Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 432 (2008) 206–211
Neuroscience Letters
www.elsevier.com/locate/neulet

NMDA receptors are involved in Ginkgo extract-induced facilitation on memory retention of passive avoidance learning in rats

Elaheh Nooshinfar[a,b], Reza Lashgari[a,d,*], Abbas Haghparast[a], Samand Sajjadi[c]

[a] Neuroscience Research Center, Shaheed Beheshti Medical University, P.O. Box 19615-1178, Tehran, Iran
[b] Physiology Department, Paramedical College, Shaheed Beheshti Medical University, Tehran, Iran
[c] English Department, Paramedical College, Shaheed Beheshti Medical University, Tehran, Iran
[d] School of Cognitive Science, Institute for Studies in Theoretical Physics and Mathematics, Tehran, Iran

Received 11 May 2007; received in revised form 25 November 2007; accepted 5 December 2007

Abstract

Herbal therapies are commonly used to enhance memory and learning. Ginkgo biloba has shown to be one of the most popular herbs that is used to treat amnesia and retard age related memory deficits. Although, there have been several reports on the memory enhancing effects of Ginkgo, involvement of glutamatergic system that plays pivotal role in learning and memory has not been precisely assessed so far. The current study intended to investigate the effect of Ginkgo intake on amnesia while NMDA (*N*-methyl D-aspartic acid) receptors blocked by the administration of MK-801. The study used passive avoidance (PA) task to investigate the effect of chronic administration of Ginkgo extract (40 and 90 mg/kg; oral) on the memory span in male Wistar rats, suffering from MK-801-induced forgetfulness (0.06 and 0.1 mg/kg; i.p.). The results indicate that Ginkgo was able to remove MK-801-induced forgetfulness, indicating that Ginkgo can affect memory retention but not effect on passive avoidance acquisition, using pathways other than glutamatergic system as well. The results might indicate that Ginkgo extract can be effective in removing forgetfulness caused by inhibiting NMDA receptors from performing their activities.
Published by Elsevier Ireland Ltd.

Keywords: Ginkgo extract; Learning and memory; NMDA receptor; MK-801; Passive avoidance learning

The enhancement of learning and memory is of special significance in man's life. Ginkgo biloba extract is widely used as an herbal medicine or dietary supplement since Ginkgo extract is effective in facilitation of learning, recollection of memories and retards Alzheimer-induced forgetfulness. The Ginkgo extract possesses several therapeutic properties and is effective for memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache [4,25]. The overall clinical effectiveness of the extract is thought to reflect the mechanisms of action of several individual components of the extract which include increase in cerebral blood supply by dilating blood vessels, reduction of blood viscosity, modification of neurotransmitter systems, increased capacity to utilize oxygen and reduction of the amount of free radicals [4,24]. Meanwhile, the psychological and physiological benefits of Ginkgo said to be based on its primary action of regulation of neurotransmitters, neuroprotective effects, prevention of oxidative damage to mitochondria and protection against or retardation of nerve cell degeneration [13,14,27]. It has well recognized that glutamatergic, cholinergic and histaminergic systems in brain related closely to learning and memory [30,31]. On the other part, little has known about the mechanism of Ginkgo extract action on enhancement of learning and memory. Yamamoto et al. have shown that Ginkgo extract improves the spatial memory deficits-induced separately by scopolamine and diphenhydramine as cholinergic and histaminergic antagonists, respectively. Their findings suggest that the effects of Ginkgo extract on learning and memory mediated by both the cholinergic and histaminergic systems [30,31]. Another study showed that Ginkgo extract reduced the density of β-adrenergic receptors in the frontal cortex and hippocampus, indicating the effects of Ginkgo on memory mediated via adrenergic system [10]. Some other studies discuss Ginkgo's role as a competitive antagonist toward GABAA receptors [11]. It has also reported that compounds

* Corresponding author at: Neuroscience Research Center, Shaheed Beheshti Medical University, P.O. Box 19615-1178, Tehran, Iran. Tel.: +98 21 22431624; fax: +98 21 22431624.
E-mail address: rezalashgari@ipm.ir (R. Lashgari).

0304-3940/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.neulet.2007.12.022

in Ginkgo can inhibit the attachment of a ligand to peripheral benzodiazepine receptor, which indicates the possible modulating effect of Ginkgo on stress [2]. Ginkgo also improves spatial memory in animals with Alzheimer disease [26]. It also shows that Ginkgo can combat forgetfulness by reducing the damaging effects of beta amyloids on the cholinergic neurotransmitters [16]. In addition, Ginkgo extract has also shown to have anti-cholinesterase properties, useful for the treatment of forgetfulness [7].

Unlike its memory enhancing effects, Ginkgo may sometimes remain ineffective or may even reversely affect the memory, by altering the level of concentration [13,25,28]. A review of the clinical studies of the effect of Ginkgo on healthy female volunteers indicated the failure of Ginkgo extract in enhancing the memory [28]. Solomon and colleagues have shown that the consumption of Ginkgo by middle age individuals would neither enhance concentration nor facilitate learning [25]. On the other hand, the consumption of certain doses of Ginkgo can reduce the speed of concentration [13]. In addition, acute consumption of Ginkgo extract would increase the attention of young healthy volunteers [13,14]. Thus, it can reasonably conclude that Gingko extract has both negative and positive effects on cognitive functions such as speed and quality of learning and level of concentration, depending on the time of its consumption and the amount of dose taken [14].

As mentioned above, it is well known that cholinergic, histaminergic and adrenergic systems play a crucial role in the effects of Ginkgo on learning and memory [23,27,30,31]. However, previous studies have not precisely tested the involvement of glutamatergic system with Ginkgo on learning and memory. In order to elucidate the involvement of glutamatergic system in memory enhancing effects of Ginkgo extract, we used MK-801, an NMDA receptor blocker and investigated its effects using passive avoidance (PA) learning task.

Adult male Wistar rats weighing 180–230 g ($n = 140$) were obtained from the breeding colony of the Pasteur Institute, Tehran. Rats classified randomly into 14 groups, with 10 rats in each group. Each cage housed four rats and maintained at the room temperature ($23 \pm 1\,^{\circ}C$) with a 12:12 h light/dark cycle with light on at 7:00 a.m. Food and water were available ad libitum in the home cages and the experiment carried out at specific times of the day.

The PA task is used as a behavioral task to model learning and memory in a variety of experimental paradigms. This task is the behavioral procedure of choice in many studies of learning and memory, probably because it requires very little specialist training of subjects and the results are available quickly [12,31]. The PA apparatus (shuttle box) and behavioral studies were described in our previous study but in this study, rats received a 50 Hz square wave, 0.3 mA constant current shock for 2 s [15].

The drugs used in this study, were pure Ginkgo biloba extract (Tolidaru Co., Iran) and MK-801 (TOCRIS Co., UK).

The aim of this experiment was to determine the effect of chronic administration of Ginkgo extract on PA acquisition and retention. Thirty rats divided into three experimental groups: saline control ($n = 10$) and Ginkgo groups (40 and 90 mg/kg; $n = 10$ for each group) receiving orally either saline or Ginkgo using Gavage needle (with a 15° curved blunt ended needle about 11 cm long) [7,10,15], daily for 7 days before the acquisition trial.

The aim of this experiment was to determine the effect of different doses of NMDA receptor antagonist, MK-801, on PA acquisition and memory retention. Thirty rats divided into three experimental groups: saline control ($n = 10$) and MK-801 groups (0.06 and 0.1 mg/kg; $n = 10$ for each group) receiving intraperitoneal (i.p.) injection of saline (1 ml/kg) or MK-801, 1 h before the acquisition trial and retrieval test.

The aim of this experiment was to determine the interaction between the chronic administration of Ginkgo (40 mg/kg), daily for 7 days before testing, and i.p. injection of MK-801, 1 h (0.06 mg/kg) or 1 day (0.1 mg/kg) before testing, on the PA acquisition and memory retention. Therefore, the groups both referred to as an acute treatment, but differed in the interval between injection and testing (i.e. 1- or 24-h delay). Eighty rats divided into eight groups in this experiment.

In all the three experiments, the number of trials to PA acquisition, step-through latency (STL) and the time spent in dark compartment (TDC) during the retrieval test were recorded.

One-way ANOVA was used to analyze the data, followed by Dunnett's and/or Tukey's tests for multiple comparisons, to find out if there were significant differences between various groups. The significance level was set at $P \leq 0.05$. Results are expressed as mean ± standard error of mean (S.E.M).

One-way ANOVA indicated that there was no significant difference in the number of acquisition trials among the three experimental groups (the number of trials to acquisition in three groups = 1). On the other hand, different doses of Ginkgo extract did not show any significant difference in STL [$F(2,29) = 1.408$; $P = 0.2620$; n.s.] and TDC [$F(2,29) = 2.421$; $P = 0.1079$; n.s.) among three experimental groups on PA retention (Fig. 1).

All experimental groups compared with saline control (saline–saline) group. One-way ANOVA indicated that there was no significant difference on the number of acquisition trials between experimental and saline groups (the number of trials to acquisition in three groups = 1). Therefore, this result indicates that MK-801 the same as Ginkgo extract has no effect on PA acquisition. On the other hand, Dunnett's multiple comparison test showed that different doses of MK-801 have a significance difference in the STL [$F(2,29) = 29.12$; $P < 0.0001$] and TDC [$F(2,29) = 94.17$; $P < 0.0001$] as compared to saline control group on PA retention (Fig. 2).

All groups received daily for 7 days saline or Ginkgo extract before PA acquisition and retention tests. Tukey's multiple comparison test indicated that there was no significant difference on the number of acquisition trials between Ginkgo + MK-801 (received MK-801; 0.06 mg/kg; i.p.; 1 h before acquisition test) and its saline control group (the number of trials to acquisition in four groups = 1; not shown in figure). In retention test (the lower panel in Fig. 3), Tukey's multiple comparison test indicated that there were significant differences among the experimental and control groups in the STL [$F(3,39) = 66.59$; $P < 0.0001$] and TDC [$F(3,39) = 151.7$; $P < 0.0001$]. Nevertheless, there were not any significant differences between control (saline; 1 ml/kg) and

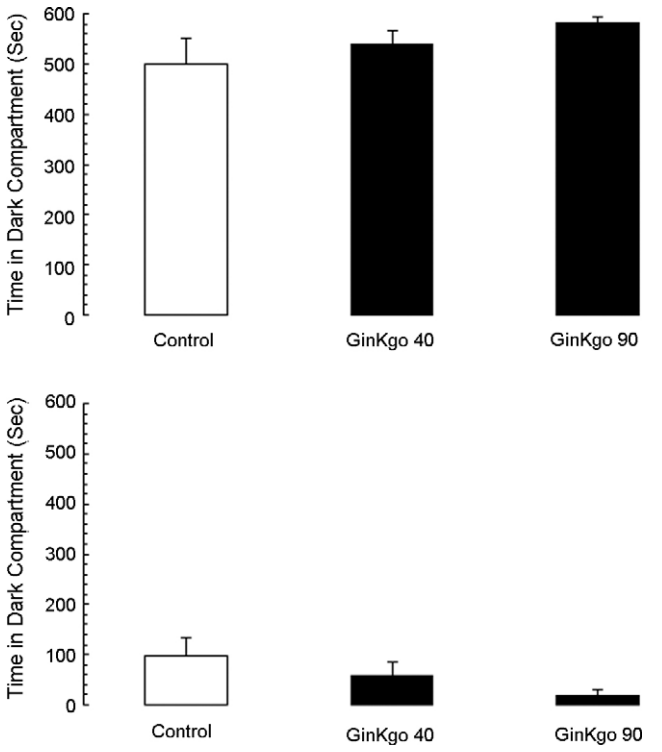

Fig. 1. Effect of Ginkgo on memory retention. Animals received oral administration of saline or Ginkgo (40 or 90 mg/kg) 7 days before retention test. STL and TDC during retrieval test were recorded 24 h after acquisition test. Each point is the mean ± S.E.M.

Gingko (40 mg/kg) groups in saline- and MK-801 (0.06 mg/kg)-treated rats (Fig. 3).

On the other hand, Tukey's test indicated that there was no significant difference on the number of acquisition trials between Ginkgo + MK-801 (received MK-801; 0.1 mg/kg; i.p.; 24 h before acquisition test) and its saline control group (the number of trials to acquisition in four groups = 1). In retention test, Tukey's multiple comparison test indicated that there were significant differences among the experimental and control groups in the STL [$F(3,39) = 25.82$; $P < 0.0001$] and TDC [$F(3,39) = 78.69$; $P < 0.0001$; Fig. 4].

The present study designed to investigate the effects of chronic administration of the Ginkgo extract in combination with MK-801 on the learning and memory using PA task paradigm. Our results indicate that the long-term administration of Ginkgo extract removes the inhibitory effect of MK-801 on memory retrieval in PA task but had no effect on acquisition test.

The role of glutamatergic system in learning and memory has been extensively studied, and especially NMDA receptors have been implicated in different learning and memory processes [9,12,21]. Involvement of NMDA receptors in learning initially suggested based on long-term potentiation (LTP) experiments. LTP is a form of synaptic plasticity, widely accepted to be the physiological substrate for many forms of learning and memory [1,3,15,17,32]. A number of publications confirmed that NMDA receptors play a prominent role in at least some forms of LTP and learning, as the blockade of NMDA receptor prevents the induction of hippocampal LTP and impairs learning [6,19]. On the other hand, Ginkgo extract exerts many pharmacological actions such as antioxidant properties and the ability of neurotransmitter/receptor modulation. The significance of Ginkgo as a memory enhancing herbal drug has already been acknowledged in several studies [22,26,27,29]. However, the results of our study showed that there were no significant differences in comparison with control group, indicating that the doses of Ginkgo used in this study had no effect on passive avoidance learning and memory retrieval. These results not only contradict earlier findings on the facilitative effects of various doses of Ginkgo on learning [22,27] but also oppose some other studies that reported the enhancing effects of Ginkgo on spatial memory in the rat model of Alzheimer's disease [26,31]. However, our findings

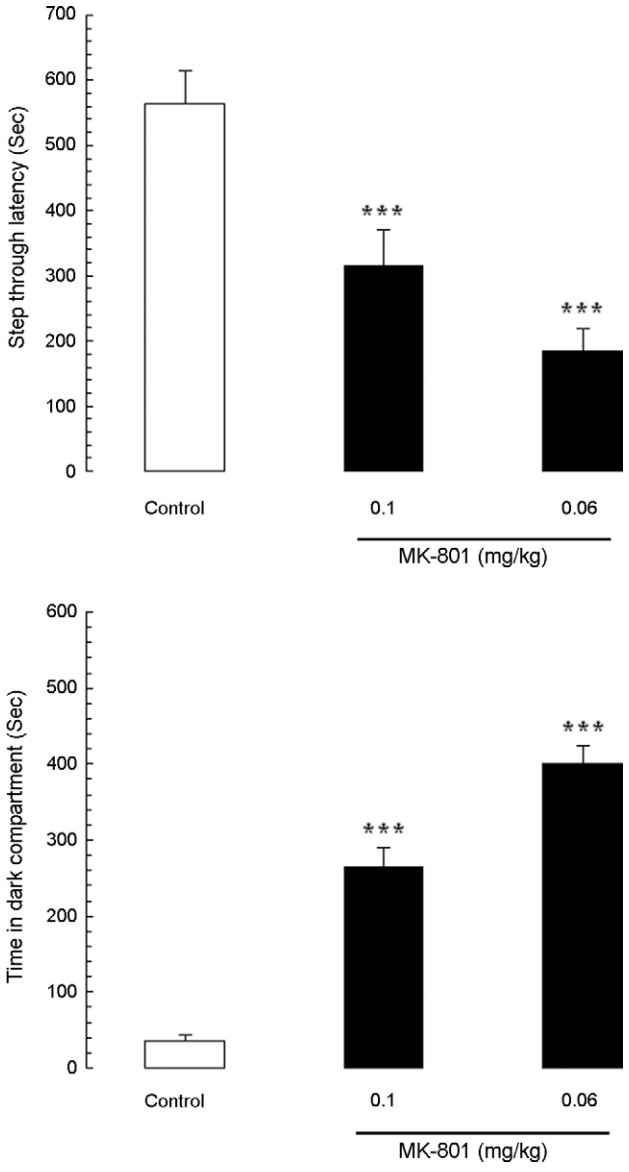

Fig. 2. Effect of MK-801 on memory retention. Animals received oral administration of saline for 7 days and different doses of MK-801 (0.06 and 0.1 mg/kg) were injected 1 or 24 h before retention test. STL and TDC during retrieval test were recorded 24 h after acquisition test. Each point is the mean ± S.E.M. ***$P < 0.001$ different from saline control (saline–saline) group.

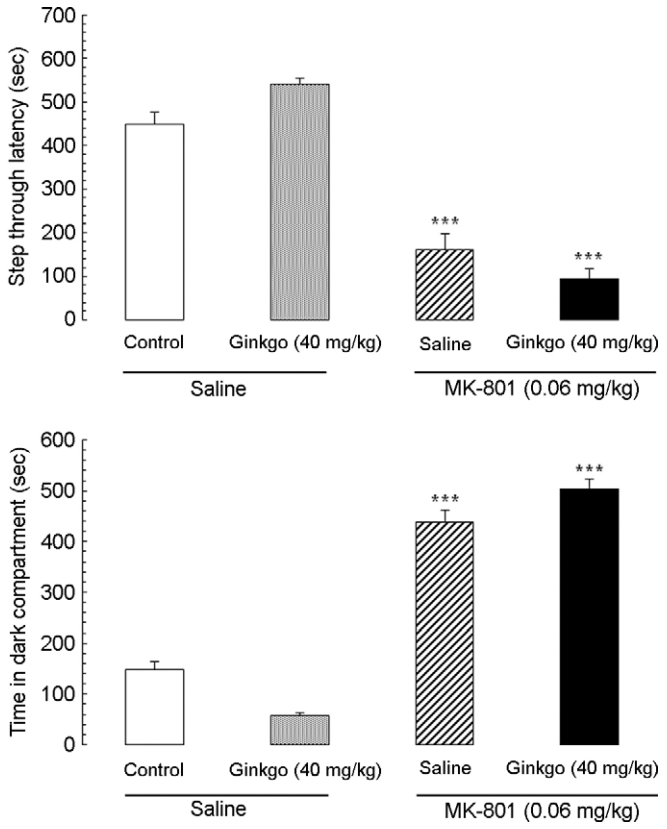

Fig. 3. Effect of interaction between MK-801 (0.06 mg/kg) and Ginkgo extract (40 mg/kg) on memory retention. Animals received oral administration of saline or Ginkgo extract for 7 days and also MK-801 or saline were only injected 1 h before retention test. STL and TDC during retrieval test were recorded 24 h after acquisition test. Each point is mean ± S.E.M. $^{**}P < 0.01$, $^{***}P < 0.001$ different from saline control (saline–saline) group.

are in line with previous studies that reported Ginkgo's failure in enhancing memory, using other methods than ours to test memory [20,25]. Our study also showed that injection of MK-801 decreased memory retention. Therefore, these findings indicated that NMDA receptors are actively involved in memory, resulting in a decrease in memory retention [12,21]. Meanwhile, doses of MK-801 and injection times (1 h versus 24 h before instruction) both resulted in decreased memory retrieval. The recipients of MK-801 (1 h before the instruction) and ones (24 h before the instruction) showed that the 1-h delay administration has a significantly greater level of memory disturbance than the 24-h delay administration. This may imply that MK-801-induced forgetfulness is in a dose- and time-dependent manner.

According to previous studies the memory enhancement effect of Ginkgo is brought about by its interference with neurotransmitters such as the cholinergic, histaminergic and adrenergic systems [23,27,31]. So we investigated the relationship between Ginkgo and glutamatergic system, something that has not been referred to or investigated in previous studies. The results on simultaneous application of Ginkgo and MK-801 showed that the administration of Ginkgo (40 mg/kg) and MK-801 (0.06 mg/kg) 1 h before the instruction cannot remove MK-801-induced forgetfulness while the same dose of Ginkgo is able to remove MK-801 (0.1 mg/kg)-induced mental disturbance, given that injection is carried out 24 h before the instruction.

There are some reports about the interaction between brain cholinergic neurons and Ginkgo extract in learning and memory. For instance, studies have reported that Ginkgo extract improved scopolamine-induced memory deficits of passive avoidance performance [5,31]. In addition, some previous studies have reported the direct effect of Ginkgo on cholinergic neurotransmitters [8], it was additionally shown that Ginkgo could decrease the controlling effects of beta amyloids on cholinergic carriers [16] and functions as an active anti-cholinesterase drug that is useful in treating forgetfulness [7].

On the one hand, NMDA receptors are involved in releasing acetylcholine from septum and striatum; indicate that glutamatergic system controls discharging of acetylcholine in these areas [18]. It has also indicated that MK-801-induced forgetfulness may not be confined to disturbance in glutamatergic system only; rather, it can be due to changes in cholinergic, adrenergic and dopaminergic systems [12]. Therefore changes in glutamatergic system can bring about changes in other neurotransmitter systems and vice versa.

As mentioned previously, Ginkgo intake could directly influence cholinergic neurotransmitters [8], indicating Ginkgo's involvement in regulating the pathways for cellular messages

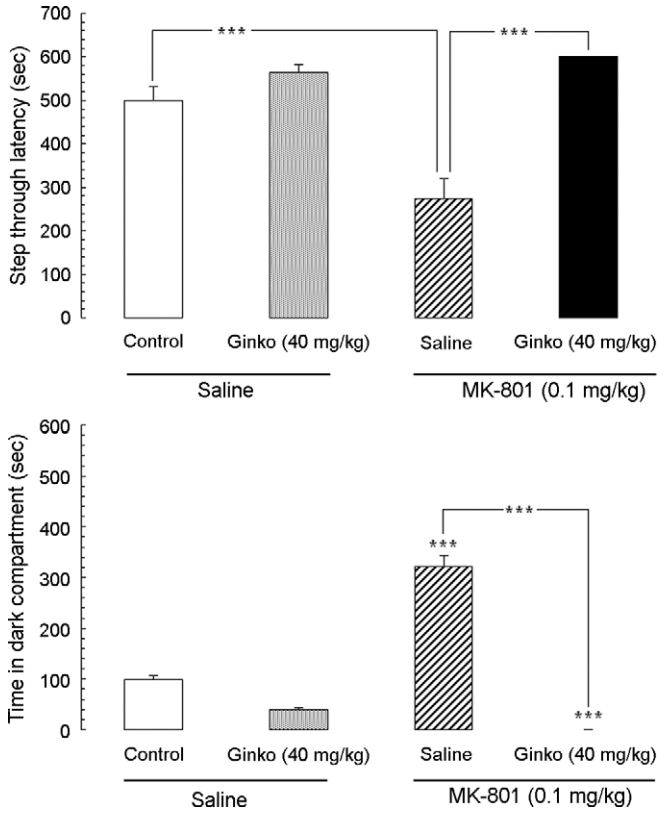

Fig. 4. Effect of interaction MK-801 (0.1 mg/kg) and Ginkgo extract (40 mg/kg) on memory retention. Animals received oral administration of saline or Ginkgo extract for 7 days and also MK-801 or saline were injected 24 h before retention test. STL and TDC during retrieval test were recorded 24 h after acquisition test. Each point is mean ± S.E.M. $^{***}P < 0.001$ different from saline control (saline–saline) group.

[23] on one hand and its interference with neurotransmitters on the other hand [27]. Therefore, bearing in mind Ginkgo's role in both activating cholinergic transmitters and reducing their controlling function, one speculation may be that the effectiveness of Ginkgo in removing forgetfulness, caused by MK-801, injected 24 h before the instruction, could have been (directly or indirectly) due to its interaction with the cholinergic system. On the other part, Ginkgo can regulate the process of genetic expression, as has been indicated in some previous studies [2,23]. Therefore, it can suggest that Ginkgo activates the process of expression the NMDA receptor genes, resulting in the synthesis of new NMDA receptors. Another possibility requiring further investigation is that Ginkgo blocks the attachment of ligands to NMDA receptors. As indicated before Ginkgo can prevent ligands from binding with local benzodiazepine receptor [2].

In summary, it could be said that the intake of Ginkgo alone will not bring about memory enhancement, although it can have a positive effect in reducing mental weaknesses and disturbances in certain conditions. Injection of the various doses of MK-801 at different times can result in forgetfulness. Ginkgo cannot remove memory disturbances brought about by the injection of MK-801 a short time (1-h delay) before the trial while it will remove such disturbances caused by the injection of MK-801 at a long period (24-h delay) before the trial. Under such conditions, therefore, with the antagonistic affect of MK-801 on NMDA receptors and its control over glutamatergic system, it seems likely that Ginkgo could not only enhance glutamatergic system but also might affect some other pathways, such as cholinergic system to improve memory.

Acknowledgements

The authors would like to thank Dr. Mohsin Raza and Sima Lashgari for their comments and editing the manuscript. This research granted by the Neurosciences Research Center, Shaheed Beheshti Medical University.

References

[1] A. Aiba, C. Chen, K. Herrup, C. Rosenmund, C.F. Stevens, S. Tonegawa, Reduced hippocampal long-term potentiation and context-specific deficit in associative learning in mGluR1 mutant mice, Cell 79 (1994) 365–375.

[2] H. Amri, K. Drieu, V. Papadopoulos, Use of ginkgolide B and a ginkgolide-activated response element to control gene transcription: example of the adrenocortical peripheral-type benzodiazepine receptor, Cell Mol. Biol. (Noisy-le-grand) 48 (2002) 633–639.

[3] D. Balschun, W. Wetzel, Inhibition of mGluR5 blocks hippocampal LTP in vivo and spatial learning in rats, Pharmacol. Biochem. Behav. 73 (2002) 375–380.

[4] J. Birks, E.V. Grimley, M. Van Dongen, Ginkgo biloba for cognitive impairment and dementia, Cochrane Database Syst. Rev. (2002), CD003120.

[5] P. Chopin, M. Briley, Effects of four non-cholinergic cognitive enhancers in comparison with tacrine and galanthamine on scopolamine-induced amnesia in rats, Psychopharmacology (Berl) 106 (1992) 26–30.

[6] W. Danysz, W. Zajaczkowski, C.G. Parsons, Modulation of learning processes by ionotropic glutamate receptor ligands, Behav. Pharmacol. 6 (1995) 455–474.

[7] A. Das, G. Shanker, C. Nath, R. Pal, S. Singh, H. Singh, A comparative study in rodents of standardized extracts of Bacopa monniera and Ginkgo biloba: anticholinesterase and cognitive enhancing activities, Pharmacol. Biochem. Behav. 73 (2002) 893–900.

[8] B.J. Diamond, S.C. Shiflett, N. Feiwel, R.J. Matheis, O. Noskin, J.A. Richards, N.E. Schoenberger, Ginkgo biloba extract: mechanisms and clinical indications, Arch. Phys. Med. Rehabil. 81 (2000) 668–678.

[9] A. Gravius, M. Pietraszek, W.J. Schmidt, W. Danysz, Functional interaction of NMDA and group I metabotropic glutamate receptors in negatively reinforced learning in rats, Psychopharmacology (Berl) 185 (2006) 58–65.

[10] Ch.I. Hadjiivanova, V.V. Petkov, Effect of Ginkgo biloba extract on beta-adrenergic receptors in different rat brain regions, Phytother. Res. 16 (2002) 488–490.

[11] S.H. Huang, R.K. Duke, M. Chebib, K. Sasaki, K. Wada, G.A. Johnston, Bilobalide a sesquiterpene trilactone from Ginkgo biloba, is an antagonist at recombinant alpha1beta2gamma2L GABA(A) receptors, Eur. J. Pharmacol. 464 (2003) 1–8.

[12] M. Jafari-Sabet, NMDA receptor blockers prevents the facilitatory effects of post-training intra-dorsal hippocampal NMDA and physostigmine on memory retention of passive avoidance learning in rats, Behav. Brain Res. 169 (2006) 120–127.

[13] D.O. Kennedy, A.B. Scholey, K.A. Wesnes, Differential, dose dependent changes in cognitive performance following acute administration of a Ginkgo biloba/Panax ginseng combination to healthy young volunteers, Nat. Neurosci. 4 (2001) 399–412.

[14] D.O. Kennedy, A.B. Scholey, K.A. Wesnes, The dose-dependent cognitive effects of acute administration of Ginkgo biloba to healthy young volunteers, Psychopharmacology (Berl) 151 (2000) 416–423.

[15] R. Lashgari, F. Motamedi, S. Zahedi Asl, S. Shahidi, A. Komaki, Behavioral and electrophysiological studies of chronic oral administration of L-type calcium channel blocker verapamil on learning and memory in rats, Behav. Brain Res. 171 (2006) 324–328.

[16] T.F. Lee, C.F. Chen, L.C. Wang, Effect of ginkgolides on beta-amyloid-suppressed acetylocholine release from rat hippocampal slices, Phytother. Res. 18 (2004) 556–560.

[17] Y.M. Lu, Z. Jia, C. Janus, J.T. Henderson, R. Gerlai, J.M. Wojtowicz, J.C. Roder, Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP, J. Neurosci. 17 (1997) 5196–5205.

[18] T. Maurice, M. Hiramatsu, J. Itoh, T. Kameyama, T. Hasegawa, T. Nabeshima, Behavioral evidence for a modulating role of sigma ligands in memory processes. I. Attenuation of dizocilpine (MK-801)-induced amnesia, Brain Res. 647 (1994) 44–56.

[19] R.G. Morris, E. Anderson, G.S. Lynch, M. Baudry, Selective impairment of learning and blockade of long-term potentiation by an *N*-methyl-D-aspartate receptor antagonist, AP5, Nature 319 (1986) 774–776.

[20] P.L. Moulton, L.N. Boyko, J.L. Fitzpatrick, T.V. Petros, The effect of Ginkgo biloba on memory in healthy male volunteers, Physiol. Behav. 73 (2001) 659–665.

[21] S. Moyano, D. Frechilla, J. Del Rio, NMDA receptor subunit and CaMKII changes in rat hippocampus induced by acute MDMA treatment: a mechanism for learning impairment, Psychopharmacology (Berl) 173 (2004) 337–345.

[22] V.D. Petkov, S. Belcheva, V.V. Petkov, Behavioral effects of Ginkgo biloba L., Panax ginseng C.A. Mey. and Gincosan, Am. J. Chin. Med. 31 (2003) 841–855.

[23] J.V. Smith, Y. Luo, Studies on molecular mechanisms of Ginkgo biloba extract, Appl. Microbiol. Biotechnol. 64 (2004) 465–472.

[24] B. Soholm, Clinical improvement of memory and other cognitive functions by Ginkgo biloba: review of relevant literature, Adv. Ther. 15 (1998) 54–65.

[25] P.R. Solomon, F. Adams, A. Silver, J. Zimmer, R. DeVeaux, Ginkgo for memory enhancement: a randomized controlled trial, JAMA 288 (2002) 835–840.

[26] R.W. Stackman, F. Eckenstein, B. Frei, D. Kulhanek, J. Nowlin, J.F. Quinn, Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment, Exp. Neurol. 184 (2003) 510–520.

[27] C. Stough, J. Clarke, J. Lloyd, P.J. Nathan, Neuropsychological changes after 30-day Ginkgo biloba administration in healthy participants, Int. J. Neuropsychopharmacol. 4 (2001) 131–134.

[28] B. Topic, R.U. Hasenohrl, R. Hacker, J.P. Huston, Enhanced conditioned inhibitory avoidance by a combined extract of Zingiber officinale and Ginkgo biloba, Phytother. Res. 16 (2002) 312–315.
[29] J.C. Winter, The effects of an extract of Ginkgo biloba, EGb 761, on cognitive behavior and longevity in the rat, Physiol. Behav. 63 (1998) 425–433.
[30] Y. Yamamoto, Y. Adachi, Y. Fujii, C. Kamei, [Effect of Ginkgo biloba extract on memory deficits in radial maze performance induced by some drugs in rats], Nihon Shinkei Seishin Yakurigaku Zasshi 25 (2005) 85–90.
[31] Y. Yamamoto, Y. Adachi, Y. Fujii, C. Kamei, Ginkgo biloba extract improves spatial memory in rats mainly but not exclusively via a histaminergic mechanism, Brain Res. 1129 (2007) 161–165.
[32] W. Zajaczkowski, T. Frankiewicz, C.G. Parsons, W. Danysz, Uncompetitive NMDA receptor antagonists attenuate NMDA-induced impairment of passive avoidance learning and LTP, Neuropharmacology 36 (1997) 961–971.