The effects of memantine on prepulse inhibition

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Abstract

Background—Reduced prepulse inhibition (PPI) of startle provides evidence of deficient sensorimotor gating in several disorders, including schizophrenia. The role of NMDA neurotransmission in the regulation of PPI is unclear, due to cross-species differences in the effects of NMDA antagonists on PPI. Recent reports suggest that drug effects on PPI differ in subgroups of normal humans that differ in levels of baseline PPI or specific personality domains; here, we tested the effects of these variables on the sensitivity of PPI to the NMDA antagonist, memantine.

Methods—PPI was measured in male Sprague-Dawley rats, after treatment with memantine (0, 10 or 20 mg/kg, sc). Baseline PPI was then measured in 37 healthy adult men. Next, subjects were tested twice, in a double-blind crossover design, comparing either: 1) placebo vs. 20 mg of the NMDA antagonist memantine (n=19), or 2) placebo vs. 30 mg memantine (n=18). Tests included measures of acoustic startle amplitude, PPI, autonomic indices and subjective self-rating scales.

Results—Memantine had dose- and interval-dependent effects on PPI in rats: compared to vehicle, 10 mg/kg increased short-interval (10-20 ms) PPI, and 20 mg/kg decreased long-interval (120 ms) PPI. In humans, memantine caused dose-dependent effects on psychological and somatic measures: 20 mg was associated with increased ratings of happiness, and 30 mg was associated with increased ratings of dizziness. PPI at the 120 ms prepulse interval was increased by 20 mg but not 30 mg of memantine. Subgroups most sensitive to the PPI-enhancing effects of memantine were those with low baseline PPI, or with personality scale scores suggestive of high novelty seeking, high sensation seeking, or high disinhibition.

Conclusion—NMDA blockade with memantine appears to have dose- and interval-dependent effects on sensorimotor gating in rats and humans, particularly among specific subgroups of normal human subjects. These findings are discussed as they relate to consistencies across other studies in humans, as well as apparent inconsistencies in the NMDA regulation of PPI across species.

Keywords

memantine; glutamate; prepulse inhibition; schizophrenia; sensorimotor gating; startle

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Introduction

Startle can be reduced when the startling stimulus is preceded by a weak non-startling prepulse (Ison *et al.*, 1971, Graham 1975), in a process called prepulse inhibition (PPI). The degree to which the weak sensory prepulse inhibits the motor reflex in PPI is used as a measure of sensorimotor gating. PPI is disrupted in specific neuropsychiatric disorders such as schizophrenia (Braff et al. 1978, cf. Braff et al. 2001), Tourette syndrome (Castellanos et al. 1996), obsessive compulsive disorder (Swerdlow *et al.*, 1993; Hoenig *et al.*, 2005), Huntington's disease (Swerdlow *et al.*, 1995) and Fragile X Syndrome (Frankland et al. 2004).

To clarify the pathophysiology of deficient sensorimotor gating in these disorders, one strategy has been to investigate the effects of pharmacological manipulations on PPI in normal human and animal models. For example, many studies document the PPI-disruptive effects of dopamine (DA) agonists on PPI in rodents and normal humans (Mansbach et al. 1988; Hutchison & Swift 1999; cf. Swerdlow et al. 2008). Even within this apparently consistent literature, there is clear evidence of cross-species differences. For example, the DAergic regulation of PPI may involve different DA receptor subtypes in rats vs. mice (Ralph & Caine 2005). Furthermore, in normal humans, the effects of DAergic manipulations on PPI may differ across subgroups characterized by low vs. high baseline PPI levels (Swerdlow et al. 2003b, Bitsios et al. 2005), and/or distinct personality dimensions (Hutchison et al. 1999; Swerdlow et al. 2006).

Perhaps even more profound cross-species differences have been identified in the NMDA regulation of PPI. In rats, PPI is reduced by non-competitive NMDA receptor antagonists, such as dizoclipine, ketamine and phencyclidine. (Mansbach & Geyer, 1989; Mansbach *et al.*, 1991a,b; Martinez et al. 1999, 2000). However, in healthy humans, ketamine has been shown to have either an *increase* of PPI at short prepulse intervals (30 ms (Duncan *et al.*, 2001; Abel *et al.*, 2003), or have no significant effect on PPI (van Berkel et al. 1998). A similar PPI-enhancing effect was reported by Swerdlow et al. (2002) in normal subjects administered the mixed NMDA antagonist / dopamine agonist, amantadine.

To better understand the role of NMDA neurotransmission in the normal regulation of PPI in humans, we tested the effects of the low- to moderate affinity NMDA-receptor antagonist *memantine* on PPI. Memantine was chosen because it is well tolerated (compared to ketamine), has linear kinetics, 100% bioavailability after oral administration and relative NMDA-receptor selectivity (Wilcock *et al.*, 2002; Aerosa *et al.*, 2005; Cummings 2004). Memantine does not cause sensory or dissociative symptoms like those reported in past PPI studies with ketamine (Duncan et al. 2001; Abel et al. 2003), and which might potentially complicate the interpretation of changes in PPI. Wiley et al. (2002) reported that, in rats, memantine produced a dose-dependent reduction in PPI, using 100 ms prepulse intervals; initial studies here were designed to extend these studies of memantine in rats, across the range of prepulse intervals (10-120 ms) with which PPI was measured in humans. Studies next examined the effects of two doses of memantine (20 and 30 mg) on PPI in normal men. Based on several reports with DA agonists, this study also assessed the possible relationship

between baseline PPI levels, normal personality dimensions, and sensitivity to the effects of memantine on PPI.

Materials and methods

The methods used in this study were approved by the UCSD Human Subject Institutional Review Board (human studies) or were in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) and approved by the UCSD Animal Subjects Committee (protocol #S01221 (rodent studies).

Rodent pilot testing

To confirm and extend findings of PPI-disruptive effects of memantine in rats (Wiley et al, 2002), adult male SD (n = 13) rats (225-250 g; Harlan Laboratories, San Diego, CA) were housed in groups of 2-3 animals per cage, and maintained on a reversed light/dark schedule with water and food available *ad libitum*. Rats were handled within 2 d of arrival. Testing occurred during the dark phase. Memantine HCl was dissolved in saline vehicle and administered subcutaneously in doses of 0, 10 or 20 mg/kg (comparable to Wiley et al. (2002)). Startle chambers (San Diego Instruments, San Diego, CA, USA) were housed in a sound-attenuated room, and consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5×25.5 cm Plexiglas frame within a ventilated enclosure. Noise bursts were presented via a speaker mounted 24 cm above the cylinder. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced motion from within the cylinder. Stimulus delivery was controlled by the SR-LAB microcomputer and interface assembly, which also digitized (0-4095), rectified, and recorded stabilimeter readings. One hundred 1-ms readings were collected beginning at stimulus onset. Startle amplitude was defined as the average of the 100 readings.

Approximately 7 days after shipment arrival, rats were exposed to a short "matching" startle session. They were placed in the startle chambers for a 5 min acclimation period with a 70 dB(A) background noise, and then exposed to a total of 17 P-ALONE trails (40 ms - 120 dB(A) noise bursts) that were interspersed with 3 PP12dB+P-ALONE trials (P-ALONE preceded 100 ms (onset-to-onset) by a 20 ms noise burst of 12dB above background). Rats were assigned to dose groups based on average %PPI from the matching session to ensure similar baseline PPI levels between groups. Four days later, rats were injected with memantine (0, 10 or 20 mg/kg), and 30 min later were placed in the startle chambers for a 5 min acclimation period with a 70 dB(A) background noise. They were then exposed to a series of trial types which were presented in pseudorandom order: (1) P-ALONE (40 ms, 120 dB(A) noise burst); or P-ALONE preceded 10, 20, 30, 60 or 120 ms (onset-to-onset) by a 5 ms noise 15 dB over background. Interspersed between these trials were trials in which no stimulus was presented, but cage displacement was measured (NOSTIM trials). The session began and ended with 3 consecutive P-ALONE trials; between these trials were 6 presentations of each trial type, in pseudo-random order. Intertrial intervals were variable and averaged 15 s. NOSTIM trials were not included in the calculation of inter-trial intervals. Total session duration was 15.5 min.

Human Participants

A total of 40 healthy right-handed male healthy volunteers participated in the study. Females were not included in the study because PPI is sexually dimorphic and fluctuates across menstrual cycle. (Swerdlow *et al.*, 1997; Jovanovic *et al.*, 2004; Aasen *et al.*, 2005). Exclusion-criteria are outlined in Table 1.

Subjects who passed a preliminary phone checklist were invited for an in-person screening session, that included a urine toxicology test (exclusion for any recreational drug), hearing test (Saico Audiometer, Assens Denmark; excluded for threshold > 40 dB(A) at 1000 Hz) and a startle reflex test (exclusion for mean startle magnitude < 50 units). During the screening, subjects also completed several questionnaires related to ethnicity, sexual preference, smoking and caffeine consumption. Personality traits were quantified using the Tridimensional Personality Questionnaire (TPQ) (Cloninger 1991) and the Sensation Seeking Scale (SSS) (Zuckerman et al 1974).

For measures of acoustic startle and PPI, Ag/AgCl electrodes (Sensor Medics) were positioned over and lateral to the obicularis oculi underneath both eyes. A ground electrode was placed behind the left ear (R<10 kΩ). Eyeblink magnitude was measured using EMG recordings (San Diego Instruments). EMG activity was band-pass filtered (1 – 1000 Hz) and 60 Hz notch filtered, digitized, and 250 1 ms readings were recorded starting at startle stimulus onset (1.22 μV/unit). The startle test started with 3 minutes of 70 dB(A) white noise, which persisted as a background noise during the test session. During acclimation, blinks were counted by trained observers using a Radio Shack Security Camera and monitor (Inter-observer R = 0.97). The startle-session consisted of 42 trials, with six conditions: a 118 dB(A) 40 ms white noise burst (pulse alone) and the same burst preceded 10, 20, 30, 60, 120 ms by a prepulse of 16 dB above background. To measure startle habituation, three pulse alone trials were presented at the session beginning and end. The variable inter-trial interval averaged 15 s (range 10-20 s). Total test time was 15 minutes.

Participants who met study inclusion criteria returned for testing after 6-10 days, and for a second day one week later. Testing was performed double-blind and drug order was randomized. Prior to the test days, subjects were instructed to maintain their normal patterns of caffeine intake prior to the testing, based on the effects of caffeine withdrawal on PPI and subjective rating scales. (Swerdlow *et al.*, 2000). After arrival at 0830 hours on the test day, subjects were given a standardized breakfast, followed by a urine toxicology test and a hearing test. At 0900 hours, either memantine hydrochloride (20 or 30 mg) or placebo was administered. For the first 20 subjects, the active dose of memantine hydrochloride was 20 mg. For the next 20 subjects, the active dose of memantine hydrochloride was 30 mg. Heart rate was measured manually and blood pressure was measured by brachial cuff. Symptom rating scales (SRS) were assessed 30, 90, 150, 200 and 230 min after pill consumption. This SRS is a visual analog scale used to assess the physical and emotional states of the subjects during testing. Each symptom was rated on a piece of paper, using a 100 mm line to separate extreme ratings ('not true' versus 'true'). The subjects rated emotional state ("happy"), somatic symptoms ("queasy", "dizzy") and consciousness ("drowsy"). The marks were manually measured by observers who were blind to the drug condition. At 1130 hours, the

subjects received a standardized lunch. Startle testing began 210 minutes after pill administration, based on the reported pharmacokinetics of memantine in normal humans (Sonkusare *et al.*, 2005), using a test session identical to that used the screening-day. Additional psychophysiological measures were completed after this startle test, which will be analyzed separately.

The primary dependent measures for rodent and human studies were startle magnitude and PPI. PPI was defined as (100- (100 × magnitude on prepulse trial/ magnitude on pulse alone trials)). Planned comparisons utilized drug and prepulse interval as within-subject factors, with separate analyses completed for the 20 mg and 30 mg doses of memantine in humans. Additional planned comparisons in humans analyzed the impact of baseline (screening) PPI levels and specific personality measures (novelty seeking based on the total NS score from the TPQ, and sensation seeking, based on the total SSS score) on memantine PPI effects. These analyses utilized categorical factors ("low" vs. "high" based on median splits) within ANOVAs, and continuous comparisons within regression analyses. Self-rating scales and autonomic measures at baseline (prior to pill administration) and immediately prior to startle testing were treated as continuous variables and analyzed by ANOVA as "change scores" (difference from baseline). Alpha was 0.05. Additional exploratory analyses were conducted, with alpha corrected for multiple comparisons. When average startle magnitude was <10 units during testing, subjects were excluded as "non-responders"; this resulted in the exclusion of one subject in the 20 mg memantine sample and two subjects in the 30 mg memantine sample.

Results

Rodent Pilot Study

Memantine caused a dose-dependent reduction in PPI for 60-120 ms prepulse intervals, confirming findings of Wiley et al. (2002). However, at short prepulse intervals (10-20 ms), the low dose of memantine increased PPI (Figure 1), comparable to effects reported with some DA agonists (e.g. Swerdlow et al. 2001, 2002, 2004). ANOVA of %PPI revealed a significant main effect of memantine (F=4.27, df 2,10, p<0.05) and prepulse interval (F=5.08, df 4,40, p<0.03), but no significant dose × interval interaction (F=1.32, df 8,40, ns). Post-hoc comparisons confirmed an overall reduction in PPI after 20 mg memantine compared to vehicle (p<0.035). One explicit goal of this exploratory study was to examine memantine effects across the range of prepulse intervals, and a separate comparison of vehicle vs. 10 mg memantine confirmed a dose × interval interaction (F=3.66, df 4,28, p<0.02), reflecting memantine-induced increases in PPI over the 10-20 ms intervals, with the opposite effect at longer intervals (Figure 1). There were no effects of memantine on startle magnitude (F<1; Fig 1, inset) or reflex habituation (not shown).

Human Study

Subject characteristics—Human subject characteristics for the final cohorts in the 20 mg and 30 mg studies are shown in Table 2. There were no differences in age, weight, ethnicity or caffeine consumption (p > 0.10) across dose groups; one subject in the 20 mg study and two subjects in the 30 mg study were smokers.

Personality questionnaire scores are shown in Table 3. ANOVA analyses for personality questionnaire scores show no difference between samples tested with 20 mg vs. 30 mg memantine, with the exception of the TPQ-subscale 'Harm Avoidance'. The values for this personality subscale were significantly higher for 30 mg than for 20 mg cohorts (F=7.65, p<0.015). Score ranges were consistent with those published in large scale studies from other groups (Earlywine et al. 1992; Eisenberg et al. 2007) and from our own group (Swerdlow et al. 2002).

Subjective and physiological measures: An increase in self-reported level of happiness at the time of startle testing was detected after administration of 20 mg of memantine (F=4.80, df 1,18, p<0.042), but not after the 30 mg dose (F<1). This effect at 20 mg reflected part of a sustained increase in "happy" ratings, from the initial evaluation (30 min post-pill), extending to the evaluation that followed the startle test (F=5.10, df 1,18, p<0.04 for minutes 30-230 post-pill) (Figure 2A). Increased dizziness ratings were evident at the time of startle testing with 30 mg of memantine (F=7.27, df 1,17, p<0.016), but not with the 20 mg dose (F=2.58, df 1,18, ns). This effect at 30 mg reflected part of a sustained increase in "dizzy" ratings, extending from the third assessment (150 min post-pill) to the evaluation after startle testing (F= 9.23, df 1,17, p<0.008 for min 30-230 post-pill) (Figure 2B). No significant changes in self-rated queasiness or drowsiness were detected at the time of startle testing with either dose of memantine (not shown). In general, subjective ratings of memantine effects ("happy" or "dizzy") during the time of startle testing were not related to personality measures (data not shown).

Autonomic measures were not significantly changed by either dose of memantine. ANOVAs of heart rate, systolic and diastolic blood pressure immediately prior to startle testing revealed no significant effects of either 20 mg memantine (F's = 1.25, < 1 and 1.07, respectively; all ns) or 30 mg memantine (F's = 3.43, <1 and 1.72, respectively; all ns). Spontaneous blink rate immediately prior to startle testing was significantly reduced after 20 mg memantine (F=4.75, df 1,18, p<0.045), but only a weak trend towards reduced blink rate was detected after 30 mg memantine (F=1.41, df 1,17, ns).

Startle magnitude and habituation: ANOVAs revealed no significant effect of 20 or 30 mg memantine on startle magnitude (F<1, both comparisons). In each case, startle magnitude was greater for right eye than left (F=9.26, df 1,18 p<0.008 and F=19.96, df 1,17, p<0.0004 for 20 and 30 mg doses, respectively), but there were no significant interactions of dose × eye side (F<1 and F=1.37, respectively). Similarly, ANOVAs revealed no significant drug effects on reflex habituation, with significant effects of trial block for 20 and 30 mg memantine tests (F's = 41.91 and 36.28, respectively), but no significant main effects of drug dose (F<1 and F=1.20, respectively) or significant dose × block interaction (F's<1).

PPI: ANOVAs of PPI yielded different outcomes for the 20 and 30 mg doses of memantine (Figure 4A). For the 20 mg dose, ANOVA revealed no significant main effect of dose (F<1), a significant main effect of prepulse interval (F=33.62, df 4,72, p<0.0001), and a significant interaction of dose × interval (F=2.70, df 4,72, p<0.038). Post-hoc comparisons revealed significant memantine-induced increases in PPI at 120 ms prepulse intervals (p<0.025). A memantine-induced reduction in PPI at 10 ms intervals was not statistically significant

(F=1.61), and achieved only a moderate effect size (d = 0.42). For the 30 mg dose of memantine, ANOVA revealed no significant main effect of dose (F<1), a significant effect of prepulse interval (F=21.07, df 4,68, p<0.0001), and no significant dose × interval interaction (F<1). For both 20 and 30 mg doses, ANOVAs of PPI noted no significant effects of eye side (F's < 1) or significant interactions of eye side with dose or interval; as a result, eye side was not entered as a factor in subsequent ANOVAs.

As planned, we next assessed the relationship between baseline PPI and memantine-induced changes in PPI, based on previous reports of differential drug effects on PPI in low- vs. high gating individuals (Swerdlow et al. 2002, 2006; Bitsios et al. 2005; Csomor et al. 2008). Because different studies have used slightly different definitions of "baseline PPI", we examined this relationship in a number of ways. For example, Bitsios et al. (2005) distinguished "low vs. high gating" subgroups based on mean screening PPI for 80 ms prepulse intervals. Because no 80 ms interval condition was included in this study, we used a similar approach, based on the averaged screening values for 60 and 120 ms prepulse intervals. Csomor et al. (2008) stratified subjects based on vehicle-PPI levels for 60 ms prepulse intervals, while we (Swerdlow et al. 2002) had previously stratified subjects based on mean screening PPI values across 10-120 ms prepulse intervals. Importantly, all of these strategies yielded comparable outcomes with the present data; for simplicity, we will report the statistical outcomes only for analyses using the methods of Bitsios et al. (2005).

For tests with 20 mg memantine (Figure 4B), ANOVA of PPI revealed significantly higher PPI levels in "high gaters" vs. "low gaters" (reflecting the fact that screening PPI levels (4A, left) significantly predict testing PPI levels) (F=8.70, df 1,17, p<0.01), no overall main effect of drug dose (F<1), a significant interaction of drug × "gating level" (F=4.96, df 1,17, p<0.04), a significant main effect of prepulse interval (F=44.12, df 4,68, p<0.0001), and significant interactions of dose × interval (F=2.75, df 4,68, p<0.04) and "gating level" × interval (F=5.88, df 4,68, p<0.0005). Based on the interaction of drug × gating levels, separate ANOVAs were conducted in each gating subgroup, that revealed a significant interaction of drug × prepulse interval in "high gaters" (F=2.66, df 4,36, p<0.05) but not "low gaters" (F=1.14, df 4,32, ns). Inspection of the data (Figure 4B) revealed that memantine increased PPI in the "low gating" group across all intervals, but particularly at the 120 ms prepulse interval (F = 11.44, df 1,9, p<0.009), and that it tended to reduce PPI in the "high gating" group at the 10-20 ms prepulse intervals (d's = 0.75-0.77).

For tests with 30 mg memantine (Figure 4C), ANOVA of PPI confirmed higher PPI levels in "high gaters" (F=5.32, df 1,16, p<0.035), no overall main effect of drug (F<1) or interaction of drug × "gating level" (F<1), a significant effect of prepulse interval (F=23.42, df 4,64, p<0.0001), and a significant interaction of gating level × interval (F=2.91, df 4,64, p<0.03), but not gating level × interval × drug (F<1). Inspection of the data confirmed no differential impact of 30 mg memantine, across groups of low vs. high gating normal subjects.

Personality and memantine effects on PPI: As planned, based on evidence for greater drug effects on PPI associated with specific personality dimensions, we assessed the relationship between memantine effects on PPI and scores for Novelty Seeking (NS total

score from the TPQ), Sensation Seeking (SSS total score) and disinhibition (DIS subscale from the Sensation Seeking Scale) (Figure 5A-B). Importantly, these scores were inter-related: NS scores correlated significantly with SSS scores ($R = 0.64$, $p<0.004$) but not DIS scores ($R = 0.17$, ns), and total SSS scores correlated significantly with scores on its DIS subscale ($R = 0.49$, $p<0.035$) (in contrast, HA scores did not correlate significantly with any of these scales). Subgroups were formed based on median splits of NS and SSS scales and the DIS subscale. We first examined the effect described above for the inclusive group of subjects tested with 20 mg memantine: a drug-induced increase in PPI at the 120 ms prepulse interval. Separate ANOVAs demonstrated that this effect was evident in subgroups with the highest scores in novelty seeking ($F=5.54$, df 1,8, $p<0.05$), sensation seeking ($F=13.50$, df 1,9, $p<0.006$) and disinhibition ($F=7.75$, df 1,8, $p<0.025$), but not in subgroups with the lowest scores in these domains (F's = 1.40, <1 and <1, respectively). Looking beyond the 120 ms interval, DIS scores significantly predicted the overall impact of 20 mg memantine on PPI: ANOVA revealed a significant interaction of dose × DIS group ($F=12.31$, df 1,17, $p<0.003$); a separate ANOVA in the high DIS subgroup revealed PPI-enhancing effects of memantine at all prepulse intervals (main effect of dose, $F=6.90$, df 1,8, $p<0.035$), while a separate ANOVA in the low DIS group revealed significant PPI-*reducing* effects of memantine ($F=5.38$, df 1,9, $p<0.05$) that were most prominent at the short prepulse intervals (dose × interval interaction: $F=3.28$, df 4,36, $p<0.025$). As a result, DIS scores correlated significantly with the impact of memantine on PPI (calculated by the difference score (memantine minus placebo) for mean %PPI across all intervals) ($Rs = 0.63$, $p < 0.009$). Importantly, only the effects of memantine on PPI, and not baseline PPI levels per se, or post-placebo or -memantine levels of startle magnitude, differed among subgroups with low vs. high NS, SSS or DIS scores.

Similar analyses using data from the 30 mg memantine trial revealed no significant differences in memantine effects among subgroups with low vs. high scores on NS, SSS or DIS scales.

Discussion

The main aim of this study was to assess the effects memantine on PPI, psychological, and somatic measures in clinically normal men. Initial pilot data obtained in rodents confirmed previous reports of memantine's PPI-disruptive effects at longer prepulse intervals (Wiley et al. 2002), but also detected PPI-enhancing properties of memantine at short prepulse intervals, at a moderate dose of memantine, i.e. one that caused a sub-maximal disruption at long intervals. Thus, even with a cursory assessment, animal data suggested both dose- and interval-dependent effects of memantine on PPI, generally consistent with those previously observed with ketamine (Mansbach & Geyer, 1989).

In humans, we detected evidence for bioactivity of both doses of memantine at the time of startle testing: 20 mg increased ratings of happiness and reduced spontaneous blink rate, while 30 mg increased ratings of dizziness. Interestingly, these drug effects did not overlap across doses: 30 mg memantine did not change "happiness" ratings, and while 20 mg memantine may have generated some mild dizziness (Figure 2B) and 30 mg memantine may have slightly slowed spontaneous blinking (Figure 2C), neither of these effects approached

statistical significance. In fact, beyond changes in happiness and blink rate (20 mg) and dizziness (30 mg), there were no significant drug effects on drowsiness, queasiness, autonomic measures, startle magnitude or startle habituation.

These findings (and lack thereof) with subjective measures are in line with effects of memantine reported in the literature. These drug effects on happiness, blink rate (20 mg memantine) and dizziness (30 mg memantine) were detected at a time-point corresponding to peak memantine blood levels (Sonkusare *et al.*, 2005). Euphoric effects were reported after 40 mg memantine in adults with a history of methamphetamine abuse, and in patients with Alzheimer's disease (Hart *et al.* 2002; cf. Aerosa Sastre *et al.*, 2005). Dizziness is one of the most common side-effects of memantine in clinical trials (Wilcock *et al.*, 2002, cf. Kumar 2004). Changes in blink rate are often viewed as a marker of central dopaminergic tone (Karson 1983); in our experience, however, this association can be complicated by levels of drowsiness (that can increase blink rates) or alertness (that can decrease blink rates).

Generally consistent with previous reports with NMDA antagonists such as ketamine (Duncan et al. 2001; Abel et al. 2003) and amantadine (Swerdlow et al. 2002 (but see Bitsios et al. 2005)), 20 mg memantine significantly increased PPI at the 120 ms prepulse interval. In previous reports, ketamine effects on PPI were either short-lived (Duncan et al. 2001), or accompanied by reduced startle magnitude (Abel et al. 2003). Abel et al. (2003) detected these PPI-enhancing effects of ketamine at both 30 and 120 ms prepulse intervals. Notably, the temporal pattern of memantine effects on PPI in humans contrasts sharply with that detected in rats: where humans exhibit maximal PPI-enhancement (120 ms intervals), rats exhibit maximal PPI-disruption; where rats exhibit maximal PPI-enhancement (10-20 ms intervals), humans exhibit a trend towards PPI disruption.

Based on recent reports of differential drug effects on PPI between individuals with low vs. high baseline PPI levels, we conducted separate analyses of 20 mg memantine effects on PPI in low vs. high "gating" subgroups. Memantine-induced increases in PPI were evident only in subjects ranked in the lowest 50% for baseline PPI; in this group, PPI-enhancing effects were apparent across the 10-120 ms range of prepulse intervals, but remained most robust at the 120 ms interval. In contrast, among "high gating" subjects, no PPI-enhancing effects of memantine were detected, and the opposite trend - decreased PPI - was apparent at short prepulse intervals.

These patterns of PPI-enhancement only in "low gating" subjects cannot be easily ascribed to a simple "regression to the mean" of PPI levels. PPI (particularly at 60-120 ms intervals), has very high test-retest reliability, exceeding 0.80 over periods as long as one year (Cadenhead et al. 1999; Light et al. 2007). This makes it very unlikely that PPI levels would systematically fluctuate between "low" and "high" PPI levels across tests. More evidence that memantine's PPI-enhancing effects do not simply reflect an arithmetic consequence of low baseline PPI was seen when subgroups were formed based on specific personality domains. These subgroups did not differ significantly in baseline PPI, and yet PPI-enhancing effects of memantine at 120 ms prepulse intervals were detected only in subjects with the highest novelty seeking, sensation seeking or disinhibition scores.

Low vs. high gating, and low vs. high DIS, subgroups differ not only in the "direction" of memantine effects on PPI, but also in the prepulse intervals most sensitive to these effects. For example, while high DIS subjects exhibited PPI-enhancing effects of memantine across all prepulse intervals, low DIS subjects exhibited significant PPI-reducing effects of memantine only at the short prepulse intervals; a similar pattern characterized low vs. high gating subgroups, respectively. In preclinical studies, short and long PPI intervals have been shown to be differentially sensitive to drug effects; indeed, this was the case in the present pilot study: short-interval PPI was increased by 10 mg/kg memantine, while at long PPI intervals, memantine produced only dose-dependent PPI-reducing effects. Some findings suggest differential neurochemical substrates regulating drug effects on short- and long-interval PPI, e.g. a prominent role of D1-like systems in regulating short interval PPI, and D2-like systems in regulating long interval PPI (Swerdlow et al. 2004). At a psychological level, short interval PPI is linked to substrates regulating more automatic, preconscious inhibition, while long interval PPI is linked to more volitional, consciously controlled inhibition (cf. Swerdlow et al. 2008). Conceivably, individuals distinguished by low vs. high DIS scores, or high vs. low baseline PPI, might be differentially sensitive to short vs. long interval PPI effects based on intrinsic differences in both these neurochemical and/or psychological substrates.

Perhaps most striking is the fact that no significant changes in PPI were evident after 30 mg memantine, regardless of baseline PPI levels, or scores on NS, SSS or DIS scales. Two parsimonious explanations for differences in memantine dose effects are: 1) different sample characteristics, or 2) a narrow range of dose sensitivity. Cohorts tested with 20 and 30 mg doses were recruited from the same populations, using identical inclusion / exclusion criteria, and did not differ significantly in age, ethnicity, education level, weight, caffeine use, scores for NS, SSS and DIS scales and baseline PPI levels (p's > 0.05, both across all intervals, and for the critical mean of 60 and 120 ms intervals used for median split analyses). Groups did differ significantly in startle magnitude (see Figure 3), with lower startle magnitude exhibited by the 30 mg dose group. However, both the PPI-enhancing effects of 20 mg memantine, and the lack thereof with 30 mg memantine, were independent of startle magnitude: median split analyses revealed no significant interaction of low vs. high startle magnitude and memantine dose effects with either 20 mg (F<1) or 30 mg (F<1) doses. Furthermore, startle magnitude was not related to low vs. high gating group assignment for either dose of memantine, nor did inclusion of low vs. high baseline startle magnitude as a grouping factor alter the critical main or interaction effects in these studies. Groups also differed significantly in HA scores (Table 3). However, a subgroup of subjects from the 30 mg dose group (n=12) with mean HA score (6.0 (SEM 0.88)) nearly identical to that of the 20 mg dose group (5.95 (1.25)) exhibited no significant effect of memantine dose on PPI (F<1) and no dose × interval interaction (F<1). Thus, group differences in HA scores do not appear to account for differential effects of 20 vs. 30 mg memantine on PPI.

A narrow dose range of memantine effects on PPI in humans would be consistent with the present animal data for short prepulse intervals. Here, an "inverted-U" dose effect was detected: the "low dose" (10 mg/kg) increased PPI compared to vehicle, while the "high dose" (20 mg/kg) reduced PPI compared to vehicle. Such a pattern suggests interactions among multiple substrates, either among different pharmacological effects of memantine

(e.g. DA agonist as well as NMDA antagonist properties (Seeman et al. 2008)), or multiple brain systems regulating PPI. For example, we could speculate that the ratio of DA agonist : NMDA antagonist effects of memantine differs at these two doses, such that a predominant NMDA antagonism at the low dose leads to increased PPI, and more prominent DA agonist effects of the high dose opposes these effects of NMDA blockade. It would be less speculative to suggest that the overall effect of systemically administered memantine on PPI will reflect its integrated effects on different brain substrates. Animal studies suggest that different NMDA systems have opposing effects on PPI. For example, PPI is disrupted by infusion of NMDA into the ventral hippocampus (Wan *et al.*, 1996, Zang *et al.*, 2002, Swerdlow *et al.* 2001b) and by infusion of NMDA *antagoni*sts into the basolateral amygdala (Fendt *et al.*, 2000). Thus, a narrow dose range for memantine-induced changes in PPI might reflect its simultaneous action within two or more brain systems with opposing effects on PPI.

It would be reasonable to ask whether different dose effects on PPI might relate to different effects of 20 vs. 30 mg memantine on subjective ratings in this study. Increased "happy" scores after 20, but not 30 mg memantine, suggests that the lower dose had mild hedonic effects, which might correspond to pro-DAergic properties of this drug (Seeman et al. 2008). However, PPI-enhancing effects of pro-DAergic drugs like amphetamine are generally not reported in humans, except perhaps among low-gating subgroups (Swerdlow et al. 2008). Also arguing against a pro-DAergic mechanism for PPI-enhancing effects of memantine is the fact that high novelty-seeking subjects - who are most sensitive to the PPI-enhancing effects of memantine - are also most sensitive to the PPI-*reducing* effects of DA agonists (Hutchison et al. 1999; Swerdlow et al. 2008). Thus, it would be challenging to propose a parsimonious neurochemical connection between the hedonic and PPI-enhancing effects of 20 mg memantine.

The present data also make it hard to explain reduced PPI in schizophrenia, simply on the basis of reduced NMDA neurotransmission. Rather, the present evidence - together with findings of increased PPI after ketamine and amantadine in normal comparison subjects - suggests that acute systemic blockade of NMDA does not reproduce the loss of sensorimotor gating exhibited by schizophrenia patients. If reduced NMDA neurotransmission contributes to PPI deficits in these patients, such effects might reflect regionally specific changes, or neuroadaptive responses to a chronic hypoglutamatergic state, that are not modeled in normal comparison subjects by an acute drug challenge.

In summary, bioactive doses of the NMDA antagonist, memantine, cause dose- and interval-dependent changes in PPI in rats and normal humans. In rats, 10 mg/kg memantine increases short-interval PPI, and 20 mg/kg decreases long-interval PPI. In humans, 20 mg memantine has mild hedonic effects and reduces spontaneous blink rate, and significantly increases long interval PPI. This latter effect is most evident among individuals with low baseline PPI, or with personality scale scores suggesting high novelty seeking, high sensation seeking, or high disinhibition. At 30 mg, memantine causes significant dizziness, but has no effects on PPI at any prepulse interval or in any sample subgroup. The PPI-enhancing effects of memantine are generally consistent with reports of other NMDA antagonist effects in

humans, but are distinct from the effects of memantine or other NMDA antagonists on PPI in rats.

Acknowledgments

References

Abel K, Waikar M, Pedro B, Hemsley D, Geyer M. Repeated testing of prepulse inhibition and habituation of the startle reflex: a study in healthy human controls. J Psychopharm. 1998; 12:330–337.

Abel KM, Allin MP, Hemsley DR, Geyer MA. Low doses of ketamine increases prepulse inhibition in healthy men. Neuropharmacology. 2003; 44:729–737. [PubMed: 12681371]

Areosa SA, Sherriff F, McShane R. Memantine for dementia. The cochrane database for systematic reviews. 2005 feb (4) CD 003154.pub3. 2005

Bakshi VP, Geyer MA. Multiple limbic regions mediate the disruption of prepulse inhibition produced in rats by the noncompetitive NMDA antagonist dizocilpine. J Neurosci. 1998; 18:8394–8401. [PubMed: 9763482]

Bitsios P, Giakoumaki SG, Frangou S. The effects of dopamine agonists on prepulse inhibition in healthy men depend on baseline PPI values. Psychopharmacology. 2005; 182:144–152. [PubMed: 16010540]

Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects patient groups and pharmacological studies. Psychopharmacology. 2001b; 156:234–258. [PubMed: 11549226]

Cloninger CR, Przybeck TR, Svrakic DM. The Tridimensional Personality Questionnaire: U.S. normative data. Psychol Rep. 1991; 69(3 Pt 1):1047–1057. [PubMed: 1784653]

Cummings JL. Alzheimer's Disease. N Engl J Med. 2004; 351:56–67. [PubMed: 15229308]

de Bruin NM, Ellenbroek BA, Cools AR, Coenen AM, van Luijtelaar EL. Differential effects of ketamine on gating of auditory evoked potentials and prepulse inhibition in rats. Psychopharmacology. 1999; 142:9–17. [PubMed: 10102777]

Duncan EJ, Madonick SH, Parwani A, Angrist B, Rajan R, Chakravorty S, Efferen TR, Szilagyi S, Stephanides M, Chappell PB, Gonzenbach S, Ko GN, Rotrosen JP. Clinical and sensorimotor gating effects of ketamine in normals. Neuropsychopharmacology. 2001; 25:72–83. [PubMed: 11377920]

Eisenberg DTA, Campbell B, Mackillop J, Lum JK, Wilson DS. Season of birth and dopamine receptor gene associations with impulsivity, sensation seeking and reproductive behaviors. PLoS ONE. 2007; 2:e1216. [PubMed: 18030347]

Earleywine M, Finn PR, Peterson JB, Pihl RO. Factor structure and correlates of the tridimensional personality questionnaire. J Stud Alcohol. 1992; 53:233–238. [PubMed: 1583902]

Fendt M, Schwienbacher I, Koch M. Amygdaloid N-methyl-D-aspartate and gamma-aminobutyric acid(A) receptors regulate sensorimotor gating in a dopamine-dependent way in rats. Neuroscience. 2000; 8:55–60. [PubMed: 10858611]

Graham FK. The more or less startling effects of weak prestimulation. Psychopsysiology. 1975; 12:238–248.

Hart CL, Haney M, Foltin RW, Fischman MW. Effects of the NMDA antagonist memantine on human methamphetamine discrimination. Psychopharmacology (Berl). 2002; 164:376–384. [PubMed: 12457267]

Hoenig K, Hochrein A, Quednow BB, Maier W, Wagner M. Impaired prepulse inhibition of acoustic startle in obsessive-compulsive disorder. Biol Psychiatry. 2005; 57:1153–1158. [PubMed: 15866555]

Ison JR, Hammond GR. Modification of the startle reflex in the rat by changes in auditory and visual environments. J Comp Physiol Psychol. 1971; 75:435–452. [PubMed: 5091224]

Jovanovic T, Szilagyi S, Chakravorty S, Fiallos AM, Lewison BJ, Parwani A, Schwartz MP, Gonzenbach S, Rotrosen JP, Duncan EJ. Menstrual cycle phase effects on prepulse inhibition of acoustic startle. Psychophysiology. 2004; 41:401–406. [PubMed: 15102125]

Kumar S. Memantine: pharmacological properties of clinical use. Neurol India. 2004; 52:307–309. [PubMed: 15472417]

Kumari V, Gray JA, Geyer MA, ffytche D, Mitterschiffthalaer MT, Vythelingum GN, Williams SCR, Simmons A, Shatma T. Neural correlates of prepulse inhibition in normal in schizophrenic subjects: a functional MRI study. Psychiatry Res Neuroimmag. 2003; 122:99–113.

Mansbach RS, Geyer MA. Parametric determinants in pre-stimulus modification of acoustic startle: interaction with ketamine. Psychopharmacology. 1991a; 105:162–168. [PubMed: 1796122]

Mansbach RS, Geyer MA. Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. Neuropsychopharmacology. 1991b; 2:229–308.

Seeman P, Caruso C, Lasaga M. Memantine agonist action at dopamine D2High receptors. Synapse. 2008; 62:149–153. [PubMed: 18000814]

Sonkusare SK, Kau CL, Ramarao P. Dementia of Alzheimer's disease and other neurodegenerative disorders- memantine, a new hope. Pharmacological Research. 2005; 52:1–17. [PubMed: 15911328]

Swerdlow NR, Bakshi V, Waikar M, Taaid N, Geyer MA. Seroquel, clozapine and chlorpromazine restore sensorimotor gating in ketamine-treated rats. Psychopharm. 1998; 140:75–80.

Swerdlow NR, Eastvold A, Uyan KM, Ploum Y, Cadenhead K. Matching strategies for drug studies of prepulse inhibition in humans. Behav Pharmacol. 2001a; 12:45–52. [PubMed: 11270511]

Swerdlow NR, Hanlon FM, Henning L, Kim YK, Gaudet I, Halim ND. Regulation of sensorimotor gating in rats by hippocampal NMDA: anatomical localization. Brain Res. 2001b; 898:195–203. [PubMed: 11306005]

Swerdlow NR, Hartman PL, Auerbach PP. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. Biol Psychiatry. 1997; 41:452–460. [PubMed: 9034539]

Swerdlow NR, Karban B, Ploum Y, Sharp R, Geyer MA, Eastvold A. Tactile prepulse inhibition of startle in children with Tourette's syndrome: in search of 'fMRI-friendly' startle paradigm. Biol Psychiatry. 2001; 50:578–585. [PubMed: 11690592]

Swerdlow NR, Paulsen J, Braff DL, Butters N, Geyer MA, Swenson MR. Impaired prepulse inhibition of acoustic and tactile startle response in patients with Huntington's disease. J Neurol Neurosurg Psychiatry. 1995; 58:192–200. [PubMed: 7876851]

Swerdlow NR, Platten A, Shoemaker J, Pitcher L, Auerbach P. Effect of pergolide on sensorimotor gating of the startle reflex in rats. Psychopharmacology. 2001; 158:230–240. [PubMed: 11713612]

Swerdlow NR, Stephany N, Shoemaker JM, Ross L, Wasserman LC, Talledo J, Auerbach PP. Effects of amantadine and bromocriptine on startle and sensorimotor gating: parametric studies and cross-species comparisons. Psychopharmacology (Berl). 2002; 164:82–92. [PubMed: 12373422]

Swerdlow NR, Shoemaker JM, Auerbach PP, Pitcher L, Goins J, Platten A. Heritable differences in the dopaminergic regulation of sensorimotor gating: II. Temporal, pharmacologic and generational analyses of apomorphine effects on prepulse inhibition. Psychopharmacology. 2004; 174:452–462. [PubMed: 15300359]

Swerdlow NR, Stephany N, Wasserman LC, Talledo J, Shoemaker J, Auerbach PP. Amphetamine effects on prepulse inhibition across-species: replication and parametric extension. Neuropsychopharmacology. 2003; 28:640–650. [PubMed: 12655308]

Van Berckel BN, Oranje B, van Ree JM, Verbaten MN, Kahn RS. The effects of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. Psychopharmacology. 1998; 137:271–281. [PubMed: 9683005]

Wan FJ, Caine SB, Swerdlow NR. The ventral subiculum modulation of prepulse inhibition is not mediated via dopamine D2 or nucleus accumbens non-NMDA glutamate receptor activity. Eur J Pharmacol. 1996; 314:9–18. [PubMed: 8957213]

Wilcock G, Mobius HJ, Stoffler A, MMM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Pychopharmacol. 2002; 17:297–305.

Wiley JL, Harvey SA, Balster RL, Nicholson KL. Affinity and specificity of N-methyl- D-aspartate channel blockers affect their ability to disrupt prepulse inhibition of acoustic startle in rats. Psychopharmacology (Berl). 2003; 165:378–385. [PubMed: 12459931]

Zhang WN, Bast T, Feldon J. Effects of hippocampal N-methyl-D-aspartate infusion on locomotor activity and prepulse inhibition: differences between the dorsal and ventral hippocampus. Behav Neurosci. 2002; 116:72–84. [PubMed: 11895185]

Zuckerman M, Bone RN, Neary R, Mangelsdorf D, Brustman B. What is the sensation seeker? Personality trait and experience correlates of the Sensation-Seeking Scales. J Consulting Clin Psychol. 1974; 39:308–321.
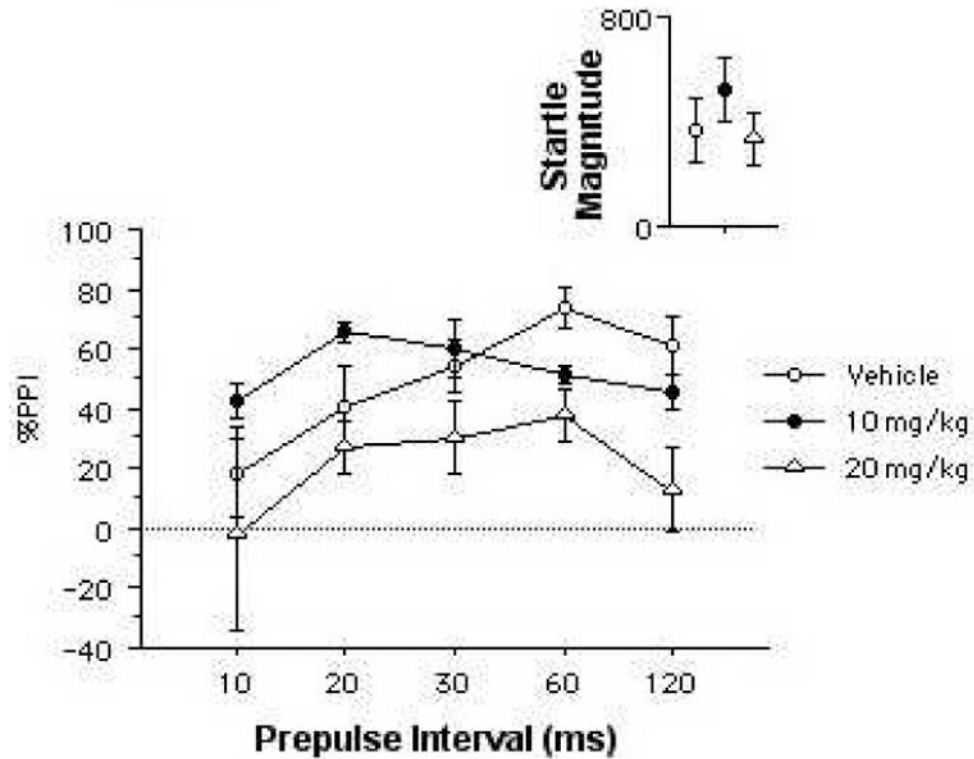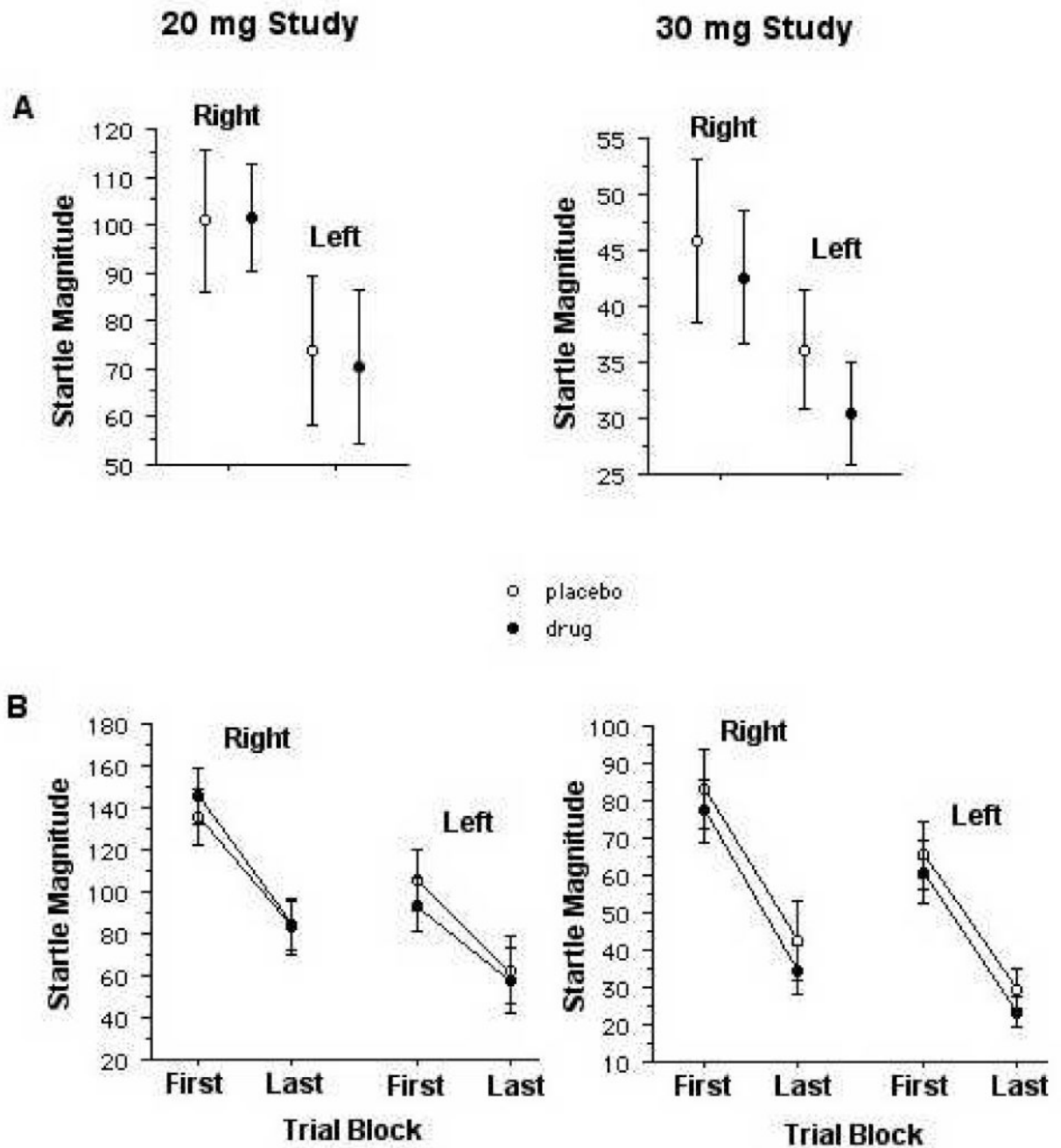
Figure 1.
Pilot data to confirm and extend previous evidence of PPI-disruptive effects of memantine in rats (Wiley et al. 2003). Memantine produced a dose-dependent reduction in PPI with 60-120 ms intervals. However, at short intervals (10-20 ms), PPI was both increased (10 mg/kg) and decreased (20 mg/kg) by memantine. Neither dose significantly altered startle magnitude (inset).
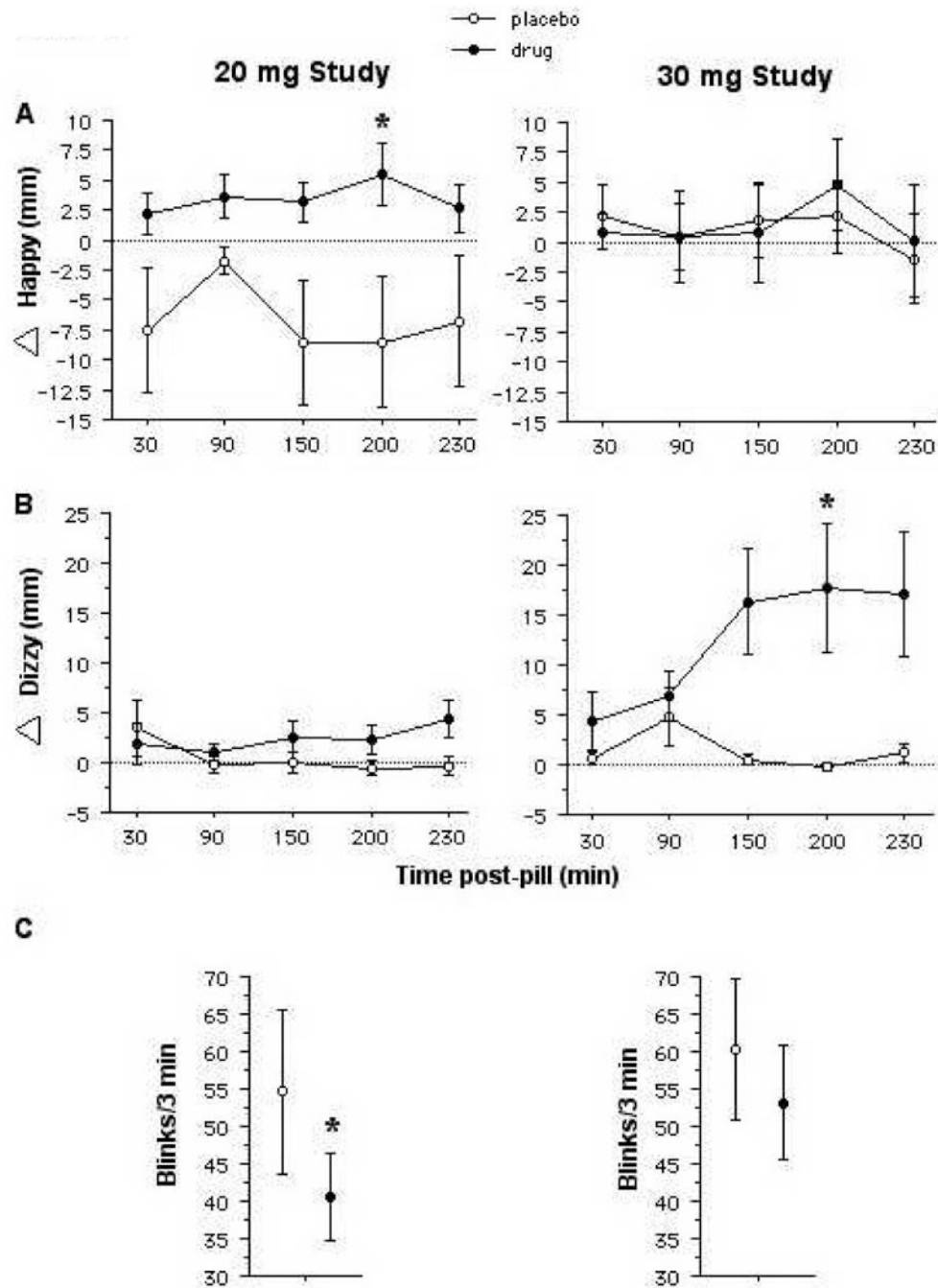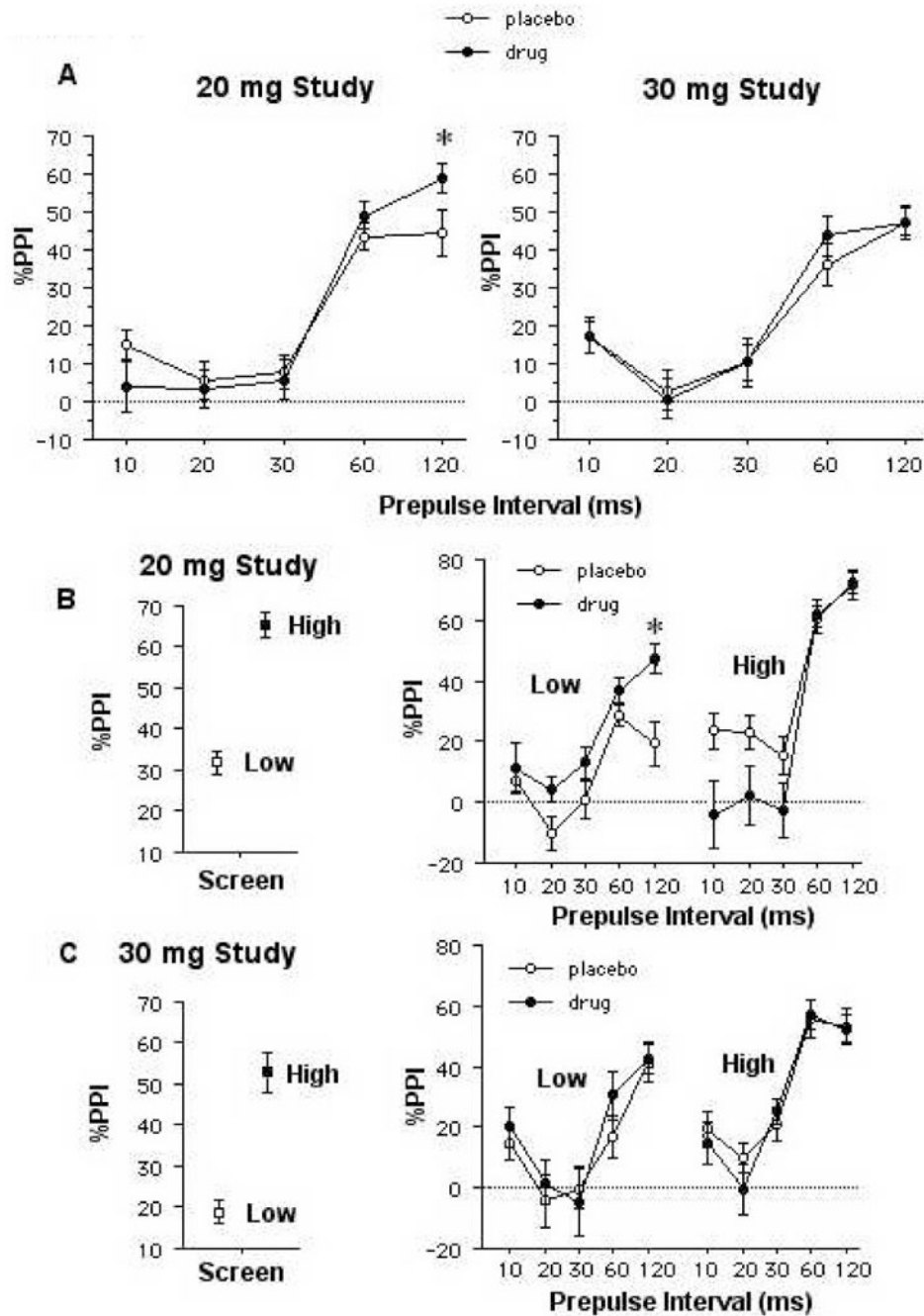
Figure 2.
Evidence of bioactivity of 20 mg (left figures) and 30 mg (right figures) memantine. The 20 mg dose increased ratings of "happy" (A) and reduced spontaneous blink rates (C); the 30 mg dose increased ratings of "dizzy" (B). Each of these effects was statistically reliable immediately prior to startle testing (*).

Figure 3.
Startle magnitude on pulse alone trials during PPI testing (A), and at the beginning and end of each test session (B) were not significantly impacted by either dose of memantine. Similarly, reflex habituation (response decrement from session beginning to end) was not impacted by memantine (B).

Figure 4.
Effects of memantine on PPI. A. PPI was significantly increased by 20 mg memantine at 120 ms prepulse intervals (left), but was not significantly affected by 30 mg memantine (right). B. When subjects in the 20 mg study were divided into those in the upper or lower 50% of screening PPI values (left figure, "high" and "low", respectively), ANOVA revealed PPI-enhancing effects of memantine only among the "low gaters". PPI-reducing effects of memantine in "high gaters" at short intervals did not reach statistical significance. C. A
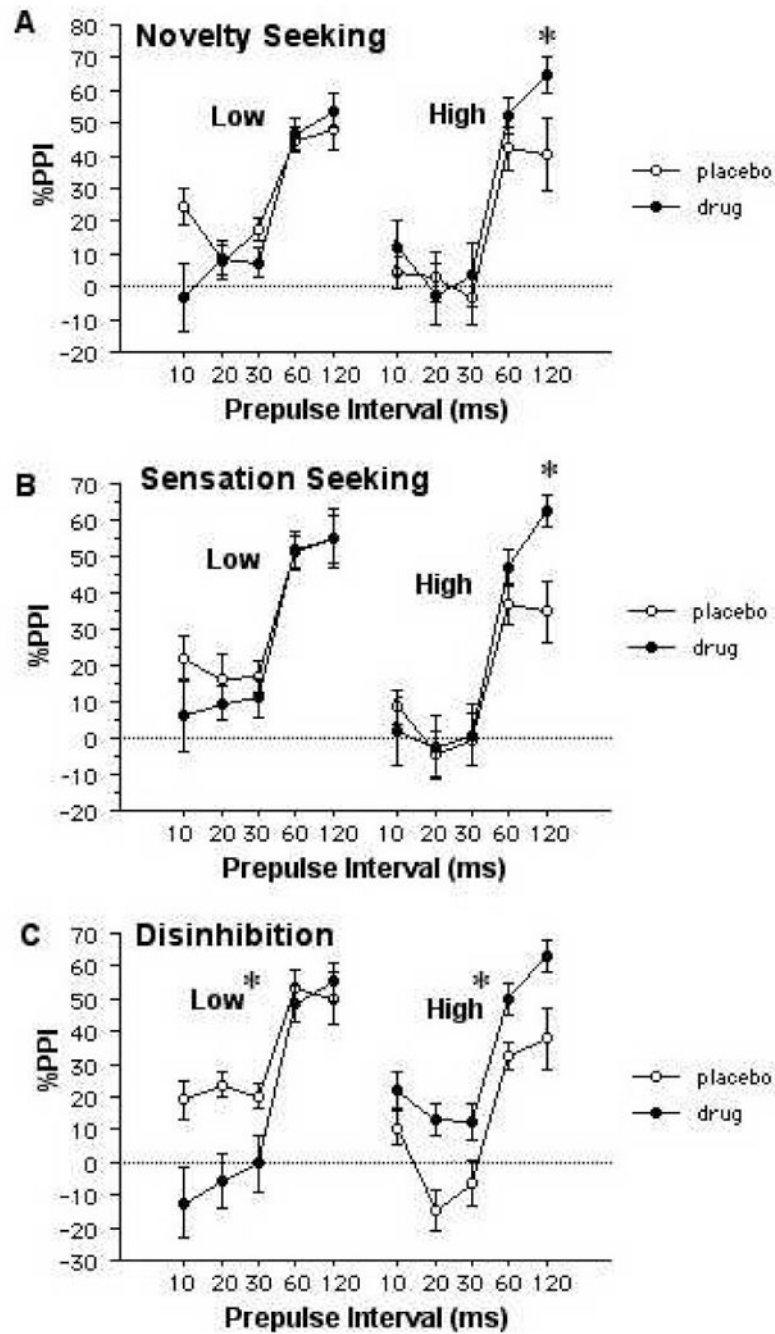
similar "low vs. high gater" split uncovered no significant effects of 30 mg memantine on PPI.

Figure 5.
Differential effects of memantine on PPI among subjects with low vs. high scores in personality measures of novelty seeking (A), sensation seeking (B) and disinhibition (C). PPI-enhancing effects of memantine at 120 ms prepulse intervals were evident only among individuals with high NS (A) or SSS scores (B). Subjects with high DIS scores exhibited PPI-enhancing effects of memantine across all prepulse intervals, while subjects with low DIS scores exhibited the opposite effects, particularly at short prepulse intervals.

Table 1

Exclusion criteria

Exclusion criteria
1. Left-handedness
2. Female
3. Age: <18 and >35
3. Previous participation in a study involving PPI
4. Medical conditions, e.g. diabetes, HIV, cancer, hypertension, cerebrovascular accident, myocardial infarction
5. Self –reported loss of consciousness for more than 1 minute
6. Current or past major mental illness as detected by SCID-NP
7. First degree relative with schizophrenia or major depression
8. Substance abuse or dependence
9. Current use of medication with potential memantine interactions or effects on central nervous system
10. Hearing impairment at 40 dB(A) at 1000 Hz
11. Mean eyeblink startle amplitude <50 startle units

Table 2

Final sample characteristics

Final Cohort:	20 mg memantine (n=19)	30 mg memantine (n=18)
Age (years) mean (range)	22.21 (18-29)	24.67 (20-34)
Weight (kg) (SEM)	75.85 (1.96)	75.42 (3.264)
Mean drug dose (mg/ kg) (SEM)	0.267 (0.007)	0.409 (0.016)
Caffeine Intake (mg/day) (SEM)	157.37 (37.59)	86.35 (22.57)
Ethnicity (C-A-H)[*]	(11-3-5)	(10-4-4)

[*] Caucasian: Asian: Hispanic

Table 3

Personality Questionnaire Scores

Final Cohort:	20 mg memantine (Mean (SEM) n=19)	30 mg memantine (Mean (SEM) n=18)
TPQ		
Novelty Seeking (SEM)	19.39 (0.90)	14.40 (1.34)
Harm Avoidance (SEM)	5.95 (1.25)	10.33 (1.53)
Reward Dependence (SEM)	21.05 (0.69)	19.72 (1.36)
SSS		
SSS Total score (SEM)	23.63 (0.96)	20.95 (1.75)
Thrill and Adventure seeking (SEM)	8.32 (0.51)	7.67 (0.63)
Experience Seeking (SEM)	6.26 (0.41)	5.33 (50.51)
Disinhibition (SEM)	5.53 (0.54)	4.56 (0.64)
Boredom Susceptibility (SEM)	3.53 (0.42)	3.11 (0.48)