and, when placed in the illuminated chamber, rapidly move to the dark chamber. Once the rat enters the dark compartment, it receives an electric shock on the feet (0.6 mA, 5 s) through the stainless steel grid floor. The time when the mouse entered the dark chamber was recorded automatically and described as latency. On the second day (testing trial), the same test procedure was followed: rats were exposed in the light compartment for 60 s in the learning trail and 300 s in the testing trail. The latency and the number of rats which did not enter the dark compartment were recorded in the testing trail.

2.3.1. Effects of single EtOH, RGTS and nootropic drugs on acquisition of normal rats in the step through test

EtOH (50%, w/v, 0.6 ml/100 g, p.o.), RGTS (100, 200 mg/kg, p.o.), *N*-methyl-glucamine (500 mg/kg, p.o.), piracetam (500 mg/kg, p.o.) were given 60 min before the learning trial to cause impairment of acquisition, respectively. The dosage and the time of administration of drugs used were chosen on the basis of a preliminary experiments (data not shown).

2.3.2. Effects of acute RGTS and nootropic drugs on impaired acquisition of EtOH-treated rats in the step through test

In acute drug studies on impairment of acquisition of ethanol-treated rats, RGTS (100, 200 mg/kg, p.o.), *N*-methyl-D-glucamine (500 mg/kg, p.o.) and piracetam (500 mg/kg, p.o.) were given 30 min before EtOH administration in separate animal groups. The control animals given only normal saline without drug following ethanol treatment.

2.3.3. Effects of repeated RGTS and nootropic drugs on impaired of acquisition induced by EtOH in the step through test

In repeated drugs studies on impairment of acquisition of ethanol-treated rats, rats were administered RGTS (200 mg/kg, p.o.), *N*-methyl-D-glucamine (500 mg/kg, p.o.) and piracetam (500 mg/kg, p.o.) for 7 consecutive days, and EtOH was administered 30 min after the last treatment of drugs to each animal group. The control animals were given only normal saline without drugs following ethanol treatment. In repeated drug studies on impairment of acquisition of ethanol-treated rats, α-MT or PCPA were given 24 and 48 h before EtOH administration in individual animal groups, respectively.

2.4. Statistics

The data were expressed as the mean ± S.E.M. The latency in the step through test was analyzed using Student's *t*-test, and the data on the number of rats which did not make errors in the step through test was analyzed using the χ^2-test.

3. Results

3.1. Effects of EtOH, RGTS and nootropic drugs on acquisition of rats in the step through test

Latency and the incidence of error were remarkably changed, but there were no differences between control and RGTS- or nootropic drugs-treated groups in the step through test (data not shown). Latency was significantly shortened and the incidence of error was scarcely shown by EtOH.

3.2. Effects of acute RGTS and nootropic drugs on impaired acquisition of EtOH-treated rats in the step through test

The shortening of latency induced by ethanol were significantly prolonged by acute RGTS (100, 200 mg/kg) and piracetam (500 mg/kg), but not by *N*-methyl-D-glucamine (500 mg/kg)

(Fig. 1), while there were no differences between control and acute RGTS, piracetam or *N*-methyl-D-glucamine on the number of successful rats decreased by EtOH (Fig. 3).

3.3. Effects of repeated RGTS and nootropic drugs on impaired acquisition of EtOH-treated rats in the step through test

In repeated administration for 7 consecutive days, the acute ameliorative effect of RGTS (200 mg/kg) still persisted and showed longer latency than acute administration, but the acute ameliorative effect of piracetam (500 mg/kg) disappeared and did not show any significant difference as compared with control groups. In contrast to piracetam, *N*-methyl-glucamine (500 mg/kg) showed significant ameliorative effect on latency by repeated administration for 7 consecutive days (Fig. 2). On the other hand, the number of successful rats inhibited by ethanol significantly increased following repeated administration of RGTS and *N*-methyl-glucamine, but not piracetam (Fig. 3).

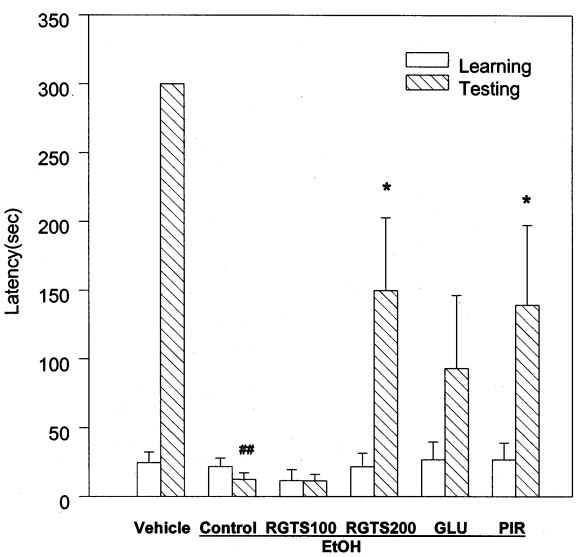

Fig. 1. Effects of a single dose of red ginseng total saponin (RGTS), *N*-methyl-D-glucamine (GLU) and piracetam (PIR) on impaired acquisition of EtOH-treated rats in the step through test. RGTS (100, 200 mg/kg, p.o.), GLU (500 mg/kg, p.o.) and PIR (500 mg/kg, p.o.) were given 30 min before EtOH injection in individual animal groups. Latency indicates the time the rat entered the dark compartment. Values represent the mean ± S.E.M. of three to 11 rats. $\#\,\#\,P<0.01$ when compared with vehicle; $*P<0.05$ when compared with control.

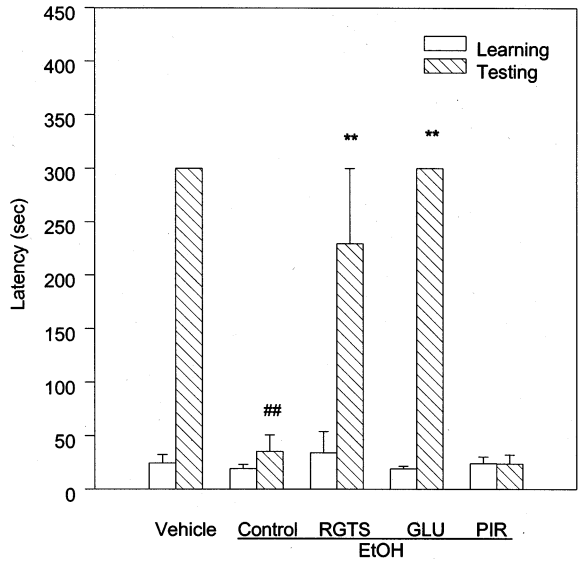

Fig. 2. Effects of repeated administration of red ginseng total saponin (RGTS), *N*-methyl-D-glucamine (GLU) and piracetam (PIR) on impaired acquisition of EtOH-treated rats in the step through test. Rats were administered RGTS (200 mg/kg, p.o.), GLU (500 mg/kg, p.o.) and PIR (500 mg/kg, p.o.) for 7 consecutive days and EtOH was injected 30 min after the last treatment of drugs in individual animal groups. The control animal were given only normal saline without drug for 7 consecutive days. Latency indicates the time the rat entered the dark compartment. Values represent the mean ± S.E.M. of three to 11 rats. $\#\,\#\,P<0.01$ when compared with vehicle; $**P<0.01$ when compared with control.

3.4. Effects of α-MT or PCPA on the ameliorative effects of repeated RGTS and N-methyl-glucamine on impaired acquisition of EtOH-treated rats in the step through test

Ameliorative effects of repeated RGTS (200 mg/kg) on latency of acquisition (Fig. 4) and on the number of successful rats in EtOH-treated rats were remarkably blocked by pretreatment with 300 mg/kg of α-MT but not by 100 mg/kg of PCPA (Fig. 5). On the other hand, ameliorative effects of repeated *N*-methyl-glucamine (500 mg/kg) on latency and on the number of successful

rats in EtOH-treated rats were inhibited neither by pretreatment of α-MT nor PCPA treatment (Fig. 5).

4. Discussion

In normal rats, single oral EtOH administration impaired the acquisition of memory, whereas RGTS and nootropic drugs did not have any effect on the acquisition of memory. In this study, acquisition for short-term memory among the step through test processes, acquisition, consolidation and retrieval were assessed. In our previous studies, oral administration of 2, 3, 4 and 5 mg/kg of EtOH to rats impaired acquisition in passive avoidance performances. EtOH (5 mg/kg) showed significant influences on the motor activity and motor coordination. Results from this investigation are in agreement with those of a number of previous investigations (Myers, 1978; Hornykiewicz, 1979; Claudio and Roberta, 1990) showing impairment of acquisition following EtOH administration. The studies on the effect of RGTS and nootropic drugs on the modulation of memory of ethanol-treated rats are lacking. A single oral administration of RGTS significantly increased the latency of acquisition induced by EtOH, but did not affect the incidence of successful rats which did not enter the dark compartment. Furthermore, impaired acquisition of EtOH-treated rats was recovered to almost the control level for both the latency and the incidence of successful rats by repeated oral RGTS administration during 7 consecutive days. On the

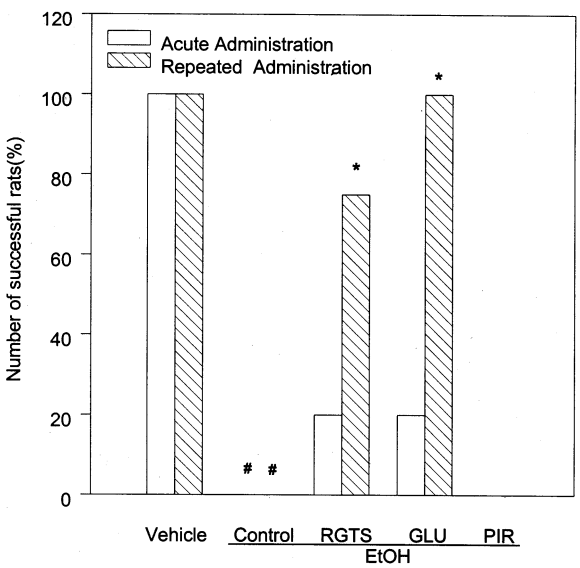

Fig. 3. Effects of single or repeated administration of red ginseng total saponin (RGTS), *N*-methyl-D-glucamine (GLU) and piracetam (PIR) on impaired acquisition of EtOH-treated rats in the step through test. Rats were administered RGTS (200 mg/kg, p.o.), GLU (500 mg/kg, p.o.) and PIR (500 mg/kg, p.o.) for 1 day or 7 consecutive days, and EtOH was injected 30 min after the last treatment of drugs in individual animal groups. The number of successful rats indicates the rats that did not enter the dark compartment within 300 s. Values represent the mean ± S.E.M. of three to 11 rats. $\# P < 0.05$ when compared with vehicle; $* P < 0.05$ when compared with control.

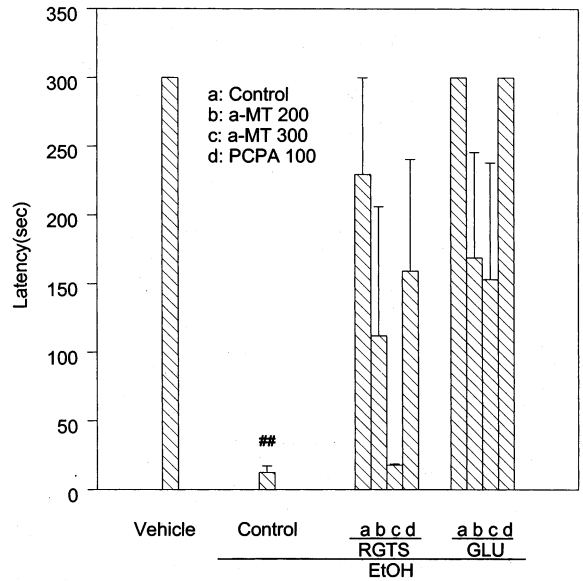

Fig. 4. Effects of α-methyl-ρ-tyrosine (α-MT) or ρ-chlorophenylalanine (PCPA) on ameliorative effect induced by repeated administration of red ginseng total saponin (RGTS) and *N*-methyl-D-glucamine (GLU) on impaired acquisition of EtOH-treated rats in the step through test. Rats were administered RGTS (200 mg/kg, p.o.) and GLU (500 mg/kg, p.o.) for 7 consecutive days and EtOH was injected 30 min after the last treatment of drugs in individual animal groups. The control animal given only normal saline without drug for 7 consecutive days. α-MT and PCPA were injected 24 and 48 h before EtOH treatment, respectively. Values represent the mean ± S.E.M. of three to 11 rats. $\# \# P < 0.01$ when compared with vehicle.

other hand, the ameliorative effect of RGTS on acquisition of EtOH-treated rats was significantly blocked by pretreatment with α-MT, a catecholamine synthesis inhibitor, but not significantly affected by pretreatment with PCPA, a serotonin synthesis inhibitor. In our previous studies, RGTS (50–200 mg/kg) changed spontaneous motor activity and increased apomorphine-induced stereotyped behaviour in normal rats, and hyperactivity induced by RGTS was blocked by pretreatment with 6-OHDA, a neurotoxin. Although the mechanism is speculative, the present results suggest that RGTS might be effective on EtOH-induced amnesia by specific stimulation of the catecholaminergic system and might be related

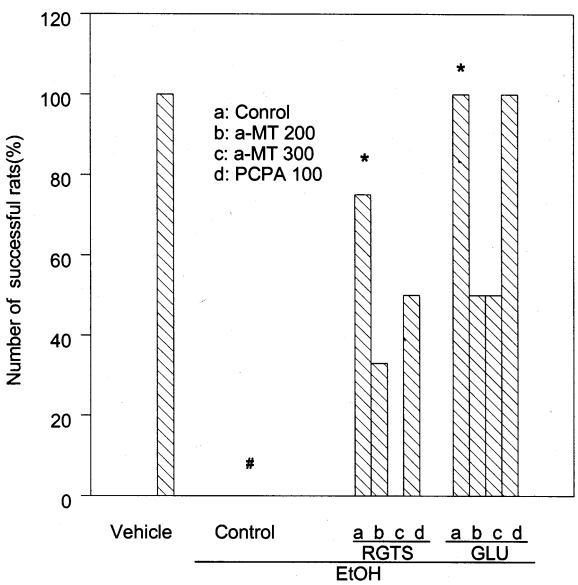

Fig. 5. Effects of α-methyl-ρ-tyrosine (α-MT) or ρ-chlorophenylalanine (PCPA) on ameliorative effect induced by repeated administration of red ginseng total saponin (RGTS) and *N*-methyl-D-glucamine (GLU) on impaired acquisition of EtOH-treated rats in the step through test. Rats were administered RGTS (200 mg/kg, p.o.) and GLU (500 mg/kg, p.o.) for 7 consecutive days and EtOH was injected 30 min after the last treatment of drugs in individual animal groups. The control animals were given only normal saline without drug for 7 consecutive days. α-MT and PCPA were injected 24 and 48 h before EtOH treatment, respectively. The number of successful rats indicates the rats that did not enter the dark compartment within 300 s. Values represent the mean ± S.E.M. of three to 11 rats. $\# P < 0.05$ when compared with vehicle; $* P < 0.05$ when compared with control.

by some other nonspecific effects, in addition to its effects on learning and memory abilities. The present results show that some difference of functional mechanism between nootropic drugs could be caused by time-course, that is, the ameliorative effect of piracetam on acquisition in EtOH-treated rats was significantly increased by single administration but was not shown to be significantly different by repeated administration as compared with control, while *N*-methyl-glucamine showed a significant increase on acquisition by repeated administration, although it did not produce significant effect by single administration. It has been reported that EtOH can cause severe memory deficiency in human beings (Goldberg, 1993), although the mechanism is not yet clear. Recent studies (Di Chiara et al., 1981; Dar and Wooles, 1984; Zhang et al., 1994) in animals have demonstrated that EtOH selectively affects several functional processes related to learning and memory in the central nervous system. It affects both the central cholinergic and adrenergic systems (Carlsson et al., 1972; Littleton, 1978; Signs et al., 1987). Many studies have reported that piracetam, a typical nootropic drug, showed an effect on impairment of memory, using the spinal cord fixation model, Y maze model, scopolamine-induced amnesia model and antihypoxia, but without sedation and stimulation in CNS, and the combination of choline/piracetam exhibited a synergistic effect of senile dementia (Ferris et al., 1982). Schmidt (1990) reported that some of the nootropics, especially after long-term treatment, enhance the K^+-stimulated dopamine release from striatum slices of rats. Typical representatives of nootropic drugs, *N*-methyl-glucamine and vinpocetin, enhance the apomorphine-induced stereotyped behaviour in rats without triggering the behaviour itself, but piracetam is ineffective. Therefore, piracetam and *N*-methyl-glucamine may seem to have a different mechanism, although it is not yet clear how piracetam and *N*-methyl-glucamine produced ameliorative effects on amnesia induced by EtOH. On the other hand, the ameliorative effect of repeated *N*-methyl-glucamine on acquisition of EtOH-treated rats was significantly blocked neither by pretreatment of α-MT nor PCPA. These results suggested

that repeated RGTS and *N*-methyl-D-glucamine ameliorate the impairing effect of EtOH on acquisition, and the effect of RGTS on EtOH-induced amnesia is dependent on the catecholaminergic but not serotonergic neuronal activity, while RGTS and *N*-methyl-D-glucamine seem to have a different mechanism on EtOH-induced amnesia.

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References

Benishim, C.G., 1992. Actions of ginsenoside Rb1 on choline uptake in central cholinergic nerve ending. Neurochem. Int. 21, 1–5.

Buresova, O., Bures, J., 1982. Radial maze as a tool for assessing the effects of drugs on the working memory of rats. Psychopharmacology 77, 268–271.

Carlsson, A., Engel, J., Svensson, T.H., 1972. Inhibition of ethanol-induced excitation in mice and rats by α-methyl-ρ-tyrosine. Psychopharmacology (Berlin) 26, 307–312.

Casamenti, F., Scale, C., Vannucchi, M.G., Bartolini, L., Pepeu, G., 1993. Long-term ethanol consumption by rats: effect on acetylcholine release in vivo, choline acetyltransferase activity and behavior. Neuroscience 56 (2), 465–471.

Claudio, C., Roberta, P., 1990. Effect of ethanol on memory consolidation in mice: antagonism by the imidazobenzodiazepine Ro 15-4513 and decrement by familiarization with the environment. Behav. Brain Res. 40, 67–72.

Corrodi, H., Fuxe, K., Kokfelt, T., 1966. The effect of ethanol on the activity of central catecholamine neurons in rat brain. J. Pharm. Pharmacol. 18, 821–823.

Dar, M.S., Wooles, W.R., 1984. The effect of acute ethanol on dopamine metabolism and other neurotransmitters in the hypothalamus and the corpus striatum of mice. J. Neural Transm. 60, 283–294.

Di Chiara, G., Porceddu, M.L., Imperato, A., Morelli, M., 1981. Role of GABA neuron in the expression of striatal motor functions. In: Di Chiara, D., Gessa, G.L. (Eds.), GABA and the Basal Ganglia. Raven Press, New York, pp. 129–163.

Ferris, S.H., Reisberg, B., Fridman, E., Schneck, M.K., Sherman, K.A., Mir, P., Bartus, R.T., 1982. Combination choline/piracetamacetam treatment of senile dementia. Psychopharmacol. Bull. 18, 94–99.

Giurgen, C., 1973. The 'nootropic' approach to the pharmacology of the integrative activity of the brain. Conditioned Reflex 8, 108–115.

Goldberg, L., 1993. Quantitative studies on alcohol tolerance in man. Acta Physiol. Scand. Suppl. 5 (16), 1–128.

Hornykiewicz, O., 1979. Brain dopamine in Parkinson's disease and other neurological disturbance. In: Horn, A.S., Korf, J., Westerink, B.H.C. (Eds.), The Neurobiology of Dopamine. Academic Press, New York, pp. 663–664.

Jaenicke, B., Kim, E.J., Ahn, J.W., Lee, H.S., 1991. Effects of panax ginseng extract on passive avoidance retention in old rats. Arch. Pharmacal Res. 14, 23–25.

Kabuta, A., Hayashi, T., Sakagami, T., Watanabe, A., Nakamura, K., 1982. Scopolamine model of retrograde amnesia: its prevention and relevant cerebral nuclei involved. In: Saito, S., Yanagita, T. (Eds.), Learning and Memory/Drug as Reinforcer. Excepta Medica, Amsterdam, pp. 96–118.

Kim, Y.H., Kim, S.J., Kim, H.S., Lee, S.C., 1992. Behavior-pharmacological studied of standardized ginseng extract G115 on the central dopaminergic activity(1). Korean J. Ginseng Sci. 16 (1), 18–23.

Kim, H.S., Jang, C.G., Oh, K.W., Seong, Y.H., Rhen, H.M., Cho, D.H., Kang, S.T., 1996. Effects of ginseng total saponin on cocaine-induced hyperactivity and conditioned place preference in mice. Pharmacol. Biochem. Behav. 53 (1), 185–190.

Lee, S.C., You, K.H., Nam, K.Y., Lee, M.J., Kim, H.S., 1993. The role of dopaminergic fibers on the action of psychotropic drugs in 6-OHDA-treated rats. Korean J. Ginseng Sci. 17 (3), 187–195.

Lee, S.C., You, K.H., Yamamoto, T., 1995a. Behaviorpharmacological studies of nootropic candidates on the central dopaminergic activity in rats. Korean J. Ginseng Sci. 19 (3), 197–201.

Lee, S.C., You, K.H., Kim, E.B., 1995b. The functional role of limbic system on memory. J. Pharm. Sci. 11, 1–10.

Littleton, J., 1978. Alcohol and neurotransmitters. Clin. Endocrinol. Metab. 7, 369–384.

Mouravieff-Lesuisse, F., Giurger, C., 1968. Pharmacological reactivity of an experimental model of memory; the spinal fixation. Arch. Int. Pharmacodyn. Ther. 176, 471–472.

Myers, R.D., 1978. Psychopharmacology of alcohol. Annu. Rev. Pharmacol. Toxicol. 18, 125–144.

Namba, T., Yoshizaki, T., Tonimori, K., Kobashi, K., Mitsui, K., Hasse, J., 1974. Fundamental studies on the evaluation of the crude drugs. Planta Med. 32, 588–594.

Oh, J.S., Park, C.W., Moon, D.Y., 1969. Effect of panax ginseng on the central nervous system. Korean J. Pharmacol. 5, 23–28.

Park, C.W., Lim, J.K., Lee, C.J., Chung, M.H., 1984. Effects of ginseng components on the actions of oxygen radicals to gelation of skin collagen. Seoul J. Med. 25 (1), 45–55.

Park, J.K., Nam, K.Y., Hyan, H.C., Jin, S.H., Chepurnov, S.D., Chepunora, N.E., 1994. Effect of red ginseng trial saponin fraction on the spatial memory function studied with 17-arm radial maze. Korean J. Ginseng Sci. 18 (1), 32–38.

Sara, S.J., Lefever, D., 1972. Hypaxia-induced amnesia in one-trial learning and pharmacological protection by piracetam. Psychopharmacologia 25, 32–40.

Schmidt, J., 1990. Influence of nootropic drugs on apomorphine-induced stereotyped behaviour in rats. Biomed. Biochem. Acta 49, 133–136.

Signs, S.A., Yamamoto, B.K., Schechter, M.D., 1987. In vivo electrochemical determination of extracellular dopamine in the caudate of freely moving rats after a low dose of ethanol. Neuropharmacology 26 (11), 1653–1656.

Tabakoff, B., Hoffman, P.L., 1979. Development of functional dependence on ethanol in dopaminergic system. J. Pharmacol. Exp. Ther 208, 216–222.

Wise, R.A., 1978. Catecholamine theories of reward: a critical review. Brain Res. 152, 215–247.

Wolthuis, D.L., 1971. Experiments with UCB 6215, a drug which enhances acquisition in rats; its effects compared with those of methamphetamine. Eur. J. Pharmacol. 16, 283–297.

Yamamoto, T., Ohno, M., Kitajima, I., Ueki, S., 1990. Effects of nootropic drugs on experimentally induced amnesia of rats in the three-panel runway task. In: Nagatsu, T., et al. (Eds.), Basic, Clinical, and Therapeutic Aspects of Alzheimer's and Parkinson's Disease, vol. 2. Plenum, New York, pp. 439–443.

Zhang, Y., Shoyama, Y., Sugiura, M., Saito, H., 1994. Effects of *Crocus sativas* L. on the ethanol induced impairment of passive avoidance performance in mice. Biol. Pharm. Bull. 17 (2), 217–221.