Enhancement of long-term spatial memory in adult rats by the noncompetitive NMDA receptor antagonists, memantine and neramexane

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Abstract

Memantine and neramexane are noncompetitive NMDA receptor antagonists which have been investigated for their promising effects in aiding memory in people with dementia. Memantine is approved for the treatment of Alzheimer’s disease, and neramexane is currently under development for this indication. Therefore, the present study provided a comparative assessment of the effects of equimolar doses of memantine and neramexane on spatial (hippocampus-dependent) memory. Adult male rats were given only 3 training trials to learn the location of a hidden platform in a water maze. In control (vehicle-injected) rats, this minimal amount of training produced intact short-term (15 min), but poor long-term (24 h), memory. Pre-training administration of memantine or neramexane produced a dose-dependent enhancement of long-term memory. Pharmacokinetic experiments with equimolar doses of both agents indicated that lower plasma levels of neramexane were more effective than memantine at enhancing memory. The effective doses of both agents in the current study produced plasma levels (and extrapolated brain CSF levels) within a range of activity at NMDA receptors and plasma levels seen in patients with Alzheimer’s disease. These findings provide support for the use of neramexane as a pharmacological intervention in the treatment of dementia.

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1. Introduction

Glutamate acts predominantly as an excitatory neurotransmitter within the central nervous system and plays a major role in synaptic transmission. While rapid transmission is mediated via ionotropic glutamate receptors such as the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), kainate, and NMDA (N-methyl-d-aspartate) receptors, transmission via the G-protein coupled metabotropic glutamate receptors (mGluRs) is of a more modulatory nature (Parsons et al., 1998; Pin and Acher, 2002). Most AMPA receptors are impermeable to Ca2+ and contribute to fast synaptic transmission. In contrast, NMDA receptors are highly permeable to Ca2+, but their voltage-dependent block by Mg2+ tends to result in slow gating kinetics. These features make NMDA receptors more suitable for mediating plastic changes in the brain, such as those involved in learning (Collingridge and Singer, 1990). Indeed, NMDA receptor activation is obligatory for some forms of long-term potentiation (LTP) (Hrabetova et al., 2000; Malenka and Bear, 2004; Malinow et al., 2000) and learning and memory (Baker and Kim, 2002; Danysz et al., 1995; de Lima et al., 2005; Flood et al., 1990; Kawabe et al., 1998; Li et al., 1997; Morris et al., 1986; Parada-Turska and Turski, 1990; Pitkanen et al., 1995; Roesler et al., 1998; Ward et al., 1990).
As a neuroprotective agent, memantine has been shown to normalize the impairments in synaptic plasticity and cognition that typically follow excitotoxic neuronal injury. For instance, memantine normalized LTP that was impaired either by the administration of NMDA or the reduction of Mg$$^{2+}$$ concentration (Frankiewicz and Parsons, 1999; Zajaczkowski et al., 1997) and improved LTP in aged rats in vivo (Barnes et al., 1996). Additionally, the administration of memantine following global ischemia resulted in significant improvements in rat spatial memory and an attenuation of ischemia-induced damage to hippocampal CA1 cells (Block and Schwarz, 1996). Others have shown that memantine-treated rats exhibit a significant decline in hippocampal cell death after traumatic brain injury (Rao et al., 2001). Memantine also prevented damage to rat hippocampal CA1 neurons after the administration of Aβ (Miguel-Hidalgo et al., 2002) and has been shown to improve spatial memory in mice carrying mutant APP and PS1 genes (Minkeviiciene et al., 2004). Although memantine has shown positive effects on cognition in experimental animals with conditions leading to cellular atrophy and glutamatergic hyperactivity, it has never been found to enhance memory processes in intact animals (Minkeviiciene et al., 2004; Zajaczkowski et al., 1997).

For the present study, we examined whether memantine and neramexane, two noncompetitive NMDA receptor antagonists, would improve learning and memory in rats trained in the radial-arm water maze (RAWM), a well-described spatial (hippocampus-dependent) learning and memory task (Diamond et al., 1999; Sandi et al., 2005; Woodson et al., 2003). Memantine is approved for the treatment of Alzheimer’s disease, and neramexane is currently under development for the same indication (Danyasz et al., 2002). Thus, we have provided a comparative assessment of the effects of administration of each agent on memory in normal adult rats. We also performed pharmacokinetic experiments to assess whether the doses which were effective in enhancing memory in water maze-trained rats would lead to plasma concentrations that are typically observed in patients.

2. Materials and methods

2.1. Subjects

2.1.1. Pharmacokinetic study

Experimentally naïve adult male Sprague-Dawley rats (220–260 g; Janvier, France) were housed in groups of four per cage. Colony room temperature and humidity were maintained respectively at 20±1 °C and 60±3%. Food and water were available ad libitum, and the animals were maintained on an alternating 12 h/12 h light-dark cycle (lights on at 0700) for at least 6 days before the experiments began. All manipulations were conducted during the light phase.

The study was approved by the Ethical Committee, Regierungspräsidium Darmstadt, Hessen and performed in accordance with the recommendations and policies of the U.S. National Institutes of Health Guidelines for the Use of Animals.
2.3.2. Extraction

All blood samples were centrifuged (3000 rpm) for 2 min. Plasma was decanted and kept in prepared glasses. The plasma samples were stored in the freezer (−18°C) until analyzed. Assays were performed by AAI (Neu-Ulm, Germany) in compliance with GLP using GC/MS (GC HP 5890 and Fisons Trio 1000 respectively). Amantadine was used as an internal standard.

2.3.4. Measurement

The analysis was performed on a GC/MS-system. A fused silica open tubular capillary column of cross-linked Cyanopropylphenyl-dimethylpolysiloxane type was used for the GC-separation. The MS was operated in the positive ion chemical ionization mode with ammonia as the reagent gas. Selected ion monitoring was performed for m/z 293, the base peak of the mass spectrum for memantine, and m/z 265, the base peak for 1-aminoadamantane. Data acquisition and integration of the peak areas were achieved using the instrument’s standard software.

2.4. Spatial memory task

2.4.1. Apparatus

Training took place in a black, galvanized round tank (168 cm in diameter, 56 cm height, 43 cm deep) filled with clear water (21±2°C) and located in a light- and sound-attenuated room. Using 6 V-shaped stainless steel walls (54 cm height, 56 cm length), the tank was divided into six arms (each of which had a width of approximately 25 cm) radiating from an open central area (56 cm in diameter). A hidden, black, plastic platform (12 cm in diameter) was located 2 cm below the surface of the water at the end of one arm (the goal arm).

2.4.2. Procedure

Prior to water maze training, all rats were transported to the laboratory and left undisturbed in the water maze room for a 30-min acclimation period. Thereafter, rats received i.p. injections of memantine hydrochloride (2.5, 3.75, 5, or 7.5 mg/kg), naramexane mesylate (3.1, 4.65, 6.2, 9.3 mg/kg), or saline vehicle (1 mL/kg). Thirty minutes later, rats began water maze training. Each rat was released in one of the arms (the start arm), at the platform by the experimenter. Once the rat found, or was guided to, the platform, it was allowed to stand on it for 15 s before the rat was gently guided to the platform within the 60-s period, it was gently guided to the platform by the experimenter. Once the rat found, or was guided to, the platform, it was allowed to stand on it for 15 s before the
next trial began. For each trial, the experimenter recorded the number of arm entry errors made by each rat and the length of time it took each rat to find the platform. An arm entry was operationally defined as a rat passing halfway down the arm. An arm entry error occurred when a rat entered an arm that did not contain the hidden platform, or entered the arm that contained the hidden platform but was unable to locate it. The latter type of entry error was extremely rare – over 98% of arm entry errors were entries into arms that did not contain the hidden platform. The goal arm was different across rats to prevent the build-up of odour cues in any one arm. The start arms varied randomly across trials, and for every trial, a different start arm was employed.

All rats received 3 acquisition trials (T1–T3) to learn the location of the hidden platform, followed by a 15-min delay period, which terminated with a memory test trial (short-term memory). Then the rats were returned to their home cages and transported back to the housing room. Twenty-four hours later, all rats were brought back to the laboratory and left undisturbed in the water maze room for a 30-min acclimation period, after which they were given a single memory test trial to assess their long-term (24 h) spatial memory. We developed this training protocol with pilot work, which indicated that under control conditions rats had intact memory at 15 min but no evidence of memory at 24 h. Thus, this procedure provided the opportunity to assess the ability of memantine and neramexane to enhance long-term memory.

2.5. Statistical analysis

The behavioral data for memantine and neramexane were analyzed separately (SigmaStat, SPSS). For each drug, arm entry errors on the acquisition trials (T1–T3) were analyzed with a mixed-model ANOVA, with group (vehicle, dose 1, dose 2, dose 3, dose 4) serving as the between-subjects factor and trials (T1, T2, T3) serving as the within-subjects factor. Separate one-way ANOVAs were employed to examine arm entry errors made on the 15-min short-term memory test trial and the 24-h long-term memory test trial. In both cases, group served as the between-subjects factor. Behavioral data were expressed as means±SEM, and Holm-Sidak post hoc comparisons were employed as indicated.

Outlier data (values greater than 3 standard deviations from the exclusive mean) were removed from the analyses. After removal of outlier data, all n = 7 or 8 rats per time point, with the exception of the vehicle group in the neramexane component, where n = 11 for all time points. Less than 2% of all data were classified as outliers.

3. Results

3.1. Plasma pharmacokinetics

Memantine hydrochloride (2.5, 5, 10 mg/kg) and neramexane mesylate (3.1, 6.2, 12.3 mg/kg) were injected i.p. and measured in plasma 30, 60, 120, 240, 420, and 600 min thereafter. Administration of increased doses of memantine hydrochloride and neramexane mesylate produced increases in plasma concentrations of each agent (Fig. 1).

Administration of neramexane (3.1, 6.2, 12.3 mg/kg) at the doses equimolar to memantine (2.5, 5, 10 mg/kg), resulted in lower plasma concentrations of neramexane. This finding is consistent with pharmacokinetic parameters such as Cmax and AUC (Table 1). However, there were no differences in Tmax and T1/2.

3.2. Effects on spatial memory performance

3.2.1. Memantine

The analysis of arm entry errors during acquisition (T1–T3) revealed a significant main effect of trial, indicating that rats made fewer errors as the trials progressed, $F_{2,70} = 3.57, P < .05$. There was no effect of group on acquisition in the RAWM.

<table>
<thead>
<tr>
<th>Substance</th>
<th>$T_{max}$</th>
<th>$T_{1/2}$</th>
<th>$C_{max}$</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine (2.5/5/10)</td>
<td>0.5/0.5/0.5</td>
<td>1.6/1.6/2.4</td>
<td>88/244/474</td>
<td>275/616/1483</td>
</tr>
<tr>
<td>Neramexane (3.1/6.2/12.3)</td>
<td>0.5/0.5/0.5</td>
<td>1.4/1.6/2.1</td>
<td>72/143/254</td>
<td>137/342/827</td>
</tr>
</tbody>
</table>

Values are means of 6 animals.
F_{4,35} = 1.07, P > .38, and there was no significant Group x Trial interaction, F_{8,70} = 1.39, P > .21 (Fig. 2A).

Memantine had no effect on performance in the 15-min short-term memory test, F_{4,33} = 1.09, P > .37. The analysis of arm entry errors on the 24-h retention trial revealed that memantine produced a dose-dependent enhancement of long-term spatial memory, F_{4,33} = 3.27, P < .05 (Fig. 2B). Post hoc comparisons demonstrated that 5 and 7.5, but not 2.5 or 3.75, mg/kg of memantine resulted in significantly fewer arm entry errors on the 24-h memory test trial (P's < .05).

3.2.2. Neramexane

The analysis of arm entry errors during acquisition (T1–T3) revealed a significant main effect of trial, indicating that rats made fewer errors as the trial progressed, F_{2,76} = 12.46, P < .001 (Fig. 3A). In contrast to memantine, there was an effect of group on acquisition in the RAWM, F_{4,38} = 3.63, P < .05. Rats that received 9.3 mg/kg of neramexane made significantly more errors during learning than controls. There was no significant Group x Trial interaction, F_{8,76} = 0.45, P > .88.

There was a significant effect of neramexane on short-term memory, F_{4,35} = 18.74, P < .001. Rats that received 9.3 mg/kg of neramexane made significantly more entry errors on the 15 min memory test trial than controls. In contrast, there was a dose-dependent enhancing effect of neramexane on long-term spatial memory, F_{4,37} = 2.73, P < .05 (Fig. 3B). Post hoc comparisons demonstrated that 4.65 and 6.2, but not 3.1 or 9.3, mg/kg of neramexane resulted in significantly fewer arm entry errors on the 24-h memory test trial (P's < .05).

3.2.3. Behavioral observations

Rats that were injected with 9.3 mg/kg of neramexane appeared to be hyperactive. They tended to jump back into the water after reaching the platform. These rats also exhibited perseverative errors, in that they repeatedly swam into the same
(incorrect) arms. Thus, it is not clear from this work if the high dose of neramexane was ineffective at enhancing memory or if the increased motor activity interfered with the ability of the rats to perform the task.

4. Discussion

The primary finding of this work is that pre-training administration of memantine or neramexane dose-dependently enhanced long-term (24 h) spatial memory. This is the first study we are aware of to show that the administration of these particular NMDA receptor antagonists can enhance long-term memory in normal adult animals which don’t have a treatment-induced deficit. This long-lasting, memory-enhancing effect is unlikely to be related to the influence of either drug at the time of memory testing; plasma levels dropped to approximately 0.1 μM concentrations 10 h after administration, a level that results in only minor activity at NMDA receptors. Neramexane appeared to be more potent than memantine, as it enhanced long-term memory at a dose (4.65 mg/kg) that was equimolar to AP5 and learning under such conditions. For example, the competitive NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5) reverses the impairment of LTP produced by the administration of NMDA (Coan et al., 1989). Similarly, 3-(2-carboxy-piperazin-4-yl)propyl-1-phosphonic acid (CPP), another competitive NMDA receptor antagonist, reverses LTP impairments produced in GLT1 knockouts (Katagiri et al., 2001). Moreover, positive effects of memantine have been reported in the Morris water maze in double transgenic (APP + PS1) mice and in APP23 mice (Minkeviciene et al., 2004; Van Dam et al., 2005). This is not unexpected bearing in mind that Aβ enhances glutamatergic function and, in particular, NMDA receptor activation (Danyasz and Parsons, 2003; Mattson et al., 1992).

The issue arises, therefore, whether similar mechanisms could be operative in the task used in the present study. In the conditions of RAWM training, there is a clear stress component (immersion in cold water) which activates the glutamatergic system. Memantine and neramexane exerted positive effects on long-term memory, perhaps, in part, because of their ability to regulate water maze training-induced NMDA receptor activity and its corresponding Ca2+ influx. Thus, the intermediate doses of memantine and neramexane may have optimized NMDA channel functioning to produce favorable circumstances for memory consolidation. In comparable preliminary work on related NMDA receptor modulators, we have shown that low doses of tianeptine or CPP enhanced long-term (24 h) spatial memory in rats (Munoz et al., 2005). Tianeptine has been shown to normalize stress-induced increases in NMDA channel currents (Kole et al., 2002) and CPP is a well-studied NMDA receptor antagonist. Thus, the current work, in conjunction with our preliminary findings, is consistent with the view that memantine- and neramexane-induced enhancements of long-term memory occur via the modification of NMDA receptor activity.

This is not the first evidence for an enhancement of long-term memory via the administration of NMDA receptor antagonists. For instance, Lederer et al. (1993) found that the administration of CGP 37849, a competitive NMDA receptor antagonist, dose-dependently enhanced rats’ long-term memory in a social learning paradigm. Specifically, the lowest dose of CGP 37849 (0.3 mg/kg) led to better social recognition memory 24 h later, while higher doses (1 and 3 mg/kg) had no effect on
performance. In addition, Puma and Bizot (1998) found that intraseptal infusions of AP5 (DL-2-amino-5-phosphonopentanoic acid) enhanced long-term object recognition memory in rats. Mondadori et al. (1989) further argued that the effects of NMDA receptor antagonists on learning and memory are dependent on the type of task employed by the experimenter. These investigators found that pre-training administration of AP7 (DL-2-amino-7-phosphonoheptanoate) or MK-801 facilitated retention in a step-down passive avoidance task but impaired retention in place navigation and step-through dark avoidance tasks. Mondadori and Weiskrantz (1993) replicated these findings when they administered CGP 37849 and MK-801 prior to step-down passive avoidance and step-through dark avoidance tasks. However, these investigators extended the original findings by showing that the enhancement of step-down passive avoidance memory was dependent on steroid manipulations, while the impairment of step-through dark avoidance memory was not. Collectively, these findings support the arguments that (a) NMDA receptor antagonists differentially affect performance on different behavioral tasks and (b) their memory-enhancing and memory-impairing effects are mediated by different neurobiological mechanisms.

Additional work by Creeley et al. (2006) questioned the efficacy of memantine in terms of facilitating learning and memory. In this study, low doses of memantine, comparable to the ones presented in the current study, disrupted rats’ locomotor activity and led to 24 h memory impairments on a spatial memory, hole-board task. The inconsistency between the findings of Creeley et al. (2006) and the ones presented here could be attributable to methodological differences between the two studies. First, Creeley et al. (2006, p. 3924) used female rats in their study because “female rats are more sensitive than males to [the] adverse side effects of NMDA antagonists.” Most, if not all, of the work that has demonstrated memory-enhancing effects of NMDA receptor antagonists has utilized male rats, and since females are more sensitive to the adverse side effects of NMDA receptor antagonists, it is not surprising that memantine led to memory impairments in this experiment.

Such greater sensitivity in older female rats [6–8 months old, as used by Creeley and colleagues (2006)] than those typically used in pharmacological studies is not surprising. Older rats exhibit higher plasma levels of memantine than young rats after the administration of an equivalent dose of the drug [e.g., in 2½-month-old rats, infusion of memantine (24 mg/kg/d) leads to plasma levels of approximately 1.4 μM, while in 24-month-old rats, it leads to plasma levels of about 4 μM (unpublished observations)]. Similarly, following the infusion or acute injection of memantine, female rats display serum levels that are almost twice as high as those observed in male rats (Zajaczkowski et al., 2000). In turn, the treatment regime employed by Creeley et al. (2006) resulted in higher levels of memantine despite the fact that the doses, per se, appeared to be low.

It is also possible that NMDA receptor antagonists differentially affect learning and memory, depending on the stressfulness of the task involved. For instance, Creeley et al. (2006) employed what might seem like a less stressful task (hole-board task) than the one employed in the present study (water maze). However, Marquez et al. (2005) found that a version of the hole-board task, similar to the one employed by Creeley et al. (2006), produced significant elevations of serum corticosterone (∼20 μg/dL) in rats, which were greater than those produced by exposure to an elevated plus maze or circular corridor. These levels of serum corticosterone (∼20 μg/dL) are comparable to those that we have recently found in rats exposed to 12 repeated training trials in the RAWM (unpublished observations). Thus, it is not clear as to whether or not these two tasks are quantitatively different in terms of their stressfulness. Furthermore, it is important to consider the minimal amount of training that rats were exposed to in the present study. The rats endured only 3 consecutive acquisition trials, which took approximately 3–4 min to complete. Even if these two tasks are different in terms of their aversiveness, it does not explain the findings that NMDA receptor antagonists can enhance memory in both aversive (Mondadori et al., 1989; Mondadori and Weiskrantz, 1993; Zajaczkowski et al., 1997) and non-aversive (Lederer et al., 1993; Puma and Bizot, 1998; Zajaczkowski et al., 1996) tasks.

In addition to the modulation of NMDA receptor activity, other mechanisms may have been involved in the memantine- and neramexane-induced enhancement of long-term memory. For instance, clinically relevant doses of memantine (e.g., 5 mg/kg) induce a significant increase in brain-derived neurotrophic factor (BDNF) mRNAs in cortical regions (Marvanova et al., 2001). This neurotrophin has been shown to acutely facilitate synaptic plasticity, and its application enhances the induction of hippocampal LTP (Figurov et al., 1996; Patterson et al., 1996). Indeed, a weak stimulation of nerve fibers results in greater LTP when it is paired with BDNF than when it is induced in isolation (Figurov et al., 1996). BDNF also has a long-term effect on synaptic development and function. In addition to playing an important role in axonal and dendritic outgrowth, BDNF is involved in activity-dependent synaptic competition and the development of late-phase LTP (L-LTP) (Lu, 2003). Perhaps the most important finding in relation to the current work is that the interaction between BDNF/trkB signaling and NMDA receptors is key for the development of spatial memory in the hippocampus (Mizuno et al., 2003). Together, these findings suggest that, in the present study, memantine and neramexane could have affected BDNF concentrations, which aided in the consolidation of long-term memory. It is also possible that the cognitive-enhancing effects of memantine and neramexane act preferentially on one mechanism (e.g., by affecting BDNF and NMDA receptors), while their hypermotoric effects occur via activation of a different mechanism.

In clinical trials, memantine has been shown to improve cognition and daily skills in patients diagnosed with moderate to severe Alzheimer’s disease (Mobius et al., 2004; Reisberg et al., 2003). Neramexane, which belongs to a different chemical class of NMDA receptor antagonists, is currently under development for the treatment of neurodegenerative dementia (Danysz et al., 2002; Parsons et al., 1999a,b), among other indications. In the present study, pre-training administration of memantine or neramexane enhanced long-term spatial memory tested 24 h later. Neramexane, a more potent modulator of NMDA receptors, produced memory enhancements at a lower
equimolar dose than memantine. In summary, the current find-
ings provide the first indication that neramexane and meman-
tine can both enhance long-term memory in normal animals,
which support the use of neramexane as a pharmacological
intervention for the treatment of Alzheimer’s disease.

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