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Research Article

Protective Effects of Aminoguanidine against Sodium Metavanadate-Induced Spatial Memory Retention Impairment in Morris Water Maze

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ABSTRACT

Background: Vanadium is a potential neurotoxic agent widely distributed in the environment. Understanding the neurotoxic mechanisms of vanadium on learning and memory seems necessary.
Methods: We investigated the time-dependent (1-week, 2- week and 4-week) effects of sodium metavanadate (SMV) (25 mg/kg/day; pre-training oral administration) and 4-day intraperitoneal injections of aminoguanidine (AG) as a selective inducible nitric oxide synthase inhibitor (10, 50, and 100 mg/kg) on spatial memory retention in Morris water maze. Animals were trained for 4 days and tested 48 h after the last training trial.
Results: The data showed that 4-week oral pre-treatment with SMV (25 mg/kg/day) induced spatial memory retention deficits and decreased the time spent in the target quadrant. We found that 4-day administration of different doses of AG during training trials significantly decreased the time and distance of finding the hidden platforms. Additionally, SMV-induced spatial memory retention impairments were prevented in animals received combined SMV (25 mg/kg/day, 4 weeks) and AG (10 mg/kg/day, 4 days).
Conclusion: Our findings showed the protective role of AG on SMV-induced spatial memory retention deficits.

Introduction

It is widely believed that vanadium as an essential trace element may cause neurotoxic effects such as learning and memory impairments in animal models.[1-3] There have been great interests on the toxic properties of vanadium compounds in mammals.[4] It has been shown that exposure to vanadium led to disturbances in human motor activities and visual memory deficits.[5] On the other hand, damage to the hippocampus, which is critical for spatial learning and memory processes, causes behavioral changes and learning deficits.[6,7] It has also been noted that vanadium exposure can lead to hippocampal CA1 damage in mice.[1,4]

In recent years, numerous studies have demonstrated the crucial role of nitric oxide (NO) in pathological effects in the CNS.[8] The alteration of NO has been shown in several CNS diseases such as depression, seizure and neurodegenerative disorders.[9-11] Different evidences suggested the importance of NO for synaptic plasticity in several brain regions such as the cerebellum and hippocampus.[8,12,13] Endothelial nitric oxide synthase (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) are three nitric oxide synthase isoforms.[14,15] All the three isoforms are expressed in the brain throughout aging and pathologic conditions.[10,15,16] Among these isoenzymes, iNOS plays roles in various inflammatory and patho-physiological processes[8] and also in oxidative/nitrosative induced cytotoxicity.[17] The expression of iNOS has been documented in the dentate gyrus and CA1 region of the hippocampus.[18] Furthermore, it has been established that selective iNOS inhibitors such as aminoguanidine (AG) can ameliorate amyloid beta (Aβ)-induced cholinergic system dysfunctions.[18]

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We previously reported that oral administration of sodium metavanadate (SMV) solution (25 mg/kg/day for 2 weeks) significantly impaired spatial learning in an acquisition model of Morris water maze (MWM). Furthermore, we demonstrated this impairment could be attenuated by nicotine via increased expression of Choline Acetyl Transferase (ChAT) and Vesicle Acetyl Choline Transporter (VAChT) as cholinergic markers in hippocampus.[1] Moreover, we have previously shown the protective effects of iNOS inhibitors on spatial learning and memory.[19] In this regard, we also demonstrated that 1400W, as a selective iNOS inhibitor, could interact with cAMP-protein kinase A (PKA) signalling pathway to protect H-89 (protein kinase AII inhibitor) -induced memory loss via the activation of the transcription factor cAMP response element binding protein (CREB) and cholinergic system alteration.[8] Considering our previous observations, the main objective of the present study was to investigate the probable time-dependent effects of SMV on spatial memory retention and potential protective effects of AG as a selective iNOS inhibitor on SMV-induced spatial memory retention deficits in MWM.

Materials and Methods

Experimental animals

Male Wistar rats (200–250 g) were provided by the Faculty of Pharmacy, Zabol University of Medical Sciences. The animals were housed and adapted to the laboratory conditions (12-h light/12-h dark cycle; room temperature (20-22ºC)) with free access to food and water. All the experimental protocols were carried out according to the guidelines of the Ethical Committee for the Care and Use of Laboratory Animals of Zabol University of Medical sciences. All animal experiments were done during the light cycle.

Drugs

SMV and AG were obtained from Sigma (St. Louis, Mo, USA) and dissolved in tap water and saline respectively to obtain desirable concentrations.

Behavioral training and testing

All the experiments were performed with 8 animals per each group. The experimental groups have been indicated in Table 1.

The effects of SMV on memory retention

Fresh solutions of SMV (25 mg/kg) were prepared daily just before administrations. The drug was orally gavaged daily for either one, two or four weeks. The training trials were performed on the days 4th, 11th and 25th and continued for 4 days (each day included one block of 4 trials) in MWM. The details of the water maze and performance of training sessions were described in our previous studies.[1,19-21] Spatial memory retention test was performed 48 h after the last training trial. The Ethovision tracking system (Noldus Information Technology, Wageningen, Netherlands) was applied to investigate behavioral parameters of spatial memory retention. Control animals received tap water by gavage for the same period of time. In testing trials, one block, including four trials was evaluated. As a probe test, after completion of spatial memory retention assessments, the platform was removed out of the task and the time spent in target quadrant (the quadrant that hidden platform was previously located there) was investigated.

Effects of AG on spatial memory

To assess this, 4-day training trials were conducted in a similar manner as described above. AG (either 10, 50, or 100 mg/kg) was injected intraperitoneally. Spatial memory retention test was performed 48 h after the last training trial. One block, including four trials, was assessed. In the fourth group as control, the animals received saline.

SMV-AG co-administration

Animals received oral fresh solutions of SMV (25 mg/kg/day) using gavage needles for 4 consecutive weeks. On the day 25th, the 4-day training of animals was started in MWM. On the day 25th onward, AG (10 mg/kg/day) was intraperitoneally injected for 4 consecutive days at 15 min prior to SMV oral administrations. Spatial memory retention test was performed 48 h after to the last training trial as described previously.

Statistical analysis

SPSS 19 software and Graph Pad Prism 5 were used for statistical analysis.

Table 1. Experimental groups in the study.

Groups	Treatments	Route	Duration	Training trials	Spatial memory test
SMV*	**SMV 25mg/kg/day**	Oral Gavage	One week Two weeks Four weeks	4-7th 11-14th 25-28th	48 h after the last training trial
	Control	Oral Gavage of Tap Water	One week Two weeks Four weeks	4-7th 11-14th 25-28th	48 h after the last training trial
AG	**AG(10 mg/kg/day)**	i.p.	Four days	Continuous	48 h after the last training trial
	AG(50 mg/kg/day)	i.p.	Four days	Continuous	48 h after the last training trial
	AG(100 mg/kg/day)	i.p.	Four days	Continuous	48 h after the last training trial
	Control (saline)	i.p.	Four days	Continuous	48 h after the last training trial
SMV-AG	**SMV (25mg/kg/day) + AG (10 mg/kg/day)**	SMV: oral Gavage AG: i.p.†	SMV: Four weeks AG: Four days	25-28th	48 h after the last training trial

* SMV: Sodium metavanadate, AG: aminoguanidine; †: AG was administrated 15 minutes prior to SMV oral Gavage on the days 25-28th

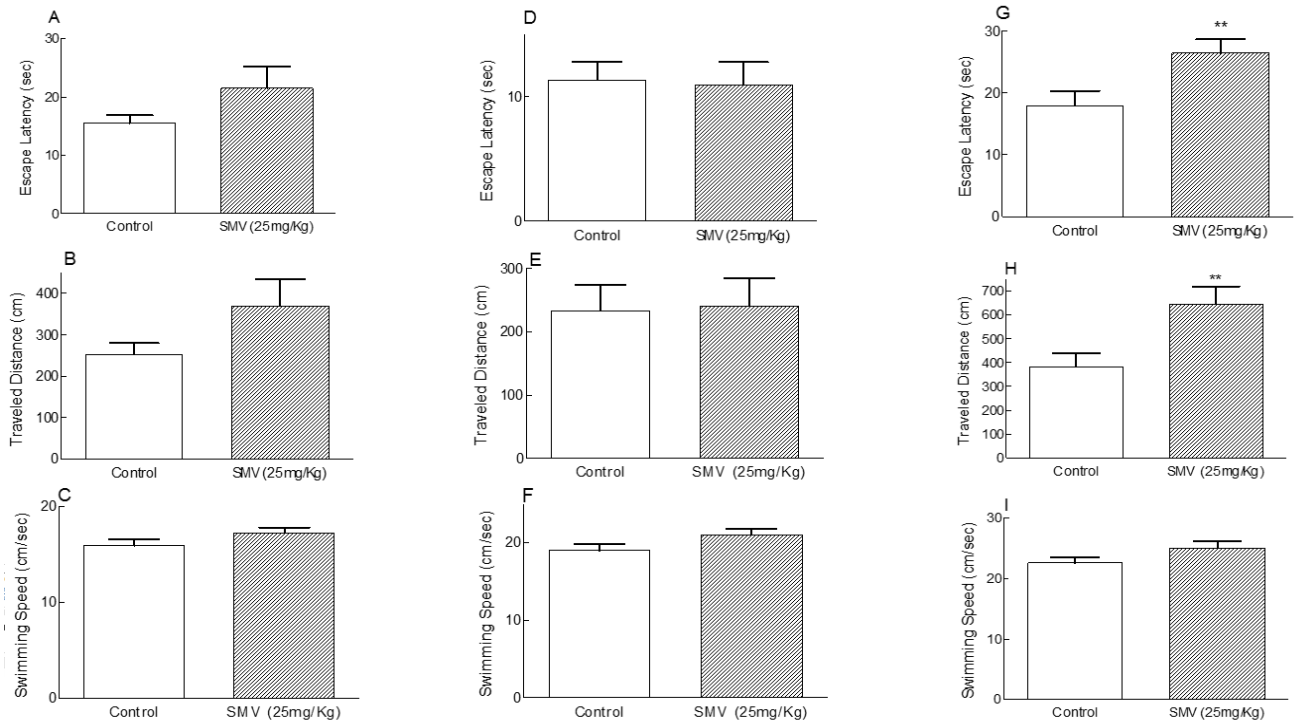

Figure 1. Time-dependent effects of oral administration of sodium metavanadate on spatial memory retention in MWM. Average of escape latency, traveled distance and swimming speed for 1week (A-C), 2weeks (D-F) and 4weeks (G-I) sodium metavanadate (SMV, 25mg/kg/day) pre-treated animals 48 h later to last training trial in MWM. Each value represents the mean ± SEM from 8 animals. **p< 0.01 significantly different from its related control group.

Independent sample student t-test (for comparison between two groups) and one-way analysis of variance (ANOVA) followed by Newman–Keuls post hoc test were used for comparison of behavioral findings. A *P*-value < 0.05 was considered as statistically significant.

Results

Time-dependent effects of SMV on spatial memory retention

One- and two-week administrations of SMV did not induce any significant changes in the time and distance parameters in comparison with their control groups, respectively (Figure 1A, 1B, 1D, and 1E). However, four-week oral administration of SMV (25 mg/kg) significantly increased the time and distance spent to find the hidden platforms compared to the control group (**p<0.01, Figure 1G and 1H).

The swimming speed was similar between SMV-treated and control animals representing no motor disturbances (Figure 1C, 1F and 1I).

In addition, four weeks oral administration of SMV (25 mg/kg) significantly decreased the time spent in the target quadrant in probe test compared to the control group indicating impaired spatial memory retention in MWM (**p<0.01, Figure 2).

The effects of intra-peritoneal injection of AG on spatial memory retention in MWM

Four-day intra-peritoneal injection of AG (either 10, 50 or 100 mg/kg) significantly decreased the time and distance for finding the hidden platforms compared to the control group (Figure 3A and 3B).

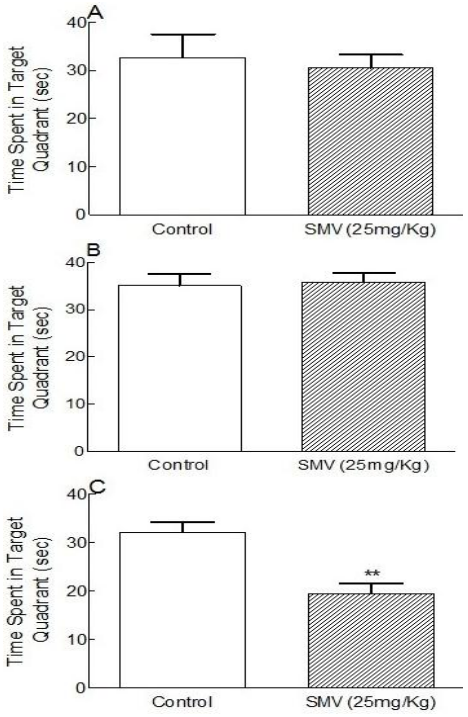

Figure 2. Time-dependent effects of oral administration of sodium metavanadate on spent time in the target quadrant in MWM at 1week (A), 2 weeks (B) and 4 weeks (C). Sodium metavanadate was administrated at the dose of 25 mg/kg/day. Each value represents the mean ± SEM from 8 animals. **p< 0.01 significantly different from its related control animals.

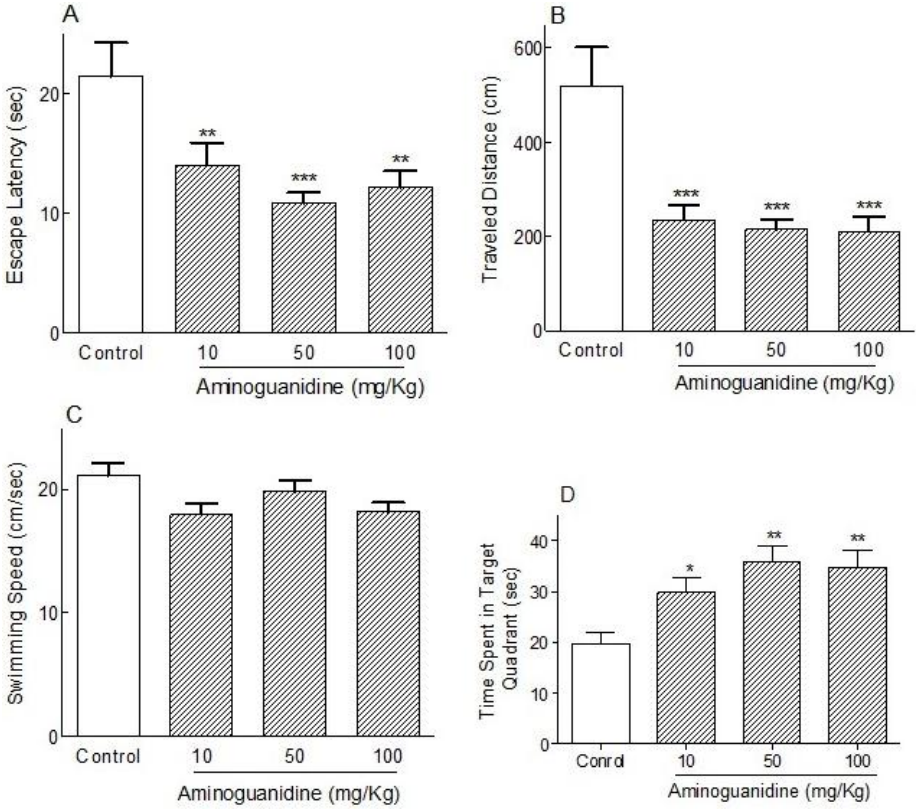

Figure 3. The effects of four-day intra-peritoneal injection of aminoguanidine (AG) on spatial memory retention parameters (48 h later to last training trials) and time spent in the target quadrant in probe tests. Escape latency (A), traveled distance (B), swimming speed (C), time spent in target quadrate (D). Each value represents the mean ± SEM from 8 animals. *p<0.05, **p< 0.01 and ***p<0.001 are significantly different from control animals.

The swimming speed was not affected by AG administration (Figure 3C).

Also, four-day intraperitoneal injections of AG (either 10, 50 or 100 mg/kg) significantly increased (*p<0.05, **p<0.01 and **p<0.01, respectively) the time spent in the target quadrant in probe test compared to the control group (Figure 3D).

Dose-dependent protective effects of AG on SMV-induced impairments of spatial memory retention in MWM

The SMV-induced spatial memory retention deficits were significantly improved in animals received four-day intra-peritoneal injection of AG (10 mg/kg) along with 4-week SMV (25 mg/kg/day) compared to control group (p<0.01, Figure 4A and 4B). Also, four-day intra-peritoneal injection of AG (10 mg/kg) along with SMV (25mg/kg/day for 4 weeks) significantly increased the time spent in the target quadrant in probe test compared to SMV treated animals (P<0.001, Figure 4C).

Discussion

We have previously demonstrated that pre-training oral administration of SMV (25 mg/kg) impaired the spatial memory acquisition in MWM and decreased ChAT and VAChT protein expressions as cholinergic system markers in the CA1 region of the hippocampus and medial septal area.[1] In the present study, we observed that four weeks administration of SMV induced memory deficit in a time dependent manner in MWM. This is while one- and two- week pre-treatment of SMV did not induce deficits on memory retention.

It has been shown that vanadium inhalation caused time dependent loss of dendritic spines in the hippocampus correlating with spatial memory impairment.[4] Conversely, Chen *et al.* indicated that vanadium improved the spatial learning and memory by interacting with the cAMP response element binding protein (CREB) pathway in diabetic mice.[22] In spite of the contraindicating neurodegenerative and neuroprotective effects of vanadium compounds, a complete explanation of underlying mechanisms has yet to be understood.[1,4,23-26] In agreement with our findings, it has been shown that the effects of vanadium compounds on CNS are mainly dependent on both the dose and the route of drug administration.[1] Experimental and histochemical studies have shown that reactive oxygen species are increased in SMV-treated rats.[27]

In this study, we examined the effects of four-day intraperitoneal injection of AG on spatial memory retention in MWM.

Behavioral findings showed that AG decreased the time and distance of finding the hidden platforms 48 hours after the last training session. Numerous studies have suggested different possible mechanisms underlying the protective effects of this iNOS inhibitor on memory.[8]

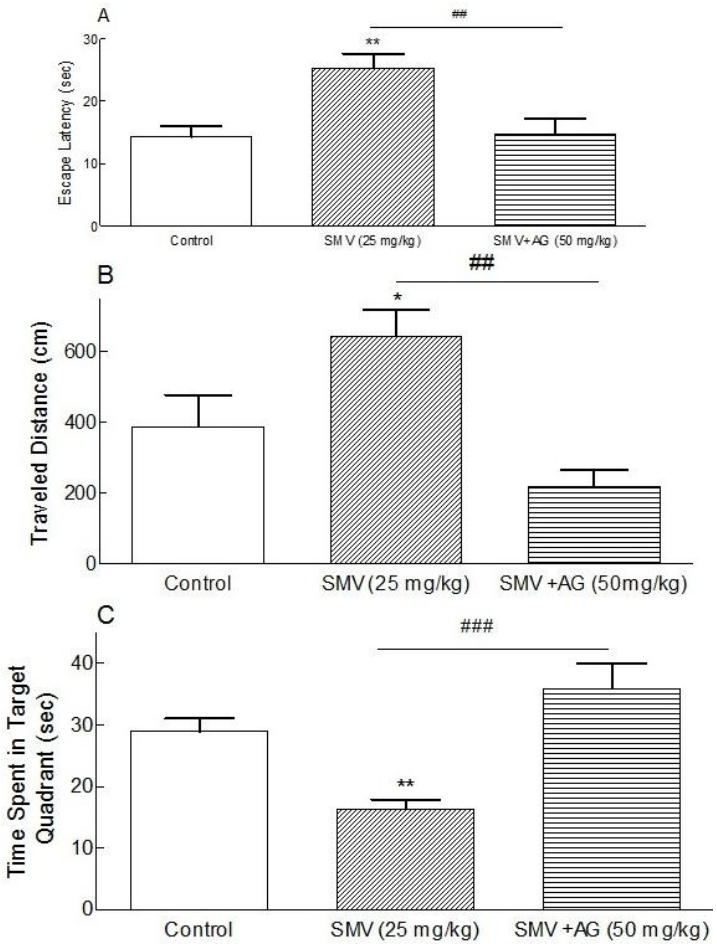

Figure 4. Effects of four-day coadministration of aminoguanidine (AG; 10 mg/kg, i.p) and sodium metavanadate (SMV; 25mg/kg/day for 4 weeks) on spatial memory retention parameters (48 h later to last training trials) and time spent in target quadrant in probe tests. Escape latency (A), traveled distance (B), time spent in target quadrate (C). Each value represents the mean ± SEM from 8 animals. *p<0.05, **p< 0.01 are significantly different from vehicle control animals. Also, ##p<0.01 and ###p<0.001 are significantly different from SMV pre-treated animals.

It has been reported that administration of peroxovanadium (pV) induced the expression of iNOS in mice livers and AG as a selective iNOS inhibitor reversed pV-induced iNOS expression.[28] Nitric oxide attenuates neurotransmitter re-uptake in glutaminergic and dopaminergic systems, which could negatively affect postsynaptic receptor regulation involved in memory formation.[8] Gene expression studies have described that the training in MVM could strongly induce iNOS.[29-32] Infusion of Aβ (amyloid beta) 1-40 to the brain (as a model of Alzheimer's disease) resulted in iNOS expression and cholinergic system dysfunction accompanied by memory loss.[18]

A considerable body of evidence has well evaluated the importance of the cholinergic system in spatial memory using the MWM task.[19,21,33] On the other hand, it has been demonstrated that AG can facilitate the Aβ-induced cholinergic system dysfunction.[18] Other experimental studies have shown an interaction between iNOS and acetylcholine esterase activity.[34] Moreover, nitric oxide produced by iNOS contributes to the inflammation and production of destructive free radical agents which may negatively impact memory function.[8,9] Thus, these implications suggest that AG-induced spatial memory retention improvement in MWM may be due to the inhibition of iNOS activity. Accordingly, there are some studies which reported protective effects of different NOS inhibitors on memory and neurodegenerative diseases.[8,9,15] Also, it has been shown that iNOS impaired spatial memory function by inducing cell death through increasing the synthesis of nitric oxide and pro-inflammatory cytokines.[35]

Our data showed that AG improved SMV-induced memory retention deficit by decreasing escape latency and travelled distance to the control levels. The biological effects of SMV and nitric oxide pathway are interrelated.[36,37] In line, our results indicated that vanadium may induce spatial memory retention deficit at least in part by affecting nitric oxide pathway and increasing the expression of iNOS.

Vanadium compounds may further lead to amyloid plaque formation through induction of oxidative stress leading to memory loss.[38]

Conclusion

In the present study, behavioral analyses in MWM

revealed that AG, as a selective iNOS inhibitor, reversed SMV-induced spatial memory retention deficits. With regards to the effects of SMV on nitric oxide, oxidative defense systems and cholinergic signaling pathway, it is reasonable to mention that AG may protect SMV-induced spatial memory retention deficits via interaction with cholinergic system and nitric oxide pathways. However, to confirm the behavioral observations of this study, molecular studies can be helpful to clarify the precise mechanisms underlying these findings.

Conflict of interests

The authors claim that there is no conflict of interest.

References

1. Azami K, Tabrizian K, Hosseini R, Seyedabadi M, Shariatpanahi M, Noorbakhsh F, et al. Nicotine attenuates spatial learning deficits induced by sodium metavanadate. Neurotoxicology. 2012;33(1):44-52. doi:10.1016/j.neuro.2011.11.004
2. Sharma RP, Coulombe RA, Srisuchart B. Effects of dietary vanadium exposure on levels of regional brain neurotransmitters and their metabolites. Biochem Pharmacol. 1986;35(3):461-5. doi:10.1016/0006-2952(86)90220-0
3. Witkowska D, Brzeziński J. Alteration of brain noradrenaline, dopamine and 5-hydroxytryptamine levels during vanadium poisoning. Pol J Pharmacol Pharm. 1979; 31(4):393-8.
4. Avila-Costa MR, Fortoul TI, Niño-Cabrera G, Colín-Barenque L, Bizarro-Nevares P, Gutiérrez-Valdez AL, et al. Hippocampal cell alterations induced by the inhalation of vanadium pentoxide (V_2O_5) promote memory deterioration. Neurotoxicology. 2006;27(6):1007-12. doi:10.1016/j.neuro.2006.04.001
5. Zhou DL, Feng CY, Lan YJ, Wang ZM, Huang S, Wang MZ, et al. [Paired-control study on the effect of vanadium on neurobehavioral functions]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2007;38(3):468-70.
6. Bannerman DM, Deacon RMJ, Offen S, Friswell J, Grubb M, Rawlins JNP. Double dissociation of function within the hippocampus: spatial memory and hyponeophagia. Behav Neurosci. 2002;116(5):884-901. doi:10.1037/0735-7044.116.5.884
7. Vitolo OV, Sant'angelo A, Costanzo V, Battaglia F, Arancio O, Shelanski M. Amyloid β-peptide inhibition of the PKA/CREB pathway and long-term potentiation: reversibility by drugs that enhance cAMP signaling. Proc Natl Acad Sci U S A. 2002;99(20):13217-21. doi:10.1073/pnas.172504199
8. Najafi S, Payandemehr B, Tabrizian K, Shariatpanahi M, Nassireslami E, Azami K, et al. The role of nitric oxide in the PKA inhibitor induced spatial memory deficits in rat: Involvement of choline acetyltransferase. Eur J Pharmacol. 2013:714(1-3):478-85. doi:10.1016/j.ejphar.2013.06.039
9. Payandemehr B, Rahimian R, Gooshe M, Bahremand A, Gholizadeh R, Berijani S, et al. Nitric oxide mediates the anticonvulsant effects of thalidomide on pentylenetetrazole-induced clonic seizures in mice. Epilepsy Behav. 2014;34:99-104. doi:10.1016/j.yebeh.2014.03.020
10. Law A, O'donnell J, Gauthier S, Quirion R. Neuronal and inducible nitric oxide synthase expressions and activities in the hippocampi and cortices of young adult, aged cognitively unimpaired, and impaired Long–Evans rats. Neuroscience. 2002;112(2):267-75. doi:10.1016/s0306-4522(02)00082-9
11. Calabresi P, Gubellini P, Centonze D, Sancesario G, Morello M, Giorgi M, et al. A critical role of the nitric oxide/cGMP pathway in corticostriatal long-term depression. J Neurosci. 1999;19(7):2489-99. doi:10.1523/jneurosci.19-07-02489.1999
12. Hawkins RD, Son H, Arancio O. Nitric oxide as a retrograde messenger during long-term potentiation in hippocampus. Prog Brain Res. 1998;118:155-72. doi:10.1016/s0079-6123(08)63206-9
13. Majlessi N, Choopani S, Bozorgmehr T, Azizi Z. Involvement of hippocampal nitric oxide in spatial learning in the rat. Neurobiol Learn Mem. 2008;90(2):413-9. doi:10.1016/j.nlm.2008.04.010
14. Salter M, Knowles RG, Moncada S. Widespread tissue distribution. species distribution and changes in activity of Ca^{2+} dependent and Ca^{2+}-independent nitric oxide synthases. FEBS lett. 1991;291(1):145-9. doi:10.1016/0014-5793(91)81123-p
15. Payandemehr B, Rahimian R, Bahremand A, Ebrahimi A, Saadat S, Moghaddas P, et al. Role of nitric oxide in additive anticonvulsant effects of agmatine and morphine. Physiol Behav. 2013;118:52-7. doi:10.1016/j.physbeh.2013.05.022
16. Siles E, MartíNez-Lara E, Cañuelo A, Sánchez M, Hernández R, López-Ramos JC, et al. Age-related changes of the nitric oxide system in the rat brain. Brain Res. 2002;956(2):385-92. doi:10.1016/s0006-8993(02)03575-8
17. Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and the ugly. Am J Physiol Cell Physiol. 1996;271(5):C1424-37. doi:10.1152/ajpcell.1996.271.5.c1424
18. Tran MH, Yamada K, Olariu A, Mizuno M, Ren XH, Nabeshima T. Amyloid β-peptide induces nitric oxide production in rat hippocampus: association with cholinergic dysfunction and amelioration by inducible nitric oxide synthase inhibitors. FASEB J. 2001;15(8):1407-9. doi:10.1096/fj.00-0719fje
19. Tabrizian K, Najafi S, Belaran M, Hosseini-Sharifabad A, Azami K, Hosseini A, et al. Effects of Selective iNOS Inhibitor on Spatial Memory in Recovered and Non-recovered Ketamine Induced-anesthesia in Wistar Rats. Iran J Pharm Res. 2010;9(3):313-20.
20. Sharifzadeh M, Sharifzadeh K, Naghdi N, Ghahremani MH, Roghani A. Posttraining intrahippocampal infusion of a protein kinase AII inhibitor impairs spatial memory retention in rats. J

Neurosci Res. 2005;79(3):392-400. doi:10.1002/jnr.20358
21. Sharifzadeh M, Zamanian AR, Gholizadeh S, Tabrizian K, Etminani M, Khalaj S, et al. Post-training intrahippocampal infusion of nicotine–bucladesine combination causes a synergistic enhancement effect on spatial memory retention in rats. Eur J Pharmacol. 2007;562(3):212-20. doi:10.1016/j.ejphar.2007.01.065
22. Chen D, Huang H, Xing Y, Liu Y, Xu Y, Zou W. A New vanadium complex improves the spatial learning and memory by activation of caveolin–MAPK–CREB pathway in diabetic mice. J Diabet Metabol. 2011; 2:114. doi:10.4172/2155-6156.1000114
23. Avila-Costa MR, Colín-Barenque L, Zepeda-Rodríguez A, Antuna SB, Saldivar O L, Espejel-Maya G, et al. Ependymal epithelium disruption after vanadium pentoxide inhalation: a mice experimental model. Neurosci Lett. 2005;381(1-2):21-5. doi:10.1016/j.neulet.2005.01.072
24. D'hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. Brain Res Rev. 2001;36(1):60-90. doi:10.1016/s0165-0173(01)00067-4
25. Han F, Shioda N, Moriguchi S, Qin ZH, Fukunaga K. The vanadium (IV) compound rescues septo-hippocampal cholinergic neurons from neurodegeneration in olfactory bulbectomized mice. Neuroscience. 2008;151(3):671-9. doi:10.1016/j.neuroscience.2007.11.011
26. Hasegawa Y, Morioka M, Hasegawa S, Matsumoto J, Kawano T, Kai Y, et al. Therapeutic time window and dose dependence of neuroprotective effects of sodium orthovanadate following transient middle cerebral artery occlusion in rats. J Pharmacol Exp Ther. 2006;317(2):875-81. doi:10.1124/jpet.105.096677
27. Cuesta S, Francés D, García GB. ROS formation and antioxidant status in brain areas of rats exposed to sodium metavanadate. Neurotoxicol Teratol. 2011;33(2):297-302. doi:10.1016/j.ntt.2010.10.010
28. Matte C, Marquis JF, Blanchette J, Gros P, Faure R, Posner BI, et al. Peroxovanadium-mediated protection against murine leishmaniasis: role of the modulation of nitric oxide. Eur J Immunol. 2000;30(9):2555-64. doi:10.1002/1521-4141(200009)30:9<2555::aid-immu2555>3.0.co;2-x
29. Cavallaro S, D'agata V, Manickam P, Dufour F, Alkon DL. Memory-specific temporal profiles of gene expression in the hippocampus. Proc Natl Acad Sci U S A. 2002;99(25):16279-84. doi:10.1073/pnas.242597199
30. Yamada K, Noda Y, Nakayama S, Komori Y, Sugihara H, Hasegawa T, et al. Role of nitric oxide in learning and memory and in monoamine metabolism in the rat brain. Br J Pharmacol. 1995;115(5):852-8. doi:10.1111/j.1476-5381.1995.tb15011.x
31. Chapman PF, Atkins CM, Allen MT, Haley JE, Steinmetz JE. Inhibition of nitric oxide synthesis impairs two different forms of learning. Neuroreport. 1992;3(7):567-70. doi:10.1097/00001756-199207000-00005
32. Estall LB, Grant SJ, Cicala GA. Inhibition of nitric oxide (NO) production selectively impairs learning and memory in the rat. Pharmacol Biochem Behav. 1993;46(4):959-62. doi:10.1016/0091-3057(93)90228-l
33. Azami K, Etminani M, Tabrizian K, Salar F, Belaran M, Hosseini A, et al. The quantitative evaluation of cholinergic markers in spatial memory improvement induced by nicotine–bucladesine combination in rats. Eur J Pharmacol. 2010;636(1-3):102-7. doi:10.1016/j.ejphar.2010.03.041
34. Udayabanu M, Kumaran D, Nair RU, Srinivas P, Bhagat N, Aneja R, et al. Nitric oxide associated with iNOS expression inhibits acetylcholinesterase activity and induces memory impairment during acute hypobaric hypoxia. Brain Res. 2008;1230:138-49. doi:10.1016/j.brainres.2008.06.081
35. Akama KT, Albanese C, Pestell RG, Van Eldik LJ. Amyloid β-peptide stimulates nitric oxide production in astrocytes through an NFκB-dependent mechanism. Proc Natl Acad Sci U S A. 1998;95(10):5795-800. doi:10.1073/pnas.95.10.5795
36. Basu A, Bhattacharjee A, Roy SS, Ghosh P, Chakraborty P, Das I, et al. Vanadium as a chemoprotectant: effect of vanadium (III)-l-cysteine complex against cyclophosphamide-induced hepatotoxicity and genotoxicity in Swiss albino mice. J Biol Inorg Chem. 2014;19(6):981-96. doi:10.1007/s00775-014-1141-6
37. Fukunaga K. Benefit of vanadium compound in therapy for cardiovascular diseases. Yakugaku zasshi. 2012;132(3):279-84. doi:10.1248/yakushi.132.279
38. Bitanihirwe BKY, Cunningham MG. Zinc: the brain's dark horse. Synapse. 2009;63(11):1029-49. doi:10.1002/syn.20683