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Comparison of behavioral effects of the NMDA receptor channel blockers memantine and ketamine in rats

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Abstract

Memantine and ketamine block *N*-methyl-D-aspartate (NMDA) receptors with similar affinity and kinetics, yet their behavioral consequences differ: e.g., memantine is used to alleviate symptoms of Alzheimer's disease, whereas ketamine reproduces symptoms of schizophrenia. The two drugs exhibit different pharmacokinetics, which may play a principal role in their differential behavioral effects. To gain insight into the drugs' behavioral consequences, we treated adult male rats acutely with varying doses (0–40 mg/kg i.p.) of memantine or ketamine and assessed exploratory behavior and spatial working memory. To examine the importance of pharmacokinetics, we assessed behavior either 15 or 45 min after drug administration. Both drugs decreased ambulation, fine movements, and rearing at the beginning of the exploratory activity test; however, at the end of the test, high doses of only memantine increased ambulation and fine movements. High doses of both drugs disrupted spontaneous alternation, a measure of working memory, but high doses of only memantine elicited perseverative behavior. Surprisingly, ketamine's effects were influenced by the delay between drug administration and testing no more frequently than were memantine's. Our findings show that, regardless of test delay, memantine and ketamine evoke similar behavioral effects at lower doses, consistent with NMDA receptors being both drugs' principal site of action, but can have divergent effects at higher doses. Our results suggest that the divergence of memantine's and ketamine's behavioral consequences is likely to result from differences in mechanisms of NMDA receptor antagonism or actions at other receptors.

Keywords

pharmacokinetics; exploratory activity; working memory; perseverative behavior; Alzheimer's disease; schizophrenia

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6. DISCLOSURE STATEMENT

The authors have no actual or potential conflict of interest with the information reported here.

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1. INTRODUCTION

Although *N*-methyl-D-aspartate (NMDA) receptor inhibitors exhibit therapeutic potential, their clinical use often is limited by their tendency to produce unacceptable side effects. For instance, the NMDA receptor channel blocker ketamine shows great promise in the treatment of both pain (Prommer, 2012) and depression (Duman and Aghajanian, 2012). However, ketamine also reproduces the positive, negative, and cognitive symptoms of schizophrenia in healthy humans, and exacerbates symptoms in schizophrenics (Krystal *et al.*, 2003, Lahti *et al.*, 2001); as a result, ketamine has been critical in furthering understanding of the pathology of schizophrenia and is widely used to generate animal models of schizophrenia (Greene, 2001, Gunduz-Bruce, 2009, Jentsch and Roth, 1999). The channel blocker memantine, which inhibits NMDA receptor activity with affinity and kinetics similar to those of ketamine (Kotermanski and Johnson, 2009, Mealing *et al.*, 1999, Parsons *et al.*, 1995), is far less prone to induce the psychotomimetic side-effects of ketamine and other NMDA receptor channel blockers. Furthermore, memantine, but not ketamine, has been approved by the Food and Drug Administration to treat moderate-to-severe Alzheimer's disease (Parsons *et al.*, 2007). Improved understanding of the bases of these drugs' differential effects could shed light on mechanisms of Alzheimer's disease therapy and the etiology of schizophrenia.

Subanaesthetic doses (100 mg/kg) of ketamine were reported to increase rats' locomotor activity and stereotypic behavior, decrease rearing and lever-pressing for food, and impair attention and spatial and non-spatial memory (Alessandri *et al.*, 1989, Danysz *et al.*, 1994, Dix *et al.*, 2010, Grant *et al.*, 1996, Hetzler and Wautlet, 1985, Koros *et al.*, 2007, Smith *et al.*, 2011, Verma and Moghaddam, 1996). Similar, although generally less pronounced, effects were observed with memantine (Creeley *et al.*, 2006, Danysz *et al.*, 1994, Dix *et al.*, 2010, Gilmour *et al.*, 2009, Grant *et al.*, 1996, Koros *et al.*, 2007, More *et al.*, 2008, Smith *et al.*, 2011). Unlike ketamine, however, low doses of memantine were found by some groups to exert beneficial effects on memory function (Danysz and Parsons, 2003, Wise and Lichtman, 2007, Yuede *et al.*, 2007, Zoladz *et al.*, 2006).

The differential behavioral effects of memantine and ketamine could arise from at least three mechanistic differences between the drugs: differences in pharmacokinetics, differences in actions at targets other than NMDA receptors, or differences in mechanism of inhibition of NMDA receptors (Danysz *et al.*, 1994, Gilmour *et al.*, 2009, Grant *et al.*, 1996, Johnson and Kotermanski, 2006, Jones *et al.*, 2001, Kotermanski *et al.*, 2009, Rogawski and Wenk, 2003). One goal of the current study was to examine the hypothesis that the pharmacokinetic differences between the drugs may explain differences in their behavioral effects. Reported pharmacokinetic differences between memantine and ketamine, which are likely to have multiple causes, including differences in drug metabolism and lipid solubility (Beconi *et al.*, 2011, Cohen *et al.*, 1973, Cohen and Trevor, 1974, White *et al.*, 1982), are substantial. After intraperitoneal (i.p.) administration in rats, memantine peak plasma concentration is reached within 30–60 min, and half-life is ~120 min (Hesselink *et al.*, 1999b, Zoladz *et al.*, 2006); the time course in brain is similar or moderately slower (Hesselink *et al.*, 1999a, Spanagel *et al.*, 1994). We could not find time course data on ketamine after i.p. administration in rats; however, after intravenous administration, peak plasma concentration is reached immediately, and half-life is ~10 min; the time course in brain is very similar (Cohen *et al.*, 1973, Marietta *et al.*, 1976, White *et al.*, 1976). After intramuscular administration, peak plasma concentration is observed within 5–20 min, and half-life is ~30 min (White *et al.*, 1976, Williams *et al.*, 2004). Because ketamine has much faster pharmacokinetics than memantine, the two drugs may inhibit NMDA receptors with different time courses (Jones *et al.*, 2001), which, in turn, may contribute to differential behavioral consequences of the two drugs (Gilmour *et al.*, 2009, Johnson and Kotermanski, 2006).

In previous studies on memantine and ketamine, behavioral testing was conducted at only one time point after drug administration (Danyasz *et al.*, 1994, Gilmour *et al.*, 2009, Koros *et al.*, 2007). Here we compared directly the behavioral effects of memantine and ketamine using two different delays after drug administration chosen to accentuate any differential effects that may result from the drugs' differences in pharmacokinetics. We found that the behavioral consequences of low doses of memantine and ketamine are similar regardless of delay. At higher doses, some divergent effects emerged; however, they too were largely delay-independent. Our findings suggest that the drugs' differential pharmacokinetics do not lead to differences in behavioral outcome.

2. MATERIAL AND METHODS

2.1 Animals

Protocols were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. Adult male Sprague-Dawley rats (Hilltop Labs, Scottsdale, PA, USA), weighing 250–275 g at the beginning of the study, were single-housed and given free access to standard rat chow and tap water. The housing facility was maintained on a 12/12 hr light-dark cycle (lights on 0700), with a temperature of $22\pm1^{\circ}\text{C}$ and a humidity level of $45\pm5\%$.

2.2 Drugs and Drug Administration

Memantine hydrochloride (Fisher Scientific, Pittsburgh, USA) and ketamine hydrochloride (racemic mixture of R(–) and S(+) enantiomers; Sigma-Aldrich Co., St. Louis, USA) were dissolved in sterile physiological saline (0.9% NaCl) and administered i.p. at a volume of 2 ml/kg.

2.3 Experimental Procedures

All handling and testing was performed in the Rodent Behavior Analysis Core of the University of Pittsburgh Health Sciences. Testing was conducted during the light phase of the light-dark cycle. Rats were handled daily for 3 days and then assigned to one of 10 drug conditions: memantine vehicle (0.9% NaCl); one of 4 doses of memantine (5, 10, 20, or 40 mg/kg); ketamine vehicle (0.9% NaCl); or one of 4 doses of ketamine (5, 10, 20, or 40 mg/kg). Rats also were assigned to one of two delays between drug administration and testing: 15 min (i.e., when ketamine concentration is near its peak whereas memantine concentration still is rising) or 45 min (i.e., when memantine concentration is near its peak whereas ketamine concentration already has declined substantially). For a given rat, drug condition and test delay were fixed throughout the study. Rats were examined first with the exploratory activity test and 8 days later with the spontaneous alternation task. The experimenter was blind to drug condition until completion of the study.

2.3.1 Exploratory Activity Test—Rats were injected with drug in a room separate from the housing and testing rooms and returned to their holding cages until testing. Testing began when rats were placed in the center of a test arena (43 cm $\times$ 43 cm $\times$ 30 cm; Med-Associates Inc., St. Albans, VT) and allowed to explore the arena freely for 30 min. Rats were tested individually and had no prior exposure to the arena. Horizontal and vertical movements were monitored with infrared light beams and detectors, spaced 2.5 cm apart, located horizontally at two different levels along the walls of the arena. Ambient illumination was ~ 10 lux. Beam interruptions were analyzed with Med-Associates software for ambulation, rearing, and fine movements. “Fine movements” were spatially restricted movements that included behaviors such as grooming, sniffing, or scratching, and were defined operationally as repeated interceptions of adjacent infrared light beams in the absence of evidence for ambulation or rearing.

2.3.2 Spontaneous Alternation Task—Rats were injected with drug and returned to their holding cages as described above. The test apparatus was a plus-shaped maze fitted with walls along the sides and at the end of each of the 4 arms (arm dimensions: 48 cm × 10 cm × 20 cm) (Lafayette Instruments, Lafayette, IN). Testing began when rats were placed in the center of the maze and allowed to explore the maze freely for 15 min. Rats were tested individually and had no prior exposure to the maze. Arm entries (order and frequency) were monitored and analyzed using an overhead digital camera and tracking software (Actimetrics/Coulbourn Instruments, Whitehall, PA). Ambient illumination was ~30 lux. An alternation was defined as an entry into four different arms during five consecutive arm entries. Percent alternation was calculated as: $100 * (\text{total number of alternations made by a rat}) / (\text{total number of possible alternations (i.e., total number of overlapping quintuplets)})$ (Ragozzino *et al.*, 1996). Perseveration was defined as a repeat entry into the same arm after only one an alternate arm entry. Percent perseveration was calculated as: $100 * (\text{total number of perseverations made by a rat}) / (\text{total number of possible perseverations (i.e., total number of overlapping triplets)})$.

2.4 Statistical Analysis

We evaluated separately for each drug (memantine, ketamine) the effect of dose (saline vs. 5, 10, 20, or 40 mg/kg) and test delay (15-min, 45-min) using two-way analyses of variance (ANOVAs), with dose and delay as between-subject factors, followed by *post-hoc* Bonferroni tests. To avoid confounds from differences between saline-treated controls at the two test delays, we subtracted at each test delay the mean value of the saline group from each animal's score before carrying out two-way ANOVAs. To compare the effects of memantine and of ketamine with one another, we first determined whether results for saline groups tested with the same delay (i.e., saline controls for memantine and saline controls for ketamine) could be pooled. Student's *t*-tests for independent groups revealed no significant differences between saline controls tested at the same delay for any of the behavioral measures. We therefore pooled the data from saline controls tested at the same delay, calculated difference scores by subtracting the mean value of the pooled saline controls from each drug-treated animal's score, and conducted two-way ANOVAs (factors: drug, dose) followed by *post-hoc* Bonferroni tests. For all analyses, the significance level was set to p 0.05.

3. RESULTS

3.1 Effects of Memantine in the Exploratory Activity Test and the Spontaneous Alternation Task

Activity patterns of rats treated with saline (open symbols) or memantine (filled/half-filled symbols) are shown for the entire 30-min test period in Supplementary Figure 1. As is typical for rats when placed into a novel environment (Creeley *et al.*, 2006, Danysz *et al.*, 1994, Suto *et al.*, 2001), saline-treated control rats were very active at the beginning of the test period. As time in and familiarity with the test environment increased, the activity levels of saline controls declined and arrived at markedly lower levels by the end of the 30-min test period. To assess the effect of memantine on behavior under each of these two conditions, we analyzed activity during the first and last 5 min of the test period separately (Fig. 1). A two-way ANOVA of ambulatory distances during the first 5 min indicated significant effects of dose ($F_{4,72}=20.59$, $p<0.001$) and test delay ($F_{1,72}=10.28$, $p=0.002$), without a significant dose x delay interaction. Post-hoc comparisons showed that each of the doses of memantine examined here caused a significant reduction in ambulatory distance ($p<0.001$, Fig. 1a), and, as shown by the main effect of delay, this effect of memantine was greater with the 15-min than the 45-min delay. Analysis of ambulatory distances during the last 5 min likewise indicated a significant effect of dose ($F_{4,72}=9.12$, $p<0.001$), but neither the

effect of delay nor the interaction was significant. In contrast to its effect during the first 5 min, memantine caused an *increase* in ambulatory distance, relative to saline controls, during the last 5 min of the test, and post-hoc comparisons revealed that this effect was significant at the highest dose (40 mg/kg, $p=0.001$; Fig. 1b).

Analysis of fine movements during the first 5 min of the test indicated significant effects of dose ($F_{4,72}=23.22$, $p<0.001$) and delay ($F_{1,72}=13.79$, $p<0.001$), but no dose x delay interaction. Post-hoc comparisons showed that fine movements were reduced significantly after each of the memantine doses tested (5 mg/kg, $p=0.002$; all higher doses, $p<0.001$; Fig. 1c), an effect that was overall more pronounced when the rats were tested with the 15-min delay. Similar to what was observed with ambulatory distance, a dose effect also was detected during the last 5 min of the test ($F_{4,72}=10.17$, $p<0.001$), due to a significant increase, relative to saline controls, in fine movements after the highest dose of memantine (40 mg/kg, $p=0.001$; Fig. 1d). Neither the effect of delay nor the dose x delay interaction was significant.

Different from its effect on ambulatory distance and fine movements, memantine caused a decrease in rearing throughout the observation period, and the effect was comparable across both test delays. Statistical analysis of rearing during both the first and the last 5 min revealed a significant effect of dose ($F_{4,72}=55.81$, $p<0.001$ and $F_{4,72}=23.61$, $p<0.001$, respectively), but no effect of delay or a dose x delay interaction. Post-hoc comparisons showed that rearing was markedly reduced from saline control levels at each of the doses examined at both delays ($p<0.001$; Fig. 1e and 1f, respectively).

To obtain a measure of memantine's effect on spatial working memory, we monitored rats' sequences of arm entries on a four-arm maze (Ragozzino *et al.*, 1996). Analysis of alternation behavior indicated a significant effect of dose ($F_{4,72}=18.73$, $p<0.001$), but neither the delay effect nor the dose x delay interaction was significant. Post-hoc comparisons revealed that memantine caused a significant reduction in spontaneous alternations after treatment with either 20 mg/kg or 40 mg/kg of memantine ($p<0.001$; Fig. 1g). To determine whether memantine treatment affected alternation behavior from the beginning of the test, before any proactive interference could have contributed to poor performance, we determined for each rat the number of arm entries required to achieve the first complete spontaneous alternation. Analysis of this measure revealed a significant effect of dose ($F_{4,72}=5.15$, $p=0.001$) but no effect of delay and no dose x delay interaction. Post-hoc comparisons indicated that rats treated with either of the two highest doses entered significantly more arms before achieving the first complete spontaneous alternation than did saline controls (saline: 6.1 ± 0.5 entries vs. 20 mg/kg: 10.8 ± 1.5 entries, $p=0.031$; saline vs. 40 mg/kg: 10.9 ± 1.7 entries, $p=0.021$). The finding that the same doses of memantine that reduced alternation behavior, as determined for the entire test period, also were associated with a greater number of arm entries required for the first complete spontaneous alternation suggests that proactive interference contributed little, if any, to impaired alternation behavior at higher drug doses. Analysis of the total number of arm entries indicated no significant dose effect, but the effect of delay and the dose x delay interaction both were significant ($F_{1,72}=8.39$, $p=0.005$ and $F_{4,72}=4.41$, $p=0.003$, respectively). Post-hoc comparisons revealed that only at the 15-min delay did memantine affect number of arm entries, causing a significant reduction from saline control levels after the highest dose (saline: 49 ± 4 entries vs. 40 mg/kg: 21 ± 5 entries, $p=0.015$). Because the pattern of effects on number of arm entries and on spontaneous alternation differed from one another, it is unlikely that the reduction in spontaneous alternation resulted from drug effects on number of arm entries.

While analyzing the pattern of arm entries, we noticed that some rats exhibited distinctly repetitive behavior, visiting pairs of arms of the maze in a perseverative manner. We

therefore quantified this behavior (see Materials and Methods). Statistical analyses revealed a significant effect of dose ($F_{4,72}=13.39$, $p<0.001$) and a significant dose x delay interaction ($F_{4,72}=2.56$, $p=0.046$). Post-hoc comparisons showed that at the 15-min delay, rats treated with 20 mg/kg of memantine exhibited significantly more perseverative behavior than saline controls ($p=0.003$; Fig. 1h), whereas at the 45-min delay, rats treated with either 20 mg/kg or 40 mg/kg exhibited increased perseverative behavior relative to saline controls ($p=0.002$ and $p=0.001$, respectively). The increase in perseverative behavior after the highest dose was significantly more pronounced after the longer, 45-min test delay than the 15-min test delay ($p<0.001$; Fig. 1h).

3.2 Effects of Ketamine in the Exploratory Activity Test and the Spontaneous Alternation Task

Activity patterns of rats treated with saline (open symbols) or ketamine (filled/half-filled symbols) are shown for the entire 30-min test period in Supplementary Figure 2. As was the case for memantine, we analyzed activity after ketamine treatment during the first and last 5 min of the test period separately (Fig. 2). Analysis of ambulatory distance during the first 5 min of the test indicated a significant effect of dose ($F_{4,72}=14.47$, $p<0.001$) but neither the effect of delay nor the dose x delay interaction was significant. Post-hoc comparisons showed that ambulatory distance was reduced significantly, relative to saline controls, after each of the three highest doses of ketamine (10 mg/kg, $p=0.003$; 20 mg/kg and 40 mg/kg, both $p<0.001$; Fig. 2a). Different from memantine, ketamine did not evoke hyperlocomotion during the last 5 min of the test but continued to exert a suppressive effect on ambulatory activity. Analysis of ambulatory distance during the last 5 min revealed a significant effect of dose ($F_{4,72}=3.69$, $p=0.009$) and delay ($F_{1,72}=4.18$, $p=0.045$), but no dose x delay interaction. Post-hoc comparisons showed that ambulatory distance at the end of the test was reduced significantly from saline control levels after the two highest doses of ketamine (20 mg/kg, $p=0.009$; 40 mg/kg, $p=0.037$; Fig. 2b), and the reducing effect of ketamine on ambulation was more pronounced after the 15-min than the 45-min delay.

Analysis of the effect of ketamine on fine movements during the first 5 min of the test indicated a significant effect of dose ($F_{4,72}=27.19$, $p<0.001$) and a significant dose x delay interaction ($F_{4,72}=2.85$, $p=0.03$), but the delay effect was not significant. Post-hoc comparisons showed that ketamine caused a reduction in fine movements from saline control levels after each of the three highest doses at the 15-min delay (10 mg/kg, $p=0.015$; 20 mg/kg and 40 mg/kg, both $p<0.001$), and after either of the two highest doses at the 45-min delay (20 mg/kg, $p=0.006$; 40 mg/kg, $p<0.001$; Fig. 2c). The reduction in fine movements was significantly more pronounced with the 15-min compared to the 45-min delay after 20 mg/kg of ketamine ($p=0.005$; Fig. 2c). Similar to its effect on ambulatory activity, ketamine continued to cause a reduction in fine movements for the entire test duration, and analysis revealed a significant effect of dose ($F_{4,72}=8.65$, $p<0.001$), but neither the delay effect nor the dose x delay interaction was significant. Post-hoc comparisons indicated that the suppressive effect of ketamine on fine movements persisted after the two highest doses (20 mg/kg, $p=0.002$; 40 mg/kg, $p<0.001$; Fig. 2d).

Ketamine also caused a long-lasting decrease on rearing. Analysis of rearing during the first 5 min and the last 5 min of the test indicated a significant effect of dose (first 5 min: $F_{4,72}=37.17$; last 5 min: $F_{4,72}=17.50$, both $p<0.001$), without an effect of delay or a dose x delay interaction during either the first or the last 5 min of the test. Post-hoc comparisons indicated that rearing activity during the first 5 min of the test was significantly lower than that of saline controls after each of the three highest doses (10–40 mg/kg, $p<0.001$; Fig. 2e), and rearing activity during the last 5 min was significantly reduced from saline control levels after both of the two highest doses (20 mg/kg and 40 mg/kg, both $p<0.001$; Fig. 2f).

Ketamine had overall little effect on behavior in the spontaneous alternation task. Analysis of alternation behavior indicated a significant effect of dose only ($F_{4,72}=7.82$, $p<0.001$), and post-hoc comparisons revealed a significant reduction in spontaneous alternation only after the highest doses of ketamine (40 mg/kg, $p=0.001$, Fig. 2g). To determine whether the effect of ketamine on spontaneous alternation was evident already at the beginning of the test, when proactive interference from previous entries was absent or low, we compared between groups the number of arm entries required to achieve the first complete spontaneous alternation. Analysis of this measure indicated a significant effect of dose ($F_{4,72}=2.94$, $p=0.026$), but neither the effect of delay or the dose x delay interaction were significant. Post-hoc comparisons of the dose effect indicated that none of the ketamine-treated groups differed significantly from saline controls (5.6 ± 0.4 entries). It therefore is possible that the overall lower level of spontaneous alternation after the highest dose of ketamine stems in part from relatively greater proactive interference of working memory in this drug condition. Analysis of total number of arm entries indicated a significant effect of dose ($F_{4,72}=7.39$, $p<0.001$) and delay ($F_{1,72}=5.93$, $p=0.017$), but no dose x delay interaction. Post-hoc comparisons revealed that different from its mild effect on alternation, ketamine caused a reduction in number of arm entries after both of the two highest doses (saline: 49 ± 2 entries vs. 20 mg/kg: 34 ± 4 entries, $p=0.001$, and vs. 40 mg/kg: 33 ± 4 entries, $p<0.01$), and the reducing effect on number of arm entries was overall more pronounced with the longer than the shorter delay. The difference in the pattern of effects on number of arm entries and spontaneous alternation suggests that it is unlikely that the reduction in spontaneous alternation resulted from drug effects on number of arm entries. Ketamine had no significant effect on perseverative behavior (Fig. 2h).

3.3 Comparison of Memantine vs. Ketamine Effects in the Exploratory Activity Test

We compared the effects of memantine and ketamine using difference scores as described in the Materials and Methods. During the first 5 min of the test, the main effect of drug on ambulatory distance was significant with the 15-min delay, as a result of a relatively greater reduction in ambulatory distance after memantine treatment ($F_{1,56}=4.25$, $p=0.044$; Fig. 3a). The differences in trends at the 45-min delay failed to reach statistical significance (Fig. 3b). During the last 5 min of the test, that effect of drug was significant at both delays (15-min: $F_{1,56}=12.71$, $p=0.001$; 45-min: $F_{1,56}=4.12$, $p=0.047$), as was the drug x dose interaction (15-min: $F_{3,56}=6.71$, $p=0.001$; 45-min delay: $F_{3,56}=4.17$, $p=0.010$). Post-hoc comparisons indicated that the difference between the two drugs was significant at the two highest doses with the 15-min delay (20 mg/kg, $p=0.002$; 40 mg/kg, $p<0.001$; Fig. 3c) and at the highest dose with the 45-min delay ($p=0.001$; Fig. 3d).

Different from ambulatory activity, we found no effect of drug on the reduction in fine movements during the first 5 min of the test with either test delay (Fig. 4a,b, respectively). However, with the 45-min delay, a significant drug x dose interaction emerged ($F_{3,56}=5.34$, $p=0.003$), due to a greater reduction in fine movements after memantine treatment at the intermediate dose of 10 mg/kg ($p=0.012$) but a greater reduction after ketamine treatment at the highest dose we examined (40 mg/kg; $p=0.011$; Fig. 4b). During the last 5 min of the test, the effect of drug was significant at both delays (15-min: $F_{1,56}=20.80$, $p<0.001$; 45-min: $F_{1,56}=7.67$, $p<0.008$). The drug x dose interaction also was significant at both test delays (15-min: $F_{3,56}=12.88$, $p<0.001$; 45-min: $F_{3,56}=7.15$, $p<0.001$), due to significantly higher levels of fine movements after memantine compared to ketamine treatment after each of the two highest doses with the 15-min delay (both $p<0.001$; Fig. 4c) and after the highest dose with the 45-min delay ($p<0.001$; Fig. 4d).

Comparisons of the drugs' effects on rearing suggest a left-shift of memantine's dose-response curve relative to ketamine's both early and late during the test and irrespective of test delay. During the first 5 min of the test, the effect of drug was significant at both delays

(15-min: $F_{1,56}=9.92$, $p=0.003$, Fig. 5a; 45-min: $F_{1,56}=19.25$, $p<0.001$, Fig. 5b), with rearing levels being lower after memantine compared to ketamine treatment. At the 45-min delay, the drug $\times$ dose interaction also was significant ($F_{3,56}=3.64$, $p=0.018$), as a result of a significant difference between the drugs at each of the three lowest doses (5 mg/kg and 10 mg/kg, both $p=0.002$; 20 mg/kg, $p=0.006$; Fig. 5b). During the last 5 min, the effect of drug was significant with both delays (15-min: $F_{1,56}=10.25$, $p=0.002$; 45-min: $F_{1,56}=10.35$, $p=0.002$), and the drug $\times$ dose interaction also was significant at both delays (15-min: $F_{3,56}=8.25$, $p<0.001$; 45-min: $F_{3,56}=3.14$, $p=0.032$). The magnitude of the drug-induced reduction in rearing was greater after memantine compared to ketamine treatment at both of the two lowest doses with the 15-min delay (5 mg/kg, $p=0.001$; 10 mg/kg, $p<0.001$; Fig. 5c) and at the two intermediate doses with the 45-min delay (10 mg/kg, $p=0.002$; 20 mg/kg, $p=0.009$; Fig. 5d).

3.4 Comparison of Memantine vs. Ketamine Effects in the Spontaneous Alternation Task

We found no main effect of drug on the reduction in spontaneous alternation with the 15-min test delay (Fig. 6a), whereas with the 45-min delay, the effect of drug was nearly significant ($F_{1,56}=3.93$, $p=0.052$), with the reduction being overall more pronounced after memantine compared to ketamine treatment (Fig. 6b). There also was no effect of drug on perseverative behavior at the 15-min delay (Fig. 6c). However, at the 45-min delay, the effect of drug was significant ($F_{1,56}=20.16$, $p<0.001$), as was the drug $\times$ dose interaction ($F_{3,56}=6.04$, $p=0.001$), with markedly higher levels of perseverative behavior after memantine compared to ketamine treatment at both of the two highest doses (20 mg/kg and 40 mg/kg, both $p<0.001$; Fig. 6d).

4. DISCUSSION AND CONCLUSIONS

Both memantine and ketamine caused a dose-dependent reduction in ambulatory distance, fine movements, and rearing at the beginning of the exploratory activity test, when the test environment was novel and evoked a high level of exploratory activity by control rats (Figs. 1–2). At the end of the exploratory activity test, when the test environment was familiar, the reduction in motor behaviors was less pronounced and high doses (≥ 20 mg/kg) of memantine, but not of ketamine, caused increases in some of the motor behaviors. Importantly, memantine and ketamine had opposite effects on exploratory activity only at relatively high doses (>10 mg/kg; Figs. 3–4).

Our observations of reductions in ambulatory activity and fine movements differ from findings that ketamine and/or memantine increase ambulatory activity (Creeley *et al.*, 2006, Danysz *et al.*, 1994, Gilmour *et al.*, 2009, Hetzler and Wautlet, 1985, Koros *et al.*, 2007) and stereotypic behavior (Danysz *et al.*, 1994, Koros *et al.*, 2007), a variable similar to our measure of fine movements. However, the previously-reported increases in motor behavior generally were observed only at higher doses (≥ 50 mg/kg) of ketamine than used here and/or after rats had been habituated to the test environment (Danysz *et al.*, 1994, Hetzler and Wautlet, 1985, Koros *et al.*, 2007). The increase in ambulatory distance and fine movements we observed at high memantine doses during the last 5 min of the test is consistent with the possibility that these drugs stimulate motor behavior only at higher doses and when animals are familiar with the test environment (see also (Creeley *et al.*, 2006)). The difference in drug effect between the first and last 5 min of the test likely resulted from changes in animals' familiarity with the test environment rather than time since drug administration: the time since drug administration was greater during the first 5 min after the 45-min delay than during the last 5 min of the test after the 15-min delay. Nevertheless, at both test delays, ambulatory activity and fine movements were reduced during the first 5 min but elevated during the last 5 min. Interestingly, we did not observe an increase in ambulatory distance or fine movements after a high dose of ketamine, including during the last 5 min of the test.

These findings show that under some conditions, higher doses of ketamine produce seemingly qualitatively different effects on some types of motor behavior than do the same doses of memantine.

We found that higher doses of either drug interfered with spatial working memory as assessed by spontaneous alternation behavior (Fig. 6). These findings are consistent with some previous reports on ketamine or memantine effects on spatial working or reference memory (Alessandri *et al.*, 1989, Creeley *et al.*, 2006, More *et al.*, 2008, Verma and Moghaddam, 1996, Wise and Lichtman, 2007). However, in rodent models of degenerative diseases and aging, memantine was shown to attenuate memory deficits (Danyasz and Parsons, 2003, Yuede *et al.*, 2007). Furthermore, low doses (5–7.5 mg/kg or 0.3–0.6 mg/kg, depending on study) of memantine were found to improve spatial reference memory (Wise and Lichtman, 2007, Zoladz *et al.*, 2006), and a low dose (0.01 mg/kg) of the NMDA receptor channel blocker MK801 was found to increase spontaneous alternation (Jackson *et al.*, 2004), both in uncompromised rats. We did not detect a significant enhancement of spontaneous alternation after either memantine or ketamine, possibly because lower doses than used here are needed to observe a beneficial effect (but see (Creeley *et al.*, 2006, Smith *et al.*, 2011)).

The effects of varying the delay between drug administration and testing were weak. Previous data indicate that in plasma and brain, memantine concentration increases, whereas ketamine concentration decreases, between 15 and 45 min after administration (Cohen *et al.*, 1973, Hesselink *et al.*, 1999b, Marietta *et al.*, 1976, Spanagel *et al.*, 1994, White *et al.*, 1976, Williams *et al.*, 2004, Zoladz *et al.*, 2006). Memantine had a more pronounced effect at the longer than the shorter delay with respect to perseverative behavior only, and only at the highest dose. Surprisingly, memantine had an overall greater effect at the shorter than the longer delay with respect to two measures, ambulatory distance and fine movements during the first 5 min of the test. Ketamine produced an overall greater effect at the shorter than the longer delay with respect to ambulatory distance during the last 5 min of the test only, and produced a dose-specific greater effect at the shorter than the longer delay with respect to fine movements during the first 5 min of the test only. Thus, neither drug's behavioral effects were very sensitive to test delay, which suggests that the time dependence of drug concentration has limited influence on the behavioral effects of memantine and ketamine examined here.

In several instances, the effects of memantine at low doses were greater than those of ketamine. Although this observation was unexpected based on the slightly higher affinity of ketamine for NMDA receptors measured *in vitro* (Kotermanski and Johnson, 2009, Mealing *et al.*, 1999, Parsons *et al.*, 1995), many factors influence the relation between the dose of a drug and the concentration (and receptor occupancy) achieved in brain. It appears likely that the slightly greater low-dose effects of memantine compared to ketamine result from the relatively rapid clearance of ketamine, due at least in part to ketamine's high lipid solubility (Cohen and Trevor, 1974, White *et al.*, 1982) and rapid metabolism (Beconi *et al.*, 2011, Cohen *et al.*, 1973, Cohen and Trevor, 1974, White *et al.*, 1982). Consistent with this conclusion, cases in which a low memantine dose had greater behavioral effects than a low ketamine dose, although infrequent, were more common at the longer than at the shorter delay. Thus, differences in pharmacokinetics may result in a small left-shift in memantine's dose-response curve relative to ketamine's, especially at longer test delays.

Low doses of memantine and ketamine caused overall similar behavioral effects, consistent with the idea that NMDA receptors are the common sites of action of the drugs. However, high doses of memantine and ketamine had qualitatively different effects on some behaviors. This divergence of behavioral effect at higher doses is reminiscent of the striking differences

in the drugs' effects on humans. Explanations for the drugs' differential effects include differences in pharmacokinetics, action at non-NMDA receptor sites, and mechanism of action on NMDA receptors. We found a similar divergence in behavioral effect at the 15- and 45-min test delays, arguing against the hypothesis that differences in pharmacokinetics can explain differences in the drugs' behavioral effects. It is plausible that the divergent behavioral effects at higher drug doses resulted from actions of the two structurally distinct drugs on different, non-glutamatergic receptors. For instance, memantine acts with much higher affinity than ketamine at $\alpha 7$ nicotinic acetylcholine receptors (Aracava *et al.*, 2005, Coates and Flood, 2001, Maskell *et al.*, 2003), whereas ketamine acts with much higher affinity than memantine at D_2^{High} dopamine receptors (Seeman *et al.*, 2008, Seeman *et al.*, 2005). The potential for action of ketamine at multiple targets is heightened by use here of a racemic mixture of the R(−) and S(+) enantiomers of ketamine, consistent with most previous studies. Based on most clinical and behavioral measures, the S(+) is moderately more potent than the R(−) enantiomer (Marietta *et al.*, 1977, Pfenninger *et al.*, 2002, Ryder *et al.*, 1978, Sinner and Graf, 2008, Vollenweider *et al.*, 1997); the enantiomers also differ in their metabolic effects (Vollenweider *et al.*, 1997), affinity for NMDA receptors (Dravid *et al.*, 2007, Yamakura *et al.*, 2000, Zeilhofer *et al.*, 1992), and affinity for other targets (Hustveit *et al.*, 1995, Sinner and Graf, 2008). In addition, magnesium at physiological levels reduces memantine and ketamine potency at NMDA receptors, particularly at GluN2A and GluN2B subunit-containing receptors (Kotermanski and Johnson, 2009), strengthening the possible relevance of the drugs' actions at other targets. However, there is substantial evidence favoring NMDARs as the principal site of action of both drugs (Lipton, 2006, Parsons *et al.*, 2007, Rogawski and Wenk, 2003, Wenk *et al.*, 2006). The divergence of the drugs' behavioral effects at higher doses may also stem from the drugs' differences in mechanism of action at NMDA receptors. Both memantine and ketamine show selectivity for GluN2C and GluN2D subunit-containing receptors in the presence of a physiological Mg^{2+} concentration (Kotermanski and Johnson, 2009). However, differences between the drug's NMDA receptor subtype selectivity are relatively small, and therefore unlikely to explain the drug's differential behavioral effects. In contrast, memantine, but not ketamine, binds to a second, lower-affinity, superficial NMDA receptor site, resulting in partial trapping of memantine (Blanpied *et al.*, 1997, Chen and Lipton, 2005, Kotermanski *et al.*, 2009, Sobolevsky and Koshelev, 1998). As a result, at higher doses, memantine and ketamine may inhibit distinct populations of NMDA receptors (Johnson and Kotermanski, 2006), an effect that may contribute to their differential behavioral effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

In rats, low doses of memantine and ketamine have similar behavioral effects.
High doses of these drugs tend to have qualitatively different behavioral effects.
Delay between drug delivery and behavioral testing has little influence on outcome.
Divergent behavioral effects cannot be explained by differences in pharmacokinetics.

Fig. 1. Effect of memantine on ambulatory distance (a, b), fine movements (c, d), and rearing (e, f) during the first 5 min (a, c, e) and the last 5 min (b, d, f) of the 30-min exploratory activity test, and on spontaneous alternation (g) and perseverative behavior (h) in the spontaneous alternation task. Displayed are group means $\pm$ SEM for rats that received either saline (2 ml/kg, i.p.; n=9; open/diagonal-line bars) or memantine (5, 10, 20, or 40 mg/kg, i.p.; n=8 per dose; filled/cross-hatched bars). **, significant difference from saline control ($p<0.01$); ***, significant difference between test delays ($p<0.01$).

Fig. 2. Effect of ketamine on ambulatory distance (a, b), fine movements (c, d), and rearing (e, f) during the first 5 min (a, c, e) and the last 5 min (b, d, f) of the 30-min exploratory activity test, and on spontaneous alternation (g) and perseverative behavior (h) in the spontaneous alternation task. Displayed are group means $\pm$ SEM for rats that received either saline (2 ml/kg, i.p.; n=9; open/diagonal-line bars) or ketamine (5, 10, 20, or 40 mg/kg, i.p.; n=8 per dose; filled/cross-hatched bars). * or **, significant difference from saline control ($p < 0.05$ or $p < 0.01$, respectively); &&, significant difference between test delays ($p < 0.01$).

Fig. 3.

Comparison between the effect of memantine and of ketamine on ambulatory distance in the exploratory activity test. Memantine (black symbols) or ketamine (grey symbols) was administered either 15 min (a, c) or 45 min (b, d) before testing. Ambulatory distance is shown separately for the first 5 min (a, b) and the last 5 min (c, d) of the 30-min test. To facilitate comparison between the dose-response relations, difference scores from the average performance of saline controls examined at the same test delay were calculated (see Material & Methods for further details) and are displayed in here as group means $\pm$ S.E.M. of 18 (saline) or 8 (per drug dose) rats. ##, significant difference between drugs at a given dose ($p < 0.01$).

Fig. 4.

Comparison between the effect of memantine and of ketamine on fine movements in the exploratory activity test. Memantine (black symbols) or ketamine (grey symbols) was administered either 15 min (a, c) or 45 min (b, d) before testing. Frequency of fine movements is shown separately for the first 5 min (a, b) and the last 5 min (c, d) of the 30-min test period. Difference scores (see Fig. 3 legend) are displayed here as group means $\pm$ S.E.M. of 18 (saline) or 8 (per drug dose) rats. ##, significant difference between drugs at a given dose ($p < 0.01$).

Fig. 5.

Comparison between the effect of memantine and of ketamine on rearing in the exploratory activity test. Memantine (black symbols) or ketamine (grey symbols) was administered either 15 min (a, c) or 45 min (b, d) before testing. Counts of rearing is shown separately for the first 5 min (a, b) and the last 5 min (c, d) of the 30-min test period. Difference scores (see Fig. 3 legend) are displayed here as group means $\pm$ S.E.M. of 18 (saline) or 8 (per drug dose) rats. ##, significant difference between drugs at a given dose ($p < 0.01$).

Fig. 6.

Comparison between the effect of memantine and of ketamine on behavior in the spontaneous alternation task. (a, b) Spontaneous alternation; (c, d) Perseveration. Memantine (black symbols) or ketamine (grey symbols) was administered either 15 min (a, c) or 45 min (b, d) before testing. Difference scores (see Fig. 3 legend) are displayed here as group means $\pm$ S.E.M. of 18 (saline) or 8 (per drug dose) rats. ^{##}, significant difference between drugs at a given dose ($p < 0.01$, respectively).