

Effects of the Uncompetitive NMDA Receptor Antagonist Memantine on Hippocampal Long-term Potentiation, Short-term Exploratory Modulation and Spatial Memory in Awake, Freely Moving Rats

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Abstract

Chronic treatment of adult male F-344 rats (9-12 months old) with therapeutically relevant doses of memantine (30 mg/kg/day in chow for >8 weeks) increased the maintenance of long-term potentiation of field excitatory postsynaptic potentials from perforant path-granule cell hippocampal synapses recorded in the fascia dentata in vivo. In contrast, there was no effect of memantine on baseline synaptic responses or population spikes. Likewise, short-term exploratory modulation of these hippocampal evoked responses was not different between memantine-treated and control rats. Both groups of rats were able to learn the spatial version of the Morris water task equally well, but the memantine-treated group showed a strong tendency to show more selective spatial search patterns in the training quadrant of the water pool during a final probe trial. As such, these studies provide the first electrophysiological evidence that memantine can increase the durability of synaptic plasticity and provide preclinical confirmation of the cognitive improvement seen with memantine in the treatment of demented patients.

Introduction

Memantine (1-amino-3,5-dimethyl adamantane) is a clinically used, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that has been used for a number of years in Europe, initially in the treatment of spasticity (for review see Komhuber et al., 1994). More recently it has also been found to produce a symptomatological improvement in aged patients with dementia syndrome (Görtelmeyer et al., 1993; Pantev et al., 1993; for review see Müller et al., 1995).

The good clinical tolerability of memantine has been attributed to its fast, strongly voltage-dependent open channel blocking kinetics that allows it to block chronic pathological activation of NMDA receptors whilst leaving their physiological activation intact (Chen et al., 1992; Parsons et al., 1993). These effects of memantine in preclinical models might indicate that memantine could slow the progression of neurodegenerative diseases like Alzheimer's dementia and multi-infarct dementia without having negative effects on cognition, if the role of excitotoxicity in the pathology of such conditions is accepted (Greenamyre et al., 1988; Palmer and Gershon, 1990). Indeed, preliminary clinical evidence suggests that memantine may be able to slow the progression of dementia (Görtelmeyer et al., 1993). It is still not clear, however, as to how memantine produces its symptomatological improvement of memory in demented patients.

Initial data indicate that even relatively high concentrations of

memantine do not block long-term potentiation (LTP) and may even enhance synaptic transmission in the CA1 region of hippocampal slices in vitro (Stieg et al., 1993; Dimpfel, 1995; Frankiewicz et al., 1996). The overall purpose of the present experiments was to investigate the effects of chronic treatment with therapeutically relevant doses of memantine on two forms of synaptic plasticity in the mammalian hippocampal formation in vivo: first, on the induction of long-term potentiation (LTP) (e.g. Collingridge et al., 1984; McNaughton and Barnes, 1990) in a region of hippocampus rich in NMDA receptors (i.e. the fascia dentata), and second, on the behaviour-induced form of plasticity that we have called short-term exploratory modulation (STEM) (Sharp et al., 1989; Barnes et al., 1991) in this same structure. Because it is possible to record stable evoked synaptic responses over weeks or months following chronic implantation of recording and stimulating electrodes, this system is ideally suited for assessing possible long-term effects of memantine on hippocampal physiology and synaptic plasticity.

Furthermore, because the hippocampal formation is known to have an important role in spatial memory in all mammals so far tested (for reviews see Barnes, 1988; Bliss and Collingridge, 1993; Danysz et al., 1995), comparison with the behavioural impact of this agent on cognitive processes is also possible. The prediction would be that

if there is a change in the electrophysiological parameters that have been hypothesized to reflect the mechanisms that underlie information storage, then behavioural learning should also be affected in a similar manner.

Materials and methods

Serum levels of memantine following semichronic oral administration

Male Sprague-Dawley rats (250 g) housed four per cage were kept under a 12 h light/12 h dark cycle at 21°C. They had free access to water whereas food was limited to 14 g/day. Memantine hydrochloride was given via the diet (Altromin, Lage, Germany) as a single administration or once daily for 14 days at 30 mg/kg/day. Rats were killed at various time points (between 0.5 and 24 h) after food consumption. Both serum and brain concentrations of memantine were determined by gas chromatography-mass spectrometry. The methods have been described in detail elsewhere (Danysz et al., 1994).

Chronic memantine administration for electrophysiological behavioural testing

Twenty-four male, retired breeder F-344 rats (250-300 g) were obtained from Charles River Laboratories at 9 months of age. All rats were handled and weighed for 1 week after arrival, before beginning the memantine and control diets. The experiment was conducted in two replicate studies, 12 animals in each, the procedure being essentially identical (unless noted below). Rats were randomly assigned to either the control or memantine diet groups, and fed rat chow containing memantine (30 mg/kg/day), or identical chow without the drug, for -2 months before the LTP induction experiments began (first replicate 54 days, second replicate 65 days). Rats were tested 5-8 h following ingestion of the diets for all components of electrophysiological and behavioural testing. All stages of these experiments were performed blind.

Surgical procedures

All rats underwent bilateral surgical implantation of stimulating electrodes in the perforant path (entorhinal cortical afferents) and recording electrodes in the hilus of the fascia dentata (Fig. 1A; for details see McNaughton et al., 1986). Briefly, rats were anaesthetized with sodium pentobarbital (Nembutal, 33 mg/kg), which was supplemented as necessary with Metofane (methoxyflurane). Recording and stimulating electrodes were constructed of 114 μm diameter Teflon-coated stainless steel wire (Medwire Corporation, USA). The recording electrode was cut flush with the insulation, while 300 μm of insulation was removed from the tips of the monopolar stimulating electrodes. The coordinates used for recording and stimulation placements were 3.8 mm posterior to bregma and 2.0 mm lateral to the midline, and 8.1 mm posterior and 4.4 mm lateral respectively (Paxinos and Watson, 1986). Final depths were adjusted under electrophysiological control to produce the maximal positive-going field response in the fascia dentata (Fig. 1B). Rats were allowed -2 weeks to recover before electrophysiological recording began (first replicate 10 days, second replicate 19 days).

Electrophysiological recording and behavioural procedures

The details of the electrophysiological recording techniques are essentially as described in McNaughton et al. (1986). The electrical

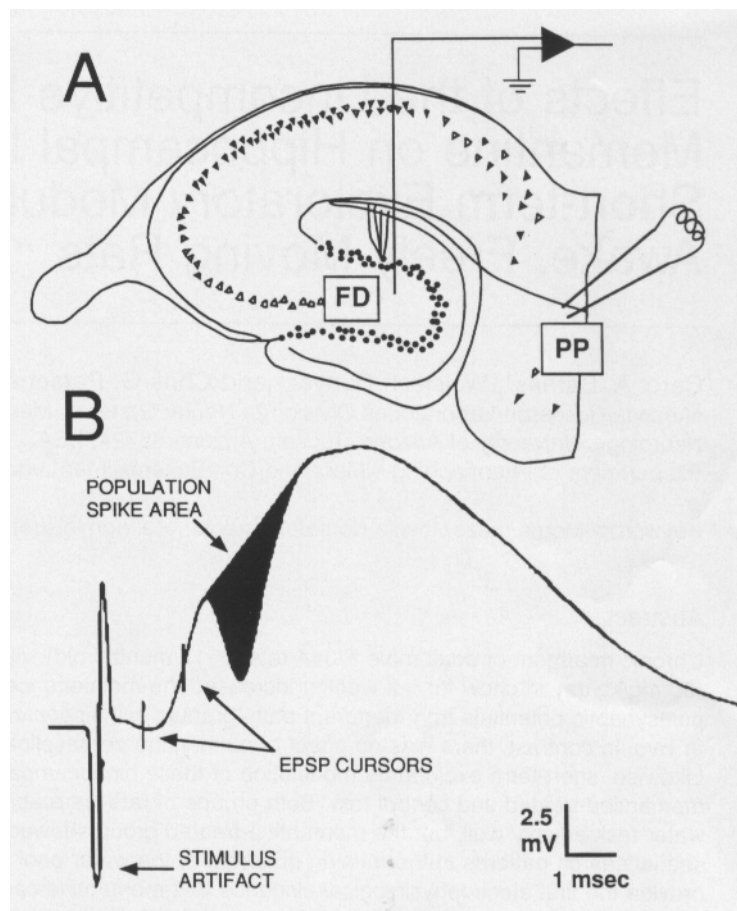


Fig. 1. (A) Schematic diagram of the hippocampus illustrating the configuration of the stimulating electrode in the perforant pathway (PP) and the recording electrode in the hilus of the fascia dentata (FD). All rats were implanted bilaterally with stimulating and recording electrodes. (B) Example of a hippocampal evoked response characteristic of these electrode placements. Slope of the EPSP was measured as voltage change/ms between two fixed cursors, and the population spike as the area under the line connecting spike onset and offset as indicated.

stimuli consisted of 200 μs diphasic, constant current pulses given at a stimulus intensity of approximately half-maximal amplitude for each rat ($\sim 250 \mu\text{A}$). Low-frequency stimulation was delivered at 0.1 Hz. The high-frequency stimulation parameters used consisted of ten repetitions of a 25 ms train delivered at 400 Hz (i.e. 10 pulses) for a total of 100 pulses within 5 min. All evoked response data were digitized by computer at 20 kHz and stored on disk for subsequent off-line analysis. The low-frequency evoked field excitatory postsynaptic potential (EPSP) slope was measured as the voltage difference between two cursors set at approximate EPSP onset and 1 ms beyond this point (Fig. 1B). The population spike was measured as the area under the tangent line marking the onset and offset of the negative-going spike.

Prior to surgical implantation of electrodes for electrophysiological recording, rats were tested in the spatial version of the Morris swim task (Morris et al., 1982), in which the rat was required to swim to find the spatial location of a hidden platform. This location could be learned by using the relationship of distal visual cues in the environment for navigation to the escape location. A total of 14 trials were given over 2 days. Latency to find the hidden platform as well as the

total path length travelled before finding the escape platform were collected via a tracking system (HVS Ltd, UK), and statistical comparisons were made using repeated measures ANOVA. Following the last trial on day 2, a probe trial was conducted in which the platform was removed, and the percentage of time the rats spent in each of the four quadrants of the water pool was calculated; differences were assessed using t-tests.

For the STEM experiment each rat underwent one 3 h continuous recording session (1080 responses were recorded, at 0.1 Hz) during two consecutive weeks to obtain measures of exploration-induced changes in hippocampal evoked responses. For the first 60 min rats were recorded while sitting quietly in their home cages; during the next 30 min rats were encouraged to engage in exploratory behaviour on the surface of a wooden triangular apparatus; recordings during the final 90 min were made after the rats were returned to their home cages. During the 30 min exploratory period brain temperature increases, and evoked response amplitudes show characteristic alterations that are tightly coupled to the amount of exploration exhibited in the individual rat. These changes typically revert to baseline within -30 min following the period of exploratory activity. The slope of the EPSP and area of the population spike were normalized for comparison of the rats fed the memantine and control diets, and the data for the two STEM sessions were averaged for each individual rat.

For the LTP experiments rats were given seven daily baseline recording sessions (at the same time each day) to establish stability of the bilateral perforant path-granule cell evoked responses. Following the low-frequency test stimuli on the 7th day, each rat was given unilateral high-frequency stimulation daily for 5 days. After the five high-frequency sessions, rats were monitored daily for 2 weeks further. In order to compare groups and individual rats, the evoked response parameters were normalized to the mean of the 7 day baseline period before the high-frequency stimulation treatment was begun. The fractional change in response amplitude was calculated as $(V_1 - V_0)/V_0$, where V_1 is the value obtained on each day and V_0 is the mean of the baseline period. Repeated measures ANOVAs were performed to assess possible group differences.

After decay day 14 following the last high-frequency stimulation session (described above), the diets were reversed for all rats (controls now received memantine, the memantine-treated rats now received control chow). During this time any residual LTP was also allowed to decay completely (first replicate, 2 weeks; second replicate, 3 weeks). Baseline responses were recorded for 5 days, and then five high-frequency stimulation sessions were given daily to the hemisphere that had previously only had low-frequency test stimuli. Recordings were then obtained for 10 days further to monitor decay.

Results

Memantine concentrations

The peak memantine concentration in both serum and brain was achieved within 5-10 h after acute and 5 h after semichronic administration of memantine (Fig. 2). Serum levels at this time point were somewhat higher after the semichronic administration, i.e. $\sim 5 \mu\text{M}$. After both forms of administration there was a much higher concentration of memantine in homogenized brain tissue, the highest level seen at the 5 h time point after semichronic administration being $\sim 200 \mu\text{M}$. This effect is likely to be related to the uptake of memantine into lysosomes (Honegger et al., 1993) and is not reflected in high cerebrospinal fluid (CSF) levels in rats (Spanagel et al., 1994) or humans (Kornhuber and Quack, 1995).

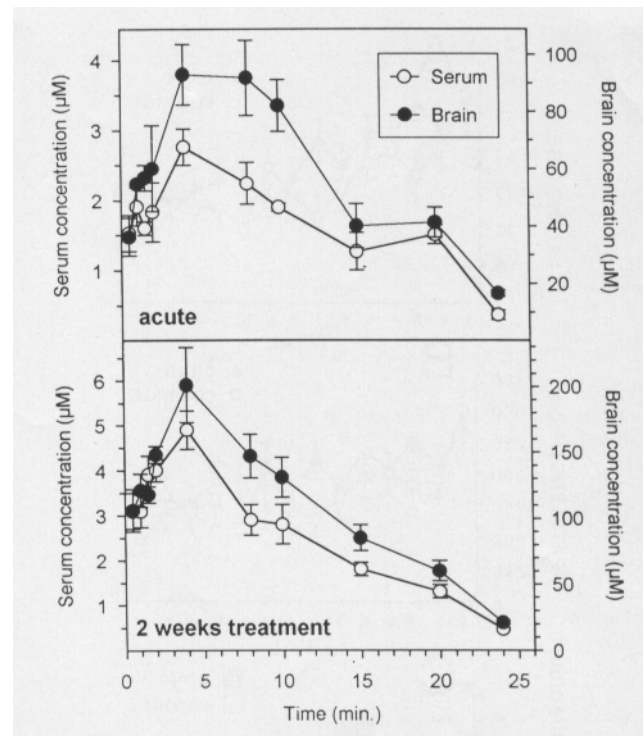


FIG. 2. Serum and brain concentrations of memantine after oral administration in chow. Rats were fed with one acute dose of 30 mg/kg (above) or for 2 weeks with the same dose daily (below). Memantine concentrations were determined in serum (open circles) and brain homogenates (closed circles) by gas chromatography. Mean concentrations are plotted against time after the last memantine treatment. Error bars represent SEM.

Effects of memantine on Morris maze learning and LTP *in vivo*

There were no statistically significant, within-treatment differences between any of the measurements obtained for the rats tested in the first and second replicate experiments, and the data have therefore been pooled for presentation. The data from the Morris swim task are shown in Figure 3. Although there was a significant effect of trial (latency, $F_{1,19} = 22.39$, $P < 0.0001$; path length, $F_{1,19} = 4.74$, $P < 0.001$), indicating that the rats learned the task, there was no statistically significant difference between the control and memantine groups in latency ($F = 0.01$) or path length ($F = 1.70$) to find the hidden platform ($P > 0.05$). On the probe trial, both groups spent the greatest amount of time searching in the training quadrant. Although the amount of time spent in the training quadrant did not differ statistically between groups, the memantine-treated rats tended to show more selectivity in their swim patterns on the probe trial than did the control rats. That is, the control rats did not spend significantly longer in the target quadrant (TG) than in one of the adjacent quadrants (Q) on the probe trial (Q1 versus TG, $t = 7.78$, $P < 0.0001$; Q3 versus TG, $t = 1.76$, $P > 0.05$; Q4 versus TG, $t = 3.85$, $P < 0.005$); however, the memantine-treated rats spent a significantly longer time in the target quadrant than in each of the other three quadrants (Q1 versus TG, $t = 7.23$, $P < 0.0001$; Q3 versus TG, $t = 2.80$, $P < 0.05$; Q4 versus TG, $t = 6.00$, $P < 0.0001$).

Twenty-two of the 24 rats operated on had good bilateral perforant path-granule cell evoked hippocampal field responses. Two rats were eliminated because one hemisphere did not have an adequate response (one control, one with memantine). The mean stimulus

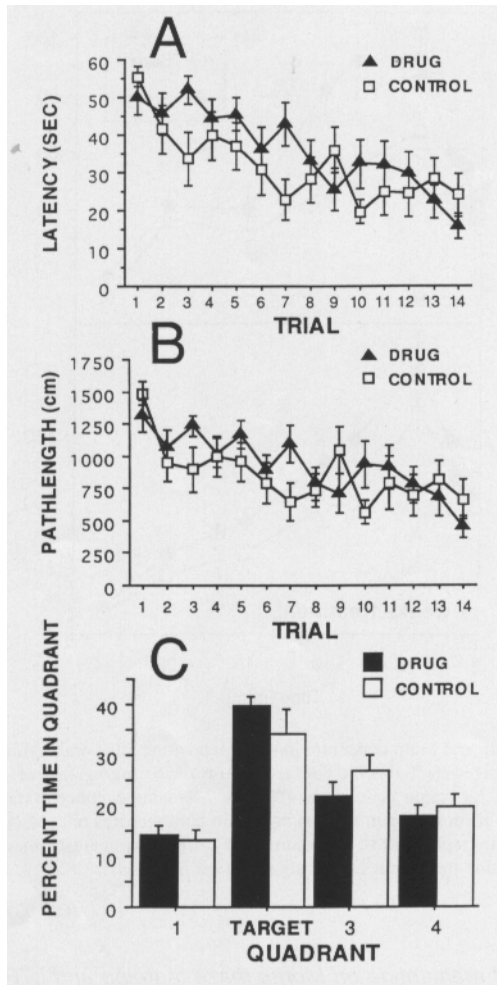


FIG. 3. Effects of memantine (30 mg/kg/day p.o.) on spatial memory in awake, freely moving rats. Latency (A) and path length (B) to find the location of a hidden platform in the Morris swim task are plotted as mean \pm SEM against trial number (seven trials per day, 2 days). The control and memantine-treated rats decreased their escape latency and total distance travelled over trials, but did not differ significantly from one another. (C) Following the 14th acquisition trial, the submerged platform was removed from the target quadrant and a 'probe' trial was conducted. Both groups spent the most time in the target quadrant, and there was no significant difference between groups on this measure. There was, however, a trend for the memantine-treated rats to dedicate a larger proportion of their search behaviour to the target quadrant than control rats.

intensities used to achieve half-maximal responses for the EPSP (mV/ms) and population spike (mV \times ms) were 287.5 and 245.5 μ A for the memantine and control rats respectively, and did not differ between groups ($t = 1.56$, $P > 0.05$). The slope of the EPSP (memantine, 2.89 mV/ms; control, 2.70 mV/ms; $t = 0.05$, $P > 0.05$) and the area of the population spike (memantine, 4.92 mV*ms; control, 5.42 mV*ms; $t = 1.05$, $P > 0.05$) also did not differ between groups. This indicates that there was no bias in the stimulus intensities used to elicit LTP between the treatment groups, and no significant effect of memantine on baseline hippocampal synaptic transmission.

Repeated measures ANOVA on the data from the STEM experiment revealed a significant effect of exploratory behaviour on the size of the evoked responses ($F_{1,16} = 108.0$, $P < 0.001$) but no main effect of diet ($F_{1,16} = 4.37$, $P > 0.05$) and no interaction (Fig. 4). This

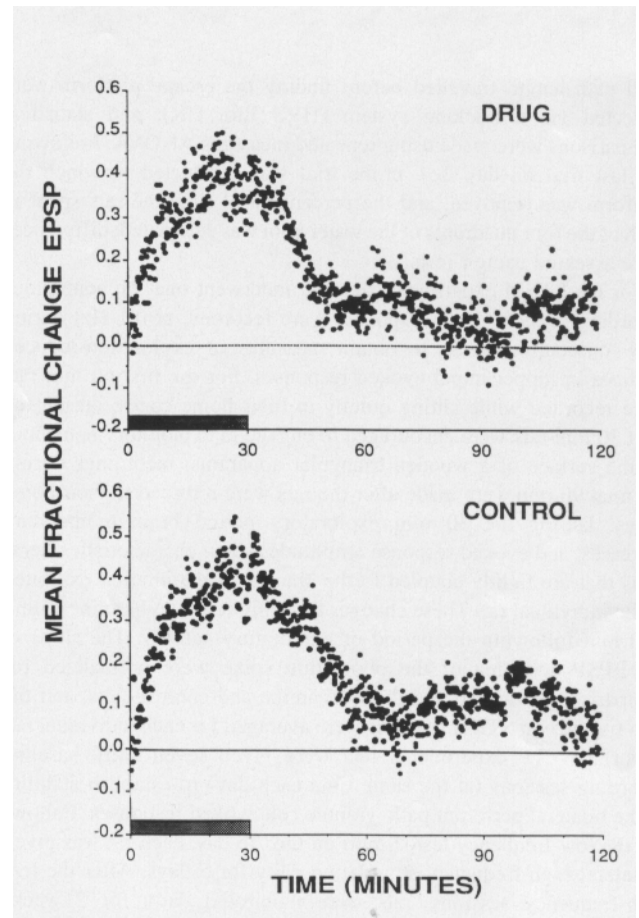


FIG. 4. Effects of memantine (30 mg/kg/day p.o.) on hippocampal short-term exploratory modulation (STEM) in awake, freely moving rats. The mean fractional change of EPSP slope, normalized to the 1 h baseline recording period collected before exploration behaviour was initiated, is plotted against time. Rats explored a triangular apparatus for 30 min. as indicated by the bar, and the EPSP grew due to activity-related brain temperature increases (see text). The rats were returned to their resting environment following this exploratory session and the responses returned towards baseline. There was no difference in the magnitude of STEM observed in the control (below) and memantine-treated groups (above).

suggests that while reliable STEM was obtained in both groups, memantine did not result in a change in exploratory behaviour or the amount of STEM observed.

As can be seen in Figure 5A and B, the responses in the hemispheres that were only given low-frequency stimulation treatment over the entire 26 day recording period remained near baseline (indicating no change) in both the control and memantine groups. This indicates that there was no significant drift of the responses across time, due to possible uncontrolled variables. Furthermore, it suggests that the changes observed in the high-frequency stimulation hemispheres were due to the stimulation treatment. Significant LTP was observed in the EPSP and population spike following the high-frequency stimulation treatment in both control and memantine groups (Fig. 5C, D). The initial magnitude of LTP induction was not found to be statistically different between memantine and control groups for either the EPSP or the population spike ($P > 0.05$). On the other hand, a comparison of the slope of the EPSP over the 14 days of decay did reveal a statistically significant difference between treatment groups ($F_{1,17} = 4.65$, $P < 0.05$), the memantine-treated rats showing prolonged maintenance of LTP. This effect was not observed in the population spike ($F_{1,17} = 0.05$; $P > 0.05$).

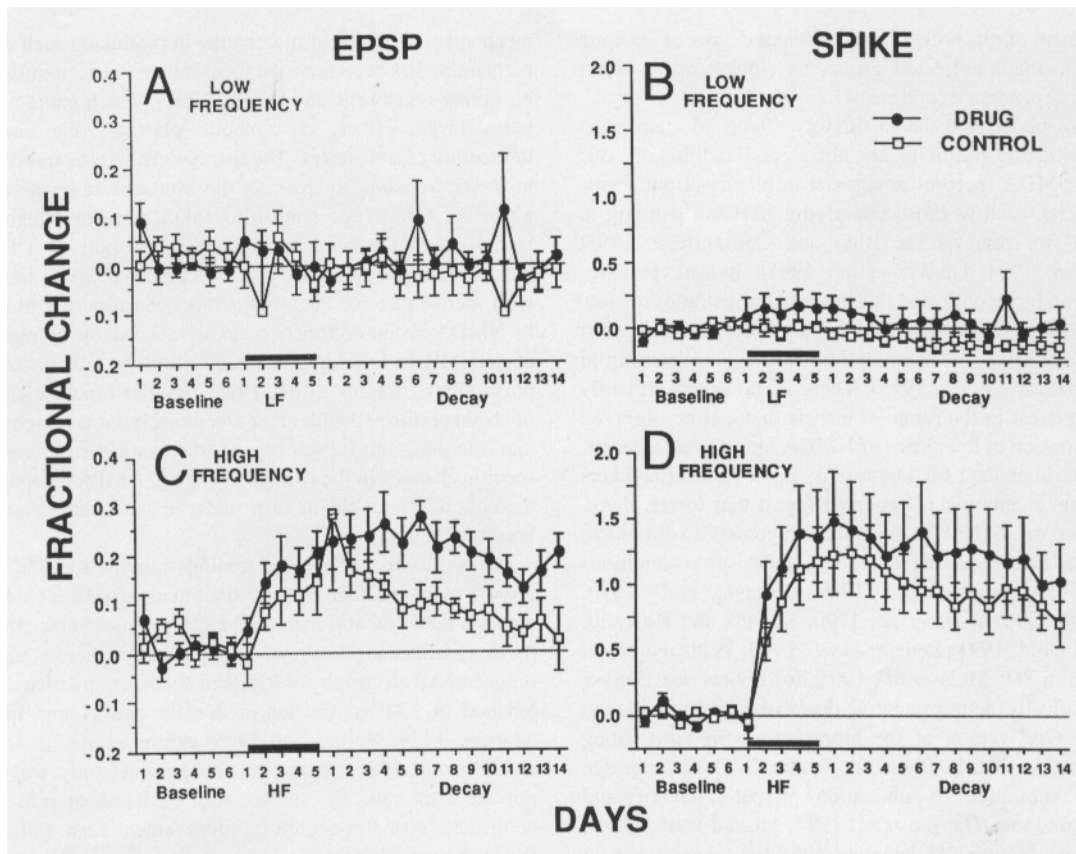


FIG. 5. Effects of memantine (30 mg/kg/day p.o.) on hippocampal long-term potentiation (LTP) in awake, freely moving rats. EPSP slope (A, C) and population spike area (B, D) were normalized relative to the 7 days before high-frequency (HF) stimulation and are plotted as mean \pm SEM against time. The EPSP (A) and population spike (B) responses for the low-frequency (LF) treated hemispheres remained stable throughout the experiment and did not differ between memantine and control groups. Both treatment groups showed LTP following five daily sessions of high-frequency stimulation (bars) in both the synaptic component, i.e. EPSP (C) and population spike (D) of the evoked responses. The memantine-treated rats, however, showed more durable LTP of the EPSP component than did the control rats.

The data from the cross-over experiment indicate that a mean reversed feeding time of 19 days cannot reverse the effects of a mean memantine pretreatment phase of 79 days. That is, the control rats in this portion of the experiment continued the tendency to show more durable EPSP enhancement (decay days 5-9, $t = 2.189$, $P < 0.05$), even after having been removed from the memantine diet and fed the control diet for an average of 19 days.

Discussion

The results of the present study indicate that semichronic treatment of rats with memantine at 30 mg/kg/day p.o. resulted in peak serum levels of 5 μM 5 h after administration, and is likely to have resulted in peak CSF levels of 2.5 μM (Komhuber and Quack, 1995). The average serum concentration over 24 h of 2.5 μM was 4-5 times higher than that measured in the serum of demented patients under semi-steady-state memantine therapy (Komhuber and Quack, 1995). Serum concentrations of 3-5 μM (CSF 1.5-2.5 μM) are likely to have been present in the memantine-treated F-344 rats at the time of behavioural testing and electrophysiological recording.

This chronic treatment with memantine at 30 mg/kg/day had no effect on baseline synaptic transmission *per se*, but it increased the durability of synaptic enhancement at perforant path-granule cell hippocampal synapses. The population spike did not show treatment

differences; however, it is well known that this measure can vary independently of the EPSP (which is a reflection of synaptic change). Moreover, although STEM was not significantly greater in the memantine-treated rats, it is known that STEM and LTP reflect largely independent mechanisms (Moser et al., 1993; Barnes et al., 1995), the former being related to brain temperature changes that arise from behavioural activity. This suggests that memantine's effects are restricted to those involved in LTP maintenance and might further be taken to imply that this uncompetitive NMDA receptor antagonist has no effect on general behaviour or brain temperature at the chronic doses tested. Although none of the behavioural performance measures on the spatial version of the Morris water task were significantly different between groups, there was a strong tendency for memantine-treated rats to show more selective spatial search patterns in the training quadrant of the water pool during the final probe trial. If, in fact, the main effect of memantine is on the persistence of LTP then it might be predicted that the largest behavioural effect should be detected at retention intervals in the range of several days or a week. We did not perform such long-term retention tests in the present study; however, it may be worthwhile to pursue this behavioural question in the future with a retention experiment and somewhat lower memantine concentrations, i.e. 1 μM steady state via osmotic minipumps. These effects of memantine on LTP, and to a lesser degree on memory in the Morris water maze, are unlikely to be due

to random assignment of rats with a better inherent degree of synaptic plasticity to the memantine-treated group, as similar results were obtained in two independent experiments.

The mechanisms underlying the facilitatory effects of memantine on hippocampal synaptic plasticity are not clear. Traditionally one would expect an NMDA receptor antagonist to block various forms of synaptic plasticity, such as those underlying LTP and learning in the Morris maze (for reviews see Bliss and Collingridge, 1993; Danysz and Archer, 1994; Danysz et al., 1995). Indeed, previous data from our laboratory confirmed that acute administration of low doses of the high-affinity, uncompetitive NMDA receptor antagonist MK-801 does, as expected, block synaptic plasticity and learning in the same models (Barnes et al., 1995). There is, however, presently a renaissance of interest in the range of effects that can be observed following administration of low doses of NMDA receptor antagonists, this being particularly evident for low-affinity open-channel blockers such as memantine. A number of reports suggest that lower, therapeutically relevant doses of NMDA receptor antagonists do not block, and may even paradoxically enhance learning under some conditions (Morris et al., 1986; Mondadori et al., 1989; Carnevale et al., 1990; Venable and Kelly, 1990; Ward et al., 1990; Sharma and Kulkarni, 1991; Walker and Gold, 1991; Lederer et al., 1993; Pellicano et al., 1993; White et al., 1993; Mele et al., 1994; for review see Danysz et al., 1995). Specifically, neuroprotective doses of memantine do not block LTP in the CA1 region of the hippocampus in vitro (Stieg et al., 1993; T. Frankiewicz, B. Potier, Z. Bashir, G. L. Collingridge and C. G. Parsons, submitted for publication) or spatial memory and ex vivo LTP in normal rats (Danysz et al., 1994; Misztal et al., 1996), and have also been reported to enhance synaptic transmission in hippocampal slices (Dimpfel, 1995) and improve spatial memory in rats with excitotoxic damage of the entorhinal cortex (Danysz et al., 1994; Zajackowski et al., 1996).

The lack of block of synaptic plasticity by low-affinity uncompetitive NMDA receptor antagonists such as memantine is probably related to their fast open-channel blocking kinetics and strong voltage-dependency. This property allows them, like Mg^{2+} to leave the NMDA receptor channel upon transient physiological activation by millimolar concentrations of synaptically released glutamate (Chen et al., 1992; Clements et al., 1992; Parsons et al., 1993). Possible mechanisms for the enhancement of synaptic plasticity by memantine include (i) selective effects on inhibitory mechanisms through NMDA receptor subtypes, i.e. disinhibition, and (ii) effects that lead to increases in the signal-to-noise ratio of the system (for review see Danysz et al., 1995). Such effects, however, would be expected to improve LTP induction as well as maintenance. Interestingly, in the studies of Danysz et al. (1994) and Zajackowski et al. (1996) memory-improving effects in rats with entorhinal cortex lesions first became apparent after 9 days of chronic infusion of memantine via osmotic minipumps, a treatment that resulted in stable serum concentrations of $-1 \mu M$ which are of particular therapeutic relevance with respect to the use of memantine in the treatment of dementia. Similarly, in patients with dementia syndrome, symptomatological cognitive enhancement is first seen after -2 weeks of treatment with oral memantine (Görtelmeyer et al., 1992). Finally, in the present study, reversal of the control and memantine diet over an average period of 19 days did not result in an equivalent reversal of the memantine-induced increase in LTP, indicating that long-term feeding (average of 79 days) may persistently alter the neurochemistry of the hippocampus in such a way that the changes in plasticity outlast the treatment.

Taken together, these observations may point to an additional

mechanism of action of memantine in producing such effects. Indeed, memantine has been reported to stimulate the accumulation of inositol phosphates (Osborne and Quack, 1992), which could have long-term, but delayed, effects on synaptic plasticity via interactions with intracellular Ca^{2+} stores. The therapeutic significance of such effects, however, remains unclear as the concentrations needed are much higher than those necessary for NMDA receptor antagonism and may be an artefact related to enhanced transport of $[^3H]$ inositol into inositol phosphates (Mistry et al., 1995). Chronic treatment of rats with memantine for 20 months has been reported to cause changes in NMDA receptor function, as evidenced by increased sensitivity of $[^3H]$ MK-801 binding to stimulation by glutamate, glycine and polyamines (Bresink et al., 1995). Similar biochemical studies have not been performed with other receptors, but it is tempting to speculate that the long-term presence of memantine may cause regionally specific changes in the expression of e.g. AMPA receptors or subtypes thereof, which could in turn underlie the changes observed in the present study.

In conclusion, the present findings provide the first electrophysiological evidence that chronic treatment of rats with therapeutically relevant doses of oral memantine can produce selective enhancement in the maintenance of synaptic plasticity. Age-related changes in hippocampal electrophysiology and behaviour involve defective maintenance of LTP in the fascia dentata and poorer spatial memory (Barnes, 1979; Barnes and McNaughton, 1985; de Toledo-Morrell and Morrell, 1985). Although the present study was performed in normal adult rats, the results may be taken to provide preclinical confirmation of the cognitive improvement seen with memantine in the treatment of dementia.

Acknowledgements

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Abbreviations

AMPA	(s)-a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANOVA	analysis of variance
CSF	cerebrospinal fluid
EPSP	excitatory postsynaptic potential
LTP	long-term potentiation
MK-801	(+)-5-methyl-10, 11-dihydro-SH-dibenzocyclohepten-5, 10-imine maleate
NMDA	N-methyl-D-aspartate
Q	quadrant
STEM	short-term exploratory modulation
TG	target quadrant

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