# Effects of Memantine on Latent Inhibition of Active Avoidance in Wistar Rats

**L. V. Loskutova and N. V. Kostjunina**

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 147, No. 6, pp. 626-630, June, 2009
Original article submitted July 22, 2008

Latent inhibition of active avoidance reaction was acquired by mature Wistar rats. It manifested in marked delay of habit acquisition after preexposure to the conditional stimulus in the first experimental session. Single dose of NMDA-receptor antagonist memantine (10 and 14 mg/kg) was applied 60 min before training in the second session. Failure of latent inhibition formation was registered after administration of the higher memantine dose; it manifested in accelerated attaining of the criterion (7 successive conditioned avoidance reactions) compared to training results after administration of the lower dose or physiological saline. The effects of memantine on attention were found to depend on the presence of pathology. It was hypothesized that the preparation can produce a positive effect on memory in Alzheimer-type dementia due to primary recovery of the inhibitory aspect of attention.

**Key Words:** *attention; latent inhibition; active avoidance; memantine*

Glutamate is a key transmitter of physiological communication between neurons. It provides neuronal plasticity and long-term potentiation associated with memory formation. In the other hand, mild but permanent tonic activation of NMDA-receptors results in apoptosis of brain neurons and cognitive disorders (Alzheimer-type dementia) [9]. In this case, NMDA-blocking agents appear to be neuroprotectors. Memantine is successfully employed in clinical practice for the treatment of brain disorder in humans. In contrast to other NMDA-agonists with high affinity and narcotic action (phencyclidine, ketamine, dizocilpine), memantine possesses unique kinetic binding properties, moderate affinity to $Mg^{2+}$, and does not induce prolonged $Ca^{2+}$ reflux into the cell, which prevents it destruction [2].

At present, memory improvement under the effect of memantine in individuals with Alzheimer disease caused by neuronal degeneration in the hippocampus, is associated with correction of primary attention and acceleration of informational processes [4,5]. Moreover, prepulse inhibition disorders, a sign of disturbed inhibitory attention processes, were found in untreated patients with moderate changes at the early stages of the disease [13]. Therefore, the positive symptomological effect of memantine on attention function is probably determined by primary recovery of subject's capacity to ignore non-relevant information.

At the same time, there are data on negative effects of memantine on prepulse inhibition in healthy rats [14], *i.e.* its effects under normal conditions correspond to those of phencyclidine derivatives with antagonistic action, which invert the parameters of both prepulse and latent inhibition (LI) in animals [1,3]. Memantine also produced a negative effect on learning and memory in normal animals. Conditioning failure in rats was observed after treatment with memantine in high [6,8], but not in low doses [11]. An opposite effect of the drug was noted during experimental neurodegenerative destruction in rat hippocampus, memantine, but not dizocilpine, prevented working memory disorders [10].

Since selective attentions plays a role in the very preliminary formation of new habits along with obli-

Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk, Russia. ***Address for correspondence:*** loskutova@physiol.ru. L. V. Loskutova

0007-4888/09/1476-0691 

gatory inhibition of reactions inadequate to current events, memory impairment caused by memantine is intimately associated with disturbances in attention inhibition process. The latter process is very interesting for our further investigations; the specificity of memantine for attention inhibition process was analyzed using prepulse inhibition test [14], but in none studies LI test was used for these purposes. Both behavioral phenomena reflect inhibition of attention to non-relevant stimuli and are extensively used in both animal and human studies; however, similar phenomena differ by not only their structure, but also neurochemical mechanisms [7]. Prepulse inhibition consists in a decrease of startle amplitude in response to intensive sound coming after less intensive sound (unconditioned reaction), whereas LI is characterized by delay in conditioning to previously quenched novelty of the future conditioned stimulus and is formed during a long time.

In the present study we studied LI formation in conditioned active avoidance task in normal rats under conditions NMDA-receptor blockage with memantine at the stage of learning.

## MATERIALS AND METHODS

Experiments were performed on 3.2-3.5-month old male Wistar rats obtained from the Animal Breeding Laboratory, Institute of Cytology and Genetics, Siberian Division, Russian Academy of Sciences. The animals were kept in plastic cages (2 rats per cage) under standard conditions with free access to water and food. The adaptation period before the experiment was 10-12 days.

Active avoidance (AA) was conditioned in automated shuttle chamber operated using IFT-04 software. The rats were allowed to explore the chamber for 3 min and then electric lamp (10 W) mounted on the chamber wall above the door in the compartment with the rat was turned on. After 5-sec exposure to the conditioned stimulus alone, electric current (0.7 mA) was delivered to the metal grid floor. Both stimuli were turned off after rat transition to another compartment. The time interval between combinations of conditioned and unconditioned stimuli randomly varied from 22 to 30 sec. One training session consisting of 100 combinations was performed. The rats were allowed to pass from one compartment to another during the period between stimulations. The following behavioral parameters were recorded during the experiment: escape and avoidance latency (latency of transition, LT), number of combinations presented before the first correct response, number of combinations presented before attaining the learning criterion (7 successive correct responses), and total number of conditioned responses and interstimulus reactions per session. For statistical analysis, the mean LT in first 5 blocks consisting of 10 combinations were calculated.

For LI induction, the learning session was preceded (24 h before learning) by the stage of preexposure (PE) under similar conditions except painful stimulus. Before the experiment, the animals were randomized into 4 groups: control group 1 (0 PE, $n$=9), control group 2 (100 PE, $n$=11), group 3 (100 PE+memantine 10 mg/kg, $n$=9), and group 4 (100 PE+memantine 14 mg/kg, $n$=7).

Memantine (memantine hydrochloride; Sigma) was dissolved in 0.9% physiological saline immediately before the experiment and was injected intraperitoneally in a volume of 1 ml/kg 50 min before training in the shuttle box. Control animals were injected with physiological solution in the same volume.

Statistical analysis of inter- and intragroup differences was carried out using one-way and two-way ANOVA using STATGRAPHICS software. The results are presented as arithmetic means and standard errors of the mean ($M\pm SEM$).

The experiments were performed in accordance with the humanitarian principles laid down in the Directives of the European Community (86/609/EC) and were approved by the Biomedical Ethics Committee of the State Research Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences.

## RESULTS

Behavioral parameters of AA conditioning under different influences are presented (Fig. 1). Overall ANOVA revealed no differences in the total number of conditioned reactions and in interstimulus transitions. However, differences were found between the major parameters: number of combinations before the first AA response ($F_{3.32}$=3.63, $p$=0.023) and before attaining the learning criterion ($F_{3.32}$=16.10, $p$<0.001). Comparison of the control groups demonstrated a delay in AA conditioning or LI effect in PE rats receiving physiological saline (Fig. 1, *a*, *b*). These animals showed significantly increased number of transitions both before the first correct response ($F_{1.18}$=7.64, $p$=0.01) and before attaining learning criterion ($F_{1.18}$=34.79, $p$<0.001); hence, the mean total number of conditioned reactions was lower and the number of interstimulus transitions was higher, but these differences were insignificant (Fig. 1, *c*, *d*).

Despite the decrease in the number of combinations to the first correct response ($F_{1.18}$=4.77, $p$=0.042 in comparison with group 2), memantine 10 mg/kg (group 3) did not affect the main parameter of conditioning under conditions of LI (Fig. 1, *b*). The total number of conditioned responses and interstimulus

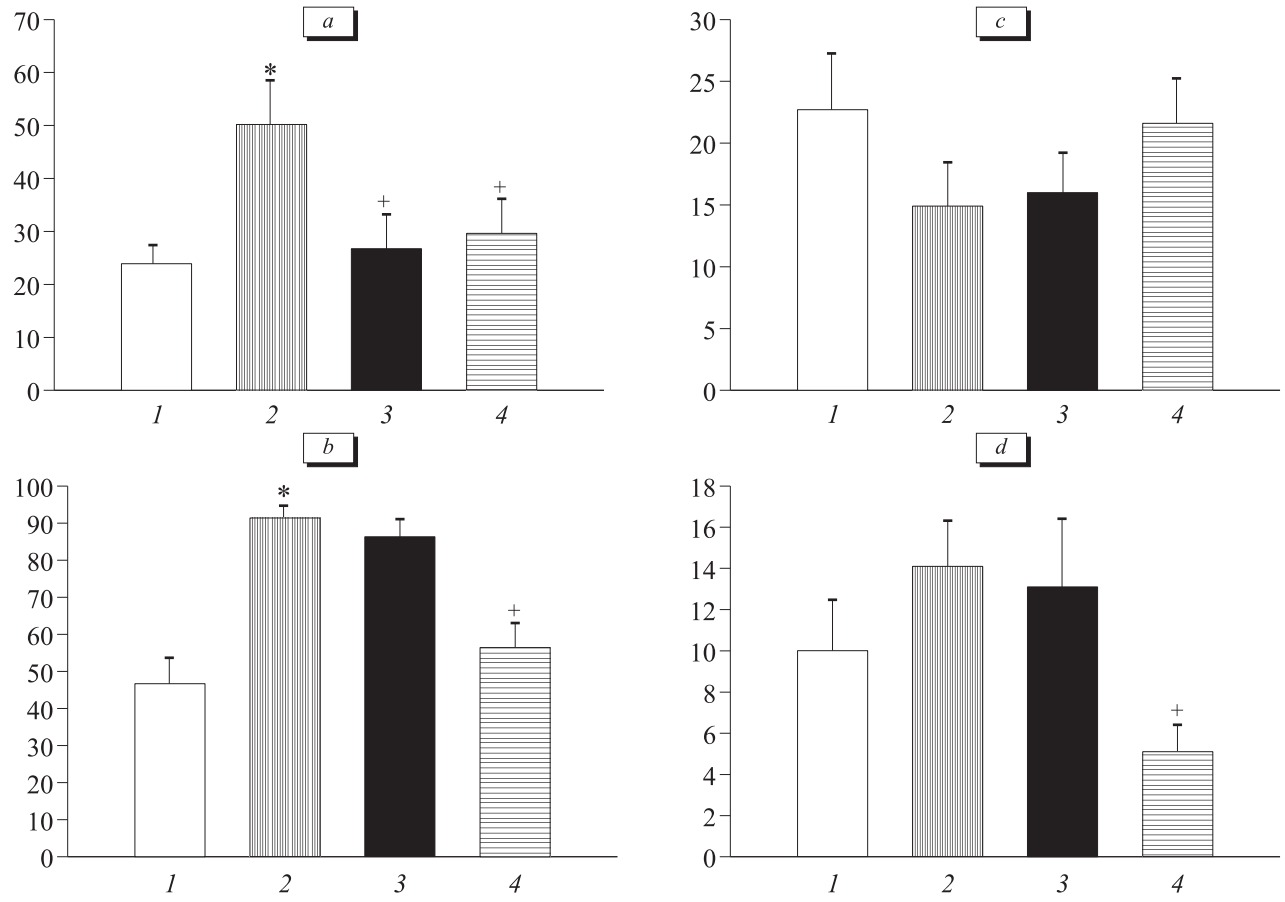


**Fig. 1**. Parameters of AA conditioning in rats. *a*) number of combinations of conditioned and unconditioned stimuli to first correct response; *b*) number of combinations toattaining learning criterion; *c*) total amount of conditioned responses in the session; *d*) number of interstimulus transitions. Light bars: control group 1; vertical shading: control group 2; dark bars: group 3, horizontal shading: group 4. $p<0.05$ compared to: *control group 1, +control group 2.

transitions was also unchanged. However, memantine in a dose up to 14 mg/ kg (group 4) facilitated conditioning of AA, which did not differ by all parameters from that in control not preexposed animals ($p>0.05$). In other words, LI was disturbed, which manifested in the appearance of significant differences between groups 2 and 4 ($F_{1.16}=26.53$, $p<0.001$) by the most important parameter, learning criterion (Fig. 1, *b*). Despite moderately increased motor activity, the number of interstimulus transitions (Fig. 1, d) decreased compared to group 2 ($F_{1.16}=9.01$, $p<0.01$) and group 3 ($F_{1.14}=4.63$, $p=0.05$).

Figure 2 shows LT of avoidance of painful stimulation in the first 5 session blocks (10 combinations in each). Overall ANOVA revealed significance of the group factor ($F_{3.32}=4.26$, $p=0.012$) and time factor ($F_{4.128}=71.31$, $p<0.001$), but not of their interaction.

Despite the fact that AA performance gradually increased in all groups, all PE rats demonstrated increased LT. Pairwise comparisons revealed significant differences between the two control groups for blocks 1 ($F_{1.32}=11.98$; $p=0.002$), 2 ($F_{1.32}=5.14$; $p=0.03$), 3 ($F_{1.32}=6.63$; $p=0.014$), and 5 ($F_{1.32}=8.27$; $p=0.007$). Injection of memantine to PE rats (groups 3 and 4) did not affect this parameter in comparison with that in the corresponding control animals (group 2). The dynamics of the decrease in reaction time was similar in all groups, which was seen from the results of intragroup comparison. In control group 1, significant decrease in LT was observed between blocks 1 and 3 ($F_{1.32}=13.93$; $p<0.001$) and continued until block 5 ($F_{1.32}=32.10$; $p<0.001$). In control group 2, the rate of this decrease was higher and significant differences were observed even between blocks 1 and 2 ($F_{1.32}=16.92$; $p<0.001$). Similar results were obtained in group 4. In group 3, significant differences were observed between blocks 1 and 3 ($F_{1.32}=11.89$; $p=0.001$). However, the reaction time in block 5 remained increased in all PE rats ($p<0.05$, compared to control 0 PE) and did not depend on the agent injected.

Our findings suggest that NMDA-receptor blockage with memantine can disturb LI formation in normal rats, at least under condition of our experiment. The possible nonspecific effect of memantine in the

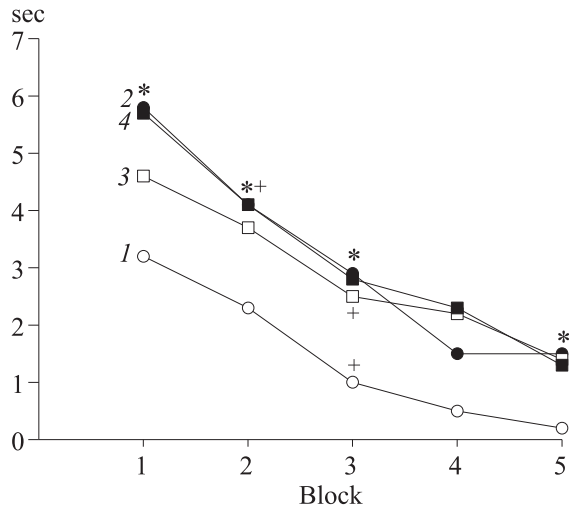


**Fig. 2**. Dynamics of LT in response to painful stimulus during training in the second session. *1*) control group 1; *2*) control group 2; *3*) group 3; *4*) group 4. $p<0.05$ compared to: *1, +for intergroup differences between the first and subsequent training blocks.

applied doses should be taken into account. Acute dosing of memantine 5 mg/kg increased motor and exploratory activity, but did not affect passive avoidance conditioning in rats in comparison with higher doses of the agent [11]. Authors associate memory disorders with increased hyperactivity. However, in our study the effects of memantine was directed more likely towards the cognitive component, since reduced number of interstimulus transitions excluded its nonspecific action. Moreover, the obtained effects correspond to the results of another study [14], where lower memantine dose (10 mg/kg) disturbed prepulse inhibition in normal rats.

Taking into account the dual effect of the preparation, the possibility of recovery of disrupted LI in Alzheimer disease model is of special interest; however, this possibility was not studied yet. The mechanism of LI disruption after acute memantine injection is also unclear, although some effects might be mediated by the increase in dopamine transmission [12]. Close interaction of the two neurotransmitter systems and their receptors in the brain regions involved in LI formation was previously demonstrated [1]. It can be expected that the obtained effect is mediated by the increase in dopamine transmission, *e.g.* in the nucleus accumbens, which negatively affects LI formation. However, this problem requires special studies, and our data support recently appeared opinion, that attention disturbances in patients with Alzheimer disease is possibly primary to memory disruption [4,5]. This point of view is supported by new results of the latest pilot studies demonstrating improvement of attention in children with deficit of the corresponding function [5].

## REFERENCES

1. M. Bortolato, G. N. Aru, M. Fa, *et al*., *Neuropsychopharmacology*, **30**, No. 3, 561-574 (2005).
2. W. Danysz and C. G. Parsons, *Int. J. Geriatr. Psychiatry*, **18**, Suppl. 1, 23-32 (2003).
3. J. A. Davis and T. J. Gould, *Behav. Neurosci.*, **119**, No. 2, 595-602 (2005).
4. S. Ferris, L. Schneider, M. Farmer, *et al*., *Int. J. Geriatr, Psychiatry*, **22**, No. 5, 448-455 (2007).
5. R. L. Findling, N. K. McNamara, R. J. Stansbrey, *et al*., *J. Child Adolesc. Psychopharmacol*, **17**, No. 1, 19-33 (2007).
6. C. Creeley, D. F. Wozniak, J. Labruyere, *et al*., *J. Neurosci*, **26**, No. 15, 3923-3932 (2006).
7. A. L. Jongen-Relo, S. Kaufmann, and J. Feldon, *Neuroscience*, **111**, No. 1, 95-109 (2002).
8. S. A. Lipton, *J. Alzheimers Dis*, **6**, Suppl. 6, S61-S74 (2004).
9. M. Misztal and W. Danysz, *Behav. Pharmacol*., **6**, Nos. 5-6, 550-556 (1995).
10. K. W. Muir, *Curr. Opin. Pharmacol*, **6**, No. 1, 53-60 (2006).
11. F. Razoux, R. Garcia, I. Lena, *Neuropsychopharmacology*, **32**, No. 3, 719-727 (2007).
12. G. Z. Reus, S. S. Valvassori, R. A. Machado, *et al.*, *Naunyn Schmiedebergs Arch. Pharmacol*., **376**, No. 5, 295-300 (2008).
13. R. Spanagel, B. Eilbacher, R. Wilke, *Eur. J. Pharmacol*., **262**, Nos. 1-2, 21-26 (1994).
14. H. Togashi, S. Kimura, M. Matsumoto, *et al*., *Stroke*, **27**, No. 3, 520-525 (1996).
15. J. L. Wiley, S. A. Harvey, R. L. Balster, K. L. Nicholson, *Psychopharmacology (Berl.)*, **165**, No. 4, 378-385 (2003).