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ORIGINAL INVESTIGATION

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Effects of amantadine and bromocriptine on startle and sensorimotor gating: parametric studies and cross-species comparisons

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Abstract *Background:* We recently reported that prepulse inhibition (PPI) in humans was increased by the dopamine (DA) agonist/*N*-methyl-D-aspartate (NMDA) antagonist amantadine (200 mg), but was not significantly altered by the DA agonist bromocriptine (1.25–2.5 mg). PPI-enhancing effects of DA agonists occur in rats under specific stimulus conditions, including short prepulse intervals (<30 ms). We characterized the effects of amantadine and bromocriptine on PPI across species, assessing: (1) dose–response effects on PPI in rats over 10- to 120-ms prepulse intervals; (2) drug effects on PPI in humans, using this same range of prepulse intervals; and (3) drug effects on measures related to PPI, including PPI of perceived stimulus intensity (PPIPSI), and startle habituation. *Methods:* Drug effects on PPI were assessed in male Sprague Dawley rats (n=90) and humans (n=49); startle habituation and PPIPSI were also studied in humans. *Results:* Amantadine and bromocriptine exhibited dose- and stimulus-dependent effects on PPI in rats, increasing PPI with short (10–20 ms) prepulse intervals, and decreasing PPI with long (60–120 ms) prepulse intervals. In humans, amantadine increased PPI with both short (20 ms) and long (120 ms) prepulse intervals. Bromocriptine had no significant effect on PPI in humans, but tended to increase PPI at short (20 ms) intervals. Amantadine eliminated PPIPSI. *Conclusions:* Amantadine modifies prepulse effects on startle in rats and humans, and disrupts prepulse effects on perceived stimulus intensity in humans; bromocriptine has clear effects on PPI in rats, but not in humans. The divergent effects of amantadine on sensorimotor and sensory effects of prepulses may reflect a divergence of brain circuitry regulating these processes.

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Introduction

Startle is inhibited when the startling stimulus is preceded by a weak prepulse (Peak 1939; Graham 1975). Prepulse inhibition (PPI) is an operational measure of sensorimotor gating that is impaired in specific disorders, including schizophrenia spectrum disorders (Braff et al. 1978, 1992, 1999; Grillon et al. 1992; Cadenhead et al. 1993, 2000; Kumari et al. 1999; Weike et al. 2000). This loss of sensorimotor gating has been linked theoretically to deficits in normal "information protective" mechanisms and is thought to contribute to cognitive fragmentation in schizophrenia (Braff et al. 1978; Braff and Geyer 1990).

Cross-species studies suggest that increased brain dopamine (DA) activity may reduce or eliminate PPI. PPI in rats is reduced or eliminated by direct and indirect DA agonists (Geyer et al. 2001; Swerdlow et al. 1998), and preliminary findings suggest similar or analogous effects in normal humans (Abduljawad et al. 1997, 1998; Hutchison and Swift 1999; Hutchison et al. 1999). This type of cross-species neurochemical homology in the regulation of PPI may allow us to translate details of the "PPI-regulatory" neural circuitry across species, to test hypotheses about the pathophysiology of gating deficits in neuropsychiatric disorders.

However, recent findings suggest greater complexity in the DAergic regulation of PPI, and its diversity across species, than may have been appreciated previously. At least two reports have now demonstrated that under specific experimental conditions in rats – e.g., very low doses, very weak prepulses or very short prepulse intervals – DA agonists can actually increase PPI (Martin-Iverson and Else 2000; Swerdlow et al. 2001b) and that the propensity for PPI-disruptive versus PPI-enhancing effects of DA agonists is strain dependent (Swerdlow et al. 2002c). Both the PPI-disruptive and PPI-enhancing effects of DA agonists can be demonstrated

within a single test session using a range of stimulus parameters (Swerdlow et al. 2001b).

In preparation for more substantial efforts to assess the nature of the DAergic regulation of PPI in humans, we explored the time course of action of several different DA agonists – amphetamine, bromocriptine, pergolide and amantadine – on startle measures (Swerdlow et al. 2002a). These drugs were selected based on: (1) previous findings that (at much higher doses on a mg/kg basis) they reduce PPI in rats (Swerdlow et al. 1998); (2) published reports that both bromocriptine (1.25 mg and 2.5 mg; Abduljawad et al. 1997, 1998) and amphetamine (20 mg; Hutchison and Swift 1999, Hutchison et al. 1999) reduce PPI in normal humans; and (3) better tolerability of these drugs relative to other DA agonists (e.g., apomorphine; Culpit and Temple 1984). Despite clear evidence of bioactivity over the 3.5 h after ingestion of each of these DA agonists, none resulted in a significant reduction in PPI (Swerdlow et al. 2002a). In fact, the only robust impact of these drugs on PPI was a significant increase in PPI observed in response to amantadine. Clearly, these findings were discrepant, not only with respect to previous preclinical findings with these drugs (Swerdlow et al. 1998), but also with respect to published reports of the PPI-disruptive effects of amphetamine (Hutchison and Swift 1999, Hutchison et al. 1999) and bromocriptine (Abduljawad et al. 1997, 1998) in humans.

To extend and better understand these findings, additional studies were undertaken, with three specific goals: (1) to assess the effects of amantadine and bromocriptine on PPI in rats over a range of prepulse intervals (10–120 ms) and doses that might be more sensitive to either PPI-disruptive or enhancing effects of DA agonists; (2) to assess the effects of these drugs on PPI in humans using comparable stimulus parameters (10–120 ms prepulse intervals) that might be sensitive to both PPI-disruptive and enhancing effects; and (3) to assess drug effects on measures related to PPI in humans, including PPI of perceived stimulus intensity (PPIPSI) and startle habituation. Amantadine was chosen because it was the only DA agonist that exhibited clear effects on PPI in our previous studies (Swerdlow et al. 2002a); bromocriptine was chosen based on published reports of PPI-disruptive effects of this drug (Abduljawad et al. 1997, 1998).

Methods

Rat studies

Ninety male Sprague Dawley rats (225–250 g; Harlan Laboratories) were housed in groups of two or three and maintained on a reversed light/dark schedule (lights off 0700 hours), with ad libitum food and water. Testing occurred between 0900 hours and 1700 hours. Rats were handled within 3 days of arrival, and two to three times per week thereafter.

Each of four startle chambers (SR-LAB, San Diego Instruments, San Diego, Calif.) was housed in a sound-attenuated room with a 60-dB(A) ambient noise level and consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5×25.5-cm Plexiglas frame in a ventilated enclosure. Acoustic noise bursts were presented via a speaker mounted 24 cm above the animal. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced motion within the cylinder. The delivery of acoustic stimuli was controlled by the SR-LAB microcomputer and interface assembly which also rectified, digitized (0–4095), and recorded stabilimeter readings, with 100 readings of 1-ms duration collected beginning at the stimulus onset. Startle amplitude was defined as the average of the 100 readings. Background noise and all acoustic stimuli were delivered through one Radio Shack Supertweeter (frequency response predominantly between 5 KHz and 16 KHz) in each chamber. Stimulus intensities and response sensitivities were calibrated to be nearly identical in each of the four startle chambers (maximum variability <1% of stimulus range and <5% of response ranges). Chambers were also balanced across all experimental groups. Sound levels were measured and calibrated using a Quest Sound Level Meter, A scale (relative to 20 $\mu N/m^2$; microphone inside the Plexiglas cylinder); response sensitivities were calibrated using a SR-LAB Startle Calibration System.

After a 5-min acclimation period with 70-dB(A) background white noise, rats were exposed to 42 trials that included six conditions: a 120-dB(A), 40-ms noise burst presented alone (P-alone); and the same 120-dB(A), 40-ms noise burst preceded 10, 20, 30, 60, or 120 ms by a prepulse (5-ms noise burst) that was 16 dB above background. The session began and ended with three consecutive P-alone trials; between these trials, the six trial types were each repeated six times in pseudorandom order. Inter-trial intervals averaged 15 s (range 10–20 s). Testing began 10 min after treatment with amantadine [vehicle (distilled water), 1, 3, 10, 30, 100 mg/kg, i.p., n=8–10 per dose] and 120 min after treatment with bromocriptine [vehicle (24:1 propylene glycol/ethanol), 0.01, 0.05, 1, 40 mg/kg, i.p., n=7–9 per dose] based on maximum drug effects on rat PPI detected in previous studies by our group (Swerdlow et al. 1998).

Human studies

Methods were similar to those described in our recent report (Swerdlow et al. 2002a), approved by the UCSD Institutional Review Board (IRB no. 991176), and approved and supported by the National Institute of Mental Health (MH 59803). Forty-nine right-handed males participated in placebo versus drug studies (Table 1), and ten additional subjects participated in a study to

Table 1 Subject characteristics

Drug group	n	Age, years (mean±SEM)	Mean drug dose (mg/kg)	Ethnicity (C:A:H)*	TPQ subscale score (mean±SEM)		
					HA	RD	NS
Amantadine 200 mg	12	21.58±1.26	2.689	8:4:0	8.67±1.81	18.33±1.14	18.75±1.68
Amantadine placebo	12	21.67±0.70	N/A	10:2:0	5.17±1.31	19.25±1.26	19.50±1.37
Bromocriptine 1.25 mg	12	23.08±0.99	0.016	6:4:2	5.67±1.40	20.58±1.30	18.17±1.14
Bromocriptine placebo	13	22.00±0.86	N/A	7:6:0	10.23±2.01	18.77±1.03	18.54±1.17

* Caucasian:Asian:Hispanic

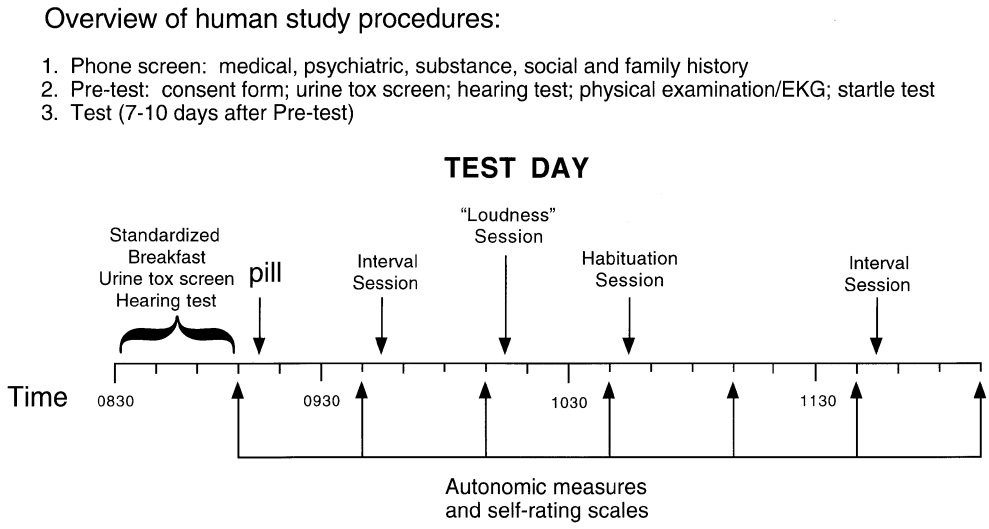

Fig. 1 Overview of human study procedures, including time line of test day

develop a paradigm to test PPI of perceived stimulus intensity (PPIPSI). Drug study participation involved phone contact and two laboratory visits (Fig. 1); subjects were paid US $140 for study completion. Phone screening procedures were identical to those described in our previous reports (Swerdlow et al. 2000, 2002a).

The human drug studies had a modified between-subject design (Fig. 1), in which all subjects received a limited startle "pre-test" without drug, followed approximately 7 days later by a more extensive test day that began with consumption of either placebo or active drug. During the "pre-testing" session, the principal investigator (NRS) informed each subject of the potential risks and benefits of the study, and, in the case of the bromocriptine study (n=25), he told them that medication would be available to reduce the nausea that they might experience as a result of the study drug (none was required during testing). Subjects also read and signed a consent for study participation, and completed a urine toxicology test with exclusion for any identified drug. Subjects completed a startle "matching test" to assess acoustic startle reflex (exclusion for mean acoustic startle magnitude <50 units). Electromyographic (EMG) methodology was identical to that in studies by Swerdlow et al. (2000, 2002a). Subjects also completed the tridimensional personality questionnaire (TPQ) (Cloninger et al. 1993) to assess the relationship between novelty-seeking (NS) scores and sensitivity to the effects of amantadine and bromocriptine on PPI, based on reports that high NS individuals are most sensitive to the PPI-disruptive effects of amphetamine (Hutchison et al. 1999).

Subjects sat upright during all startle sessions, were directed to look straight ahead and to stay awake. Acoustic stimuli were delivered by Telephonics (TDH-39-P, Maico) headphones. During each startle session, a background 70-dB(A) white noise continued throughout the session and was followed 3 min after onset by the startle trials. The startle session during pre-testing consisted of the "interval session", 42 trials that included six conditions: a 118-dB(A), 40-ms noise burst presented alone (P-alone); and the same P-alone preceded 10, 20, 30, 60, or 120 ms by a prepulse (5-ms noise burst) that was 16 dB above background. The session was structured identically to that described above for rat studies, except that intertrial intervals averaged 20 s (range 15–25 s). Subjects who passed the "pre-test" screening returned for the test 7–10 days later, having been instructed to maintain their normal patterns of caffeine intake prior to testing, based on effects of caffeine withdrawal on PPI (Swerdlow et al. 2000). Subjects were recruited for studies continuously over an approximate 3-month period for each drug and were assigned to active drug versus placebo groups for each drug based on a "rolling average" strategy, using pre-test mean acoustic PPI measures to obtain groups with comparable "baseline" acoustic PPI values.

Consistent with the work of several others (Peak 1939; Cohen et al. 1981; Perlstein et al. 1993; Blumenthal et al. 1996, 2001; Norris and Blumenthal 1996), our group (Swerdlow et al. 1999) reported the ability of prepulses to inhibit the perceived intensity of startling stimuli. To test drug effects on this form of sensory gating, we first sought to identify stimulus parameters that would be maximally sensitive to these prepulse effects, to allow the testing of drug effects in a single, relatively simple session. Ten subjects participated in this paradigm development, but did not participate in drug studies. Briefly, startle equipment were as described above. A background 70-dB(A) white noise continued throughout the session and was followed 5 min after onset by startle trials. The session consisted of 72 trials that included nine conditions: 95, 100, 105, 100, or 115-dB(A), 40-ms noise bursts presented alone (P95, P100, P105, P110, and P115); and P95, P100, P105, and P110 stimuli preceded 60 ms by a prepulse (20-ms noise burst) 12 dB above background. The session began and ended with four P115 trials; between these trials, the remaining trial types were each repeated eight times in pseudorandom order. Inter-trial intervals averaged 20 s (range 15–25 s). During this test, subjects held a pen and sat in front of a music stand that held a stack of papers, each sheet containing a 100-mm line. Subjects were instructed to make a mark on the line corresponding to their perceived intensity of each noise, with the left end of the line corresponding to "can't hear" and the right end corresponding to "intolerably loud". Subjects were observed remotely to verify that one piece of paper was used for each trial. Based on the results, the P105 and PP12/105 stimuli were selected for the drug studies "loudness session" (below), along with a 16-dB prepulse trial (PP16/105).

On the drug test day, subjects arrived at 0830 hours, received a standardized breakfast and a second urine toxicological examination, and hearing was re-tested as described in Swerdlow et al. (2001a). At 0915 hours, subjects consumed either active or inactive (placebo) pills; neither subject nor experimenter knew the pill identity. Testing started at 0940 hours. The test began and ended with the interval sessions (INT1 and INT2). Between these sessions, tests were conducted to assess startle habituation (HAB session) and PPIPSI (loudness session). The HAB session consisted of 50 repetitions of 40-psi, 40-ms air bursts (puff) delivered from a compressed air tank aimed under the subject's chin via a small rubber tube. Inter-trial interval was 15 s. The loudness session consisted of 48 trials that included three conditions: P105 and P105 preceded 120 ms by either a 12-dB prepulse (PP12/P105) or a 16-dB prepulse (PP16/105) to permit detection of intensity-dependent prepulse effects. This session began with three P105 trials, followed by 15 repetitions of each of the three trial types in pseudorandom order. During the loudness session, subjects scored the perceived intensity of each stimulus as described above.

Heart rate and blood pressure were determined (sitting, brachial cuff), and subjects completed a symptom rating scale every 30–45 min, the first one before pill ingestion, the second immediately before the first startle session and, thereafter, between each startle session and after the final session. Symptom scales were designed to assess general somatic and psychological symptoms and level of consciousness (modified from Norris 1971; Bond and Lader 1974; Bunney et al. 1998) and were identical to those described in Swerdlow et al. (2002a). Ratings were treated as continuous variables and analyzed using mixed-design analyses of variance (ANOVAs).

For both rat and human studies, PPI was defined as (100–[100×magnitude on prepulse trial/magnitude on pulse alone trial]). Startle magnitude and PPI were analyzed using mixed-design ANOVAs, with trial type and block as within-subject factors and drug condition as between-subject factors. To assess startle habituation in humans, the HAB session was divided into five blocks of ten trials each, and startle magnitude was analyzed using block as a within-subject factor. No consistent differences were noted between right and left eye measures, and thus main effects of eye side and interactions are not reported. In humans, ANOVAs were completed for each of the two active drugs, using both raw data collected from INT1 and INT2 sessions on the test day, and during the "pre-test" session (for startle measures) or from values recorded prior to drug administration (for autonomic and self-rating measures). Cell sizes (n=12–13) were based on power analyses from our previous studies (Swerdlow et al. 2002a). For the loudness session, due to the relatively weak startle pulse [105 dB(A)], several test subjects exhibited minimal or no startle responses to P105 trials; any subject whose mean startle value on these trials was <10 units was categorized as a "non-responder", and their data was not included in the analysis of %PPI. Finally, self-ratings for the loudness session were treated as raw (non-transformed) data and were also "range-corrected" as previously described (Swerdlow et al. 1998) so that each value was expressed as a fraction of the range (maximum minus minimum) ratings for that subject. Specific post-hoc comparisons were made using a Fisher's protected least significant difference (PLSD) test. Alpha was 0.05.

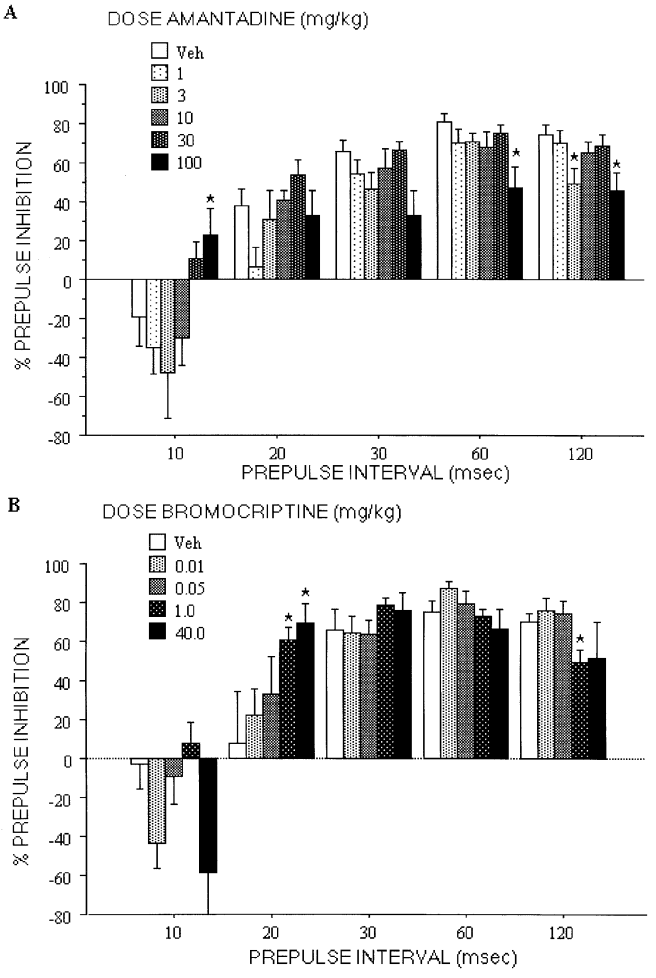

Fig. 2 Prepulse inhibition (PPI) in rats treated with amantadine (**A**) or bromocriptine (**B**). Both drugs exhibit dose- and interval-dependent effects on PPI. **A** Amantadine increases PPI elicited with 10-ms prepulse intervals [*significantly greater than vehicle dose (*V*), P<0.05], and decreases PPI elicited with 60-ms and 120-ms prepulse intervals (*significantly greater than V dose, P<0.05). **B** Bromocriptine increases PPI elicited with 20-ms prepulse intervals (*significantly greater than V dose, P<0.05), and decreases PPI elicited with 120-ms prepulse intervals (*significantly greater than V dose, P<0.05)

Results

Rat studies

Amantadine exhibited dose- and interval-dependent effects on PPI consistent with previous findings with some DA agonists (Swerdlow et al. 2002a); it increased PPI at very short prepulse intervals and reduced PPI at longer prepulse intervals (Fig. 2A). ANOVA revealed a significant effect of interval ($F_{4,176}$=99.89, P<0.0001) and a significant dose × interval interaction ($F_{20,176}$=3.40, P<0.0001). Post-hoc comparisons revealed significant main dose effects for the 10-ms interval [P<0.02; PPI for 100-mg/kg group greater than vehicle (P=0.05), 1, 3, and 10-mg/kg groups (P<0.03–0.003)], the 60-ms interval [P<0.025; PPI for 100-mg/kg group less than vehicle (P<0.001)] and the 120-ms interval [P<0.015; PPI for 100-mg/kg group less than vehicle (P<0.005), and for 3-mg/kg group less than vehicle (P<0.007)]. Main dose effects only reached trend levels for the 20-ms (P<0.07) and 30-ms (P<0.06) intervals. Amantadine had no significant effects on startle magnitude on trials without prepulses ($F_{5,44}$=1.15, n.s.) or on startle habituation (data not shown).

Bromocriptine also exhibited dose- and interval-dependent effects on PPI. ANOVA revealed a significant effect of interval ($F_{4,140}$=43.10, P<0.0001) and a significant dose × interval interaction ($F_{16,140}$=2.11, P<0.015). Post-hoc comparisons revealed no significant main effect of dose at any interval (P>0.05, all comparisons). Inspection of the data (Fig. 2B) revealed an orderly, dose-dependent increase in PPI at the 20-ms prepulse interval that reached significance at doses of 1.0 mg/kg (P<0.05) and 40 mg/kg (P<0.025). PPI was significantly reduced by bromocriptine only at the 120-ms interval (vehicle vs 1.0 mg/kg: P<0.02). As with amantadine, bromocriptine had no significant effects on P-alone startle magnitude ($F_{4,35}$=1.36, n.s.) or on startle habituation (data not shown).

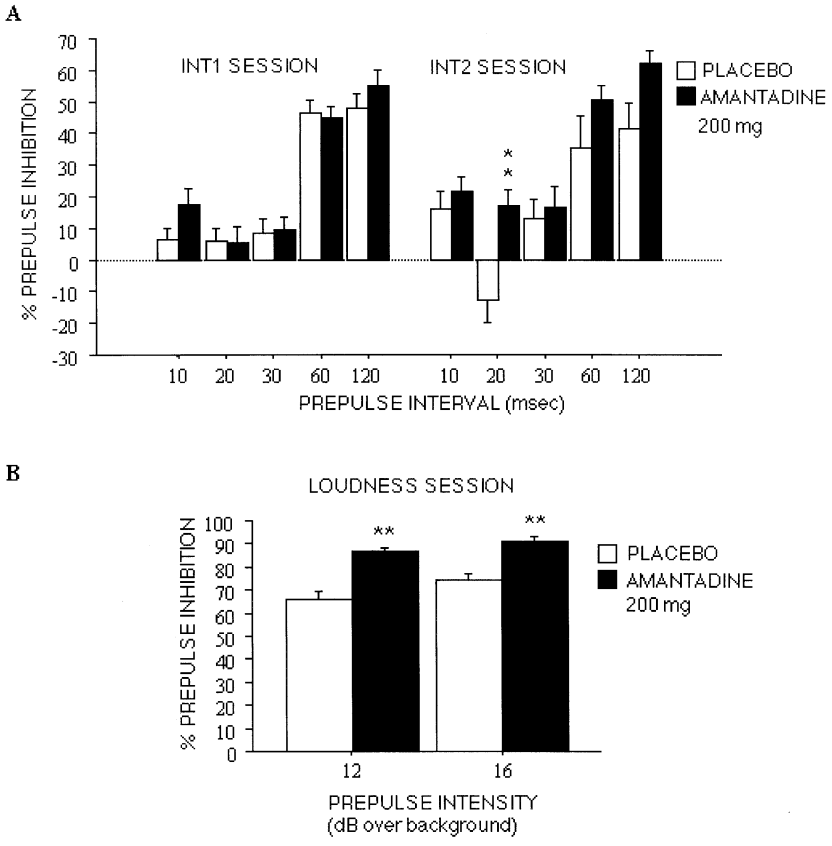

Fig. 3 Prepulse inhibition (PPI) in placebo and amantadine group subjects during interval session (**A**) and loudness session (**B**). Pre-test PPI levels across groups were nearly identical. On the test day, ANOVA revealed a significant interaction of drug × test run × prepulse interval. Post-hoc comparisons in INT2 revealed that PPI in amantadine subjects was significantly increased relative to placebo subjects for 20-ms prepulse intervals (*double asterisk*, *vertical*, $P<0.015$) and that the mean PPI across all intervals reached one-tailed significance in the predicted direction ($P<0.10$). PPI in the loudness session (**B**) was also significantly increased in the amantadine subjects relative to placebo subjects (*double asterisk*, *horizontal* $P<0.006$)

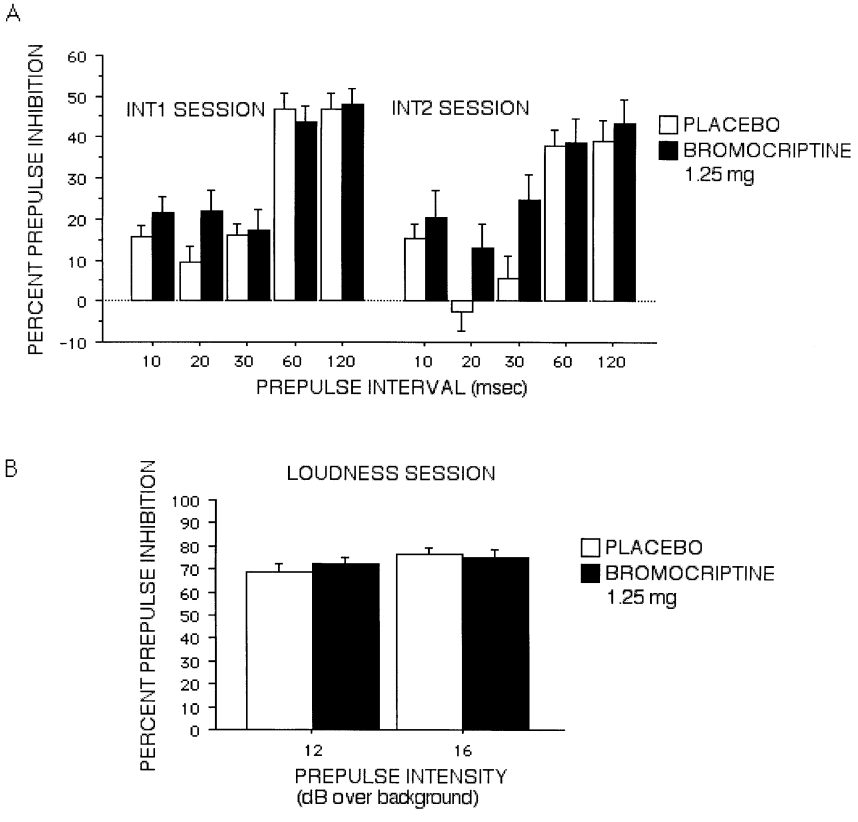

Fig. 4 Prepulse inhibition (PPI) in placebo- and bromocriptine-group subjects during interval session (**A**) and loudness session (**B**). No significant effects of bromocriptine on PPI were detected in any test session

Human studies

PPI of startle

As reported previously (Swerdlow et al. 2002a), amantadine increased PPI, but this effect varied with time of testing (greatest later in the test session, similar to previous findings) and stimulus parameters. In the interval sessions, placebo and amantadine groups exhibited nearly identical levels of PPI during pre-testing (F<0.02). On the test day, ANOVA revealed a significant effect of prepulse interval ($F_{4,88}$=39.13, P<0.0001), as well as a significant interaction of drug × time × interval ($F_{4,88}$=2.50, P<0.05). To understand this three-way interaction, post-hoc comparisons in the second interval session (INT2) revealed that amantadine increased PPI across all prepulse intervals to a level that reached one-tailed significance in the predicted direction ($F_{1,22}$=3.12, P<0.095); the PPI-increasing effects of amantadine at the 20-ms interval were most robust (P<0.015) and only approached significance at the 120-ms interval (P=0.10). In the loudness session (Fig. 3B), ANOVA revealed more robust PPI-increasing effects of amantadine ($F_{1,16}$=10.06, P<0.006); there was also a near-significant effect of prepulse intensity ($F_{1,16}$=4.00, P<0.065). Amantadine had no significant effects on startle magnitude on P-alone trials in any test session.

While the predicted effects of amantadine on PPI were observed in the loudness and INT2 sessions, these effects in the INT2 session were relatively weak. One explanation is that there was a restricted range in a session dominated by short prepulse intervals (i.e., a "ceiling" effect), and that amantadine would have a greater effect on PPI if there were greater possible "upward range" in PPI values. To test this explanation, PPI was compared in placebo relative to amantadine subgroups, excluding individuals in the highest quartile of pre-test PPI values, to permit more "upward range" in the influence on PPI by either placebo or amantadine. These subgroups exhibited near-identical pre-test PPI values (F<0.1). In INT2, the PPI-increasing effects of amantadine in these subgroups was substantially more pronounced ($F_{1,16}$=9.19, P<0.009) than was evident using the full sample, with the pattern across prepulse intervals remaining unchanged (amantadine > placebo: P<0.005 for 20-ms intervals and P<0.045 for 120-ms intervals).

Bromocriptine had no significant effects on PPI in any test session. No significant effects of drug group were identified in either the pre-test session (subjects drug free: $F_{1,23}$=3.28, n.s.) or in the interval sessions on the test day ($F_{1,23}$=1.61, n.s.; Fig. 4A). On the test day, there were no significant interactions of drug with interval or run, or any significant three-way interactions. Bromocriptine also had no significant effect on PPI in the loudness session (Fig. 4B), nor was there any significant effect of bromocriptine on P-alone startle magnitude in any PPI test session (all P values >0.19).

Based on reports of greater sensitivity to PPI-disruptive effects of amphetamine in individuals with high NS scores, we examined the impact of amantadine and bromocriptine on PPI, separating drug groups into "low" versus "high" NS subgroups, based on a median split. No significant interactions of NS were observed with drug, prepulse interval, and/or session time that might suggest an increased sensitivity of high NS individuals to PPI-disruptive effects of these drugs.

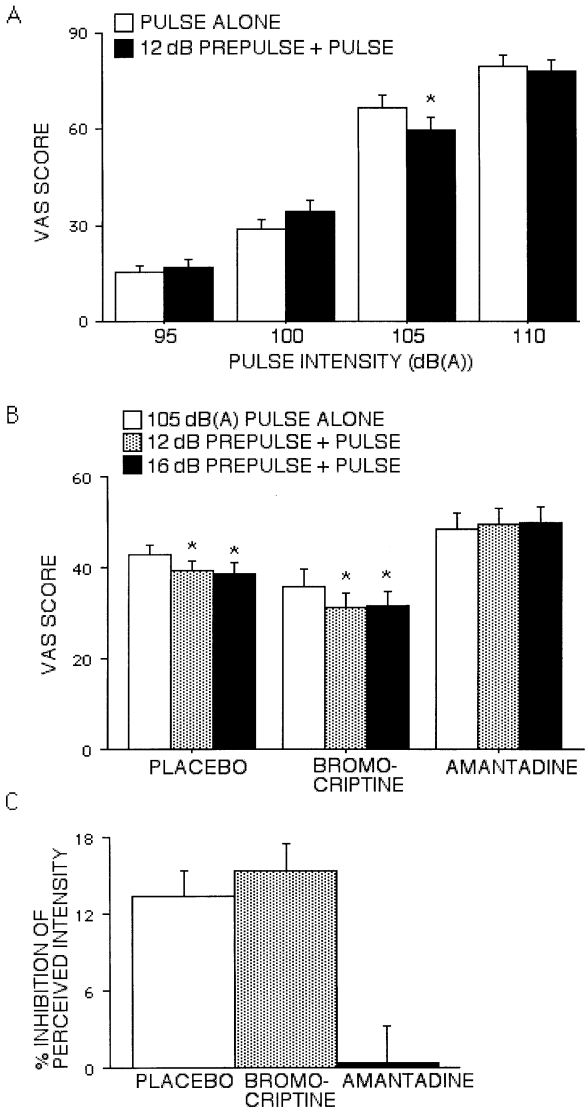

Fig. 5 (**A**) Prepulse inhibition (PPI) of perceived stimulus intensity (PPIPSI) was evident with 105-dB startle pulses in ten drug-free subjects (*significantly less intense than pulse-alone trials, P<0.035, after significant interaction of trial type × intensity). **B** Perceived intensity of 105-dB pulses are significantly reduced by 12 dB and 16 dB prepulses (*) in placebo- and bromocriptine-group subjects, but not in amantadine-group subjects. **C** Placebo- and bromocriptine-group subjects exhibited approximately 15% PPIPSI, while amantadine-group subjects exhibited near-zero levels of PPIPSI. *VAS* visual analog scale

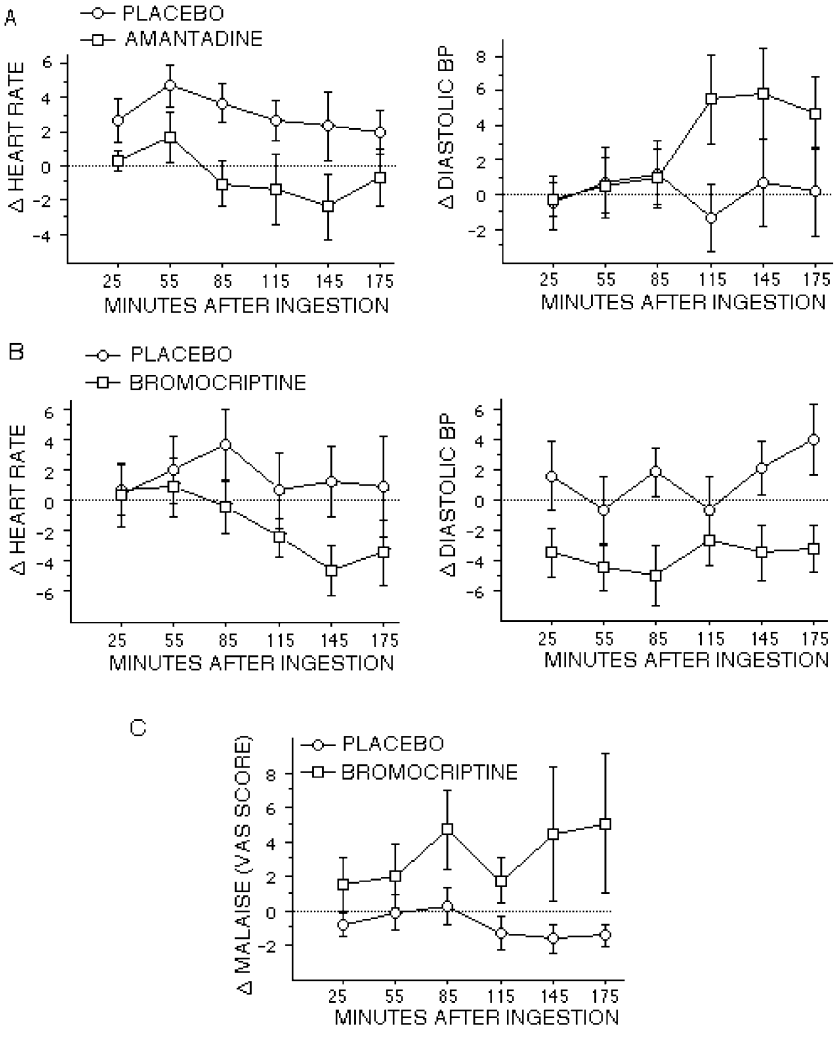

Fig. 6 Evidence of "bioactivity" of these drug doses in humans, based on autonomic and subjective measures. **A** Amantadine- and placebo-group subjects differed significantly in their change in heart rate across the entire test session (*left* $F_{1,22}$=5.72, P<0.03, with a trend toward greater diastolic blood pressure later in the test session; *right* drug × time interaction $F_{5,110}$=2.41, P<0.045). **B** Bromocriptine- and placebo-group subjects differed significantly in their diastolic blood pressure across the entire test session (*right* $F_{1,23}$=6.51, P<0.02), with a trend toward differences in the change in heart rate across the second half of the test session (*left*). **C** Bromocriptine and placebo subjects differed in self-reported malaise ($F_{1,23}$=4.68, P<0.045; based on the change in composite VAS scores for "queasy" and "dizzy")

Perceived stimulus intensity

Studies in ten drug-free subjects revealed pulse intensity-dependent effects on PPIPSI, with robust inhibition of perceived intensity evident only with 105-dB(A) startle pulses (Fig. 5A). ANOVA of perceived intensity revealed a significant effect of startle pulse intensity ($F_{3,27}$=223.89, P<0.0001), no overall effect of trial type (P-alone vs prepulse + pulse), and a significant interaction of pulse intensity × trial type ($F_{3,27}$=6.31, P<0.003). Post-hoc comparison using 105-dB(A) pulses revealed a significant effect of prepulses on perceived intensity (P<0.035). This 105-dB(A) pulse intensity was thus used in studies with amantadine and bromocriptine.

Analysis of drug effects on PPIPSI (Fig. 5B) revealed that prepulses reduced perceived intensity in placebo (effect of trial type: $F_{2,48}$=9.18, P<0.0005) and bromocriptine group subjects (effect of trial type: $F_{2,22}$=3.43, P=0.05), but not in amantadine group subjects (effect of trial type: F<0.15). For ease of reporting, groups were combined to compare a common placebo group versus amantadine and bromocriptine groups (analyses using separate placebo groups yielded outcomes comparable to the combined comparison). The range-corrected percentage PPIPSI is seen in Fig. 5C, showing approximately 15% PPIPSI in both placebo and bromocriptine groups, and near-0% PPIPSI in the amantadine group.

Habituation

Robust habituation was observed in tests with both amantadine and bromocriptine, and neither drug had significant effects on this measure (data not shown).

Autonomic and subjective measures provided evidence for "bioactivity" of both drugs (Fig. 6). Compared with placebo, subjects receiving either amantadine or bromocriptine exhibited decreased heart rate and changes in diastolic blood pressure. Amantadine effects on diastolic blood pressure followed a time course similar to its effects on PPI. Bromocriptine also caused mild dizziness and malaise.

Discussion

The present findings both replicate and extend our previous observation (Swerdlow et al. 2002a) that amantadine (200 mg) increases PPI of acoustic startle in humans and that bromocriptine (1.25 mg) has no robust effect on PPI of acoustic startle under the test conditions of our laboratory. Our previous study also identified a trend toward an amantadine-induced reduction in PPI at a post-amantadine time interval corresponding to the current INT1 session (Cohen's d=0.81; Cohen 1988); this effect was not replicated in the present experimental design. The previous report had utilized relatively small samples and simple, long prepulse interval stimuli, for the purpose of establishing a useful time course to study drug effects on PPI. The present study extended this effort by: (1) assessing parallel measures in rats using a wide range of doses and prepulse intervals (10–120 ms) that demonstrated both PPI-disruptive and PPI-enhancing effects of amantadine and, to a lesser degree, bromocriptine; (2) increasing the sample size of human subjects to detect relatively subtle effects of amantadine on PPI; (3) demonstrating both similar (PPI-increasing) and different (no PPI-reducing) effects of amantadine on PPI in humans using the same range of short and long prepulse intervals studied in rats; (4) demonstrating the opposite effects of amantadine on PPI versus "sensory gating" effects of prepulses (PPIPSI); and (5) demonstrating the lack of a significant effect of both amantadine and bromocriptine on another form of startle plasticity, tactile startle habituation.

The present studies confirm that the impact of increased dopaminergic activity in rats is not simply to decrease or increase PPI but, rather, it is to change the pattern of prepulse modification of startle during the initial 120 ms after the prepulse. Increased DA tone increases gating in the immediate aftermath (10–20 ms) of a weak stimulus and reduces gating later (60–120 ms); this provides a "signal-to-noise ratio" that is enhanced early and degraded later in the post-stimulus period. We previously speculated that this process might enable brain DA systems to provide dynamic control over information "gating", by regulating not simply the amount, but also the content (temporal characteristics) of "gated" (or "ungated") information (Swerdlow et al. 2001b). While it is possible that some of the PPI-enhancing and PPI-disrupting effects of amantadine reflect non-dopaminergic effects of this drug, the present findings with amantadine are at least qualitatively similar to those reported for the D2-family agonist pergolide (Swerdlow et al. 2001b) and the mixed D1/D2 agonists PNHO (Martin-Iverson and Else 2000) and apomorphine (Swerdlow et al. 2002c).

However, the present findings also underscore the difficulty in extrapolating such hypotheses – based on infra-human data – to concepts relevant to the regulation of sensorimotor gating in humans. Thus, while in rats amantadine clearly causes both an increase in PPI at short intervals (10 ms) and a reduction in PPI at longer prepulse intervals (60–120 ms), only the PPI-increasing effects were evident in humans. In fact, in addition to their detection at short intervals (20 ms) in humans, these PPI-enhancing effects in humans were evident at longer intervals, both in the loudness session, and in the INT2 session when the "ceiling" on PPI values was artificially lifted by excluding the highest quartile of PPI values from both placebo and amantadine groups. These data are consistent with results of our previous study, in which amantadine increased PPI using 100-ms prepulse intervals (Swerdlow et al. 2002a).

We have previously discussed the many factors that might contribute to cross-species discrepancies in the PPI-disruptive effects of DA agonists, such as differences in dose, route of administration, pharmacokinetics, etc., across species (Swerdlow et al. 1998, 2001b, 2002a). Another possible cross-species difference might have contributed to the present pattern of results. In the loudness session, humans were asked to rate the intensity of the noise – a process that requires focused attention on the startling stimulus. Interestingly, the PPI-enhancing effects of amantadine appear to have been most robust in this test session, compared either with our previous findings with amantadine (Swerdlow et al. 2002a) or with the effects of amantadine during the INT1 or INT2 sessions. It is thus conceivable that the robust PPI-enhancing effects of amantadine in part reflected an interaction with attentional mechanisms and their underlying neural substrates (Filion et al. 1993; Hazlett et al. 2001), which may be capable of enhancing PPI, at least for prepulse intervals greater than 60 ms (Bohmelt et al. 1999). This type of interaction would not be expected in rats, for whom the PPI test session included no "instructions" that might alter directed attention. One might even argue that – having been instructed to "attend" to the startling stimuli during the loudness session, human subjects automatically continued this directed attention during the subsequent INT2 session, accounting (at least partly) for the PPI-enhancing effects of amantadine during that session. Because no attentional instructions had been used in our previous study with amantadine (which used 100-ms prepulse intervals), it is not likely that attentional processes can fully explain the PPI-enhancing effects of this drug, even at long prepulse intervals.

Consistent with our previous report, but not with those of others (Abduljawad et al. 1997, 1998), we detected no PPI-disruptive effects of bromocriptine in humans, despite evidence for bromocriptine "bioactivity". There are many possible explanations for our inability to detect PPI-disruptive effects of bromocriptine. Our experience (Swerdlow et al. 2002a and present study) now totals 24 subjects treated with bioactive doses of bromocriptine – including 1.25 mg (total n=18) and 2.5 mg (total n=6) – using a wide range of stimulus parameters and time points, so neither sample size nor restricted parametric design seem to be likely explanations for this negative finding. The only trend for an effect of bromocriptine in our past report (Swerdlow et al. 2002a) and the present one consists of a bromocriptine-induced increase in PPI;

in our past report, this effect reached only small-to-moderate effect sizes (Cohen's d=0.41–0.63), and, in the present study, it was limited to the 20-ms prepulse interval (Fig. 4a). Clearly, some difference in experimental design – e.g., subject characteristics and repeated drug testing designs – must account for the discrepancies between our findings and those of Abduljawad et al. (1997, 1998), and we are pursuing several possible sources via subgroup analyses of our combined bromocriptine samples.

The present study also provided new information related to the impact of amantadine (and lack of impact of bromocriptine) on prestimulus effects on information processing. Since its first published description in 1939 (Peak 1939), PPIPSI has received relatively less attention than prestimulus effects on reflex magnitude. Nonetheless, several groups have demonstrated that, under specific stimulus conditions, prepulses can inhibit the perceived intensity of startling (and even noxious) stimuli. In a particularly striking example of this phenomenon, Blumenthal et al. (2000) demonstrated that prepulses can significantly blunt the perceived painfulness of 170-V cutaneous shocks. Consistent across nearly all studies of this phenomenon is the observation that the magnitude of PPIPSI – under optimal conditions – rarely exceeds 15%: in other words, while prepulses can completely inhibit the startling effects of intense stimuli, they only appear to slightly diminish the perceived intensity of these stimuli. The magnitude of this PPIPSI effect makes it relatively less-well suited for studies of between-subject interventions such as drug treatments, and is only partly compensated for by its substantial within-subject consistency. To maximize sensitivity, studies of this phenomenon – which is an operational measure of "sensory gating" – have required the type of labor-intensive parametric verification utilized in the present study (Blumenthal et al. 2000).

Perhaps the most intriguing finding of this study is that – in one session, using the same set of stimuli – amantadine both increased prestimulus-induced sensorimotor gating (PPI) and disrupted prestimulus-induced sensory gating (PPIPSI). This finding suggests a divergence in the neural substrates regulating these two forms of prestimulus effects. Whether such a divergence applies to other measures of sensorimotor or sensory gating, e.g., paired-pulse inhibition (Peak 1939; Smith and Lees 1989) or suppression of P50 event-related potentials ("P50 gating") (Freedman et al. 1996), is a question that can be answered using paradigms that simultaneously assess multiple measures of gating (Light and Braff 2001; Swerdlow et al. 2002b). Most generally, however, this finding supports the notion that, despite structural similarities in stimulus delivery or response acquisition, measures of "gating" cannot be assumed to be assessing features of a common, unified brain inhibitory process. These different "gating" measures in clinical populations should thus not be redundant, but rather might be informative about different neural substrates and have different implications ranging from genetics to functional outcome.

Because amantadine is neurochemically complex, it is not easy to use the present results to understand the neurochemical basis for PPI deficits in neuropsychiatric disorders, such as schizophrenia. Ironically, two major neurochemical properties of amantadine – increased DA release and uncompetitive *N*-methyl-D-aspartate (NMDA) receptor blockade (Kornhuber et al. 1991; Parsons et al. 1995; Takahashi et al. 1996) – are consistent with two substrates frequently implicated in the pathogenesis of schizophrenia: DA hyperfunction (Randrup and Munkvad 1968) and NMDA hypofunction (Javitt and Zukin 1991). In the rat striatum, DA release is triggered only by high systemic doses of amantadine (e.g., 100 mg/kg; Takahashi et al.1996), and a lower dose appears to block striatal NMDA receptors (e.g., 40 mg/kg; Fisher et al. 1998) but also may trigger striatal glutamate release (Takahashi et al. 1996). It is impossible to extrapolate these complex neurochemical changes in rats to the effects of 200 mg of amantadine in humans, but it is clear that this dose of amantadine does not result either in psychosis or in changes in PPI that reproduce those seen in schizophrenia. We can thus conclude that amantadine-induced changes in PPI in normal humans does not have validity as a model for PPI deficits in schizophrenia.

Like amantadine, both ketamine (van Berckel et al. 1998) and methylene-dioxy-methamphetamine (MDMA; Creighton et al. 1991) disrupt PPI in rats (Mansbach and Geyer 1989; Mansbach et al. 1989) and increase PPI in humans (van Berckel et al. 1998; Vollenweider et al. 1999; Duncan et al. 2001). The present results suggest that PPI can be significantly increased in humans using a drug that lacks the potential toxicity associated with both ketamine (Jevtovic-Todorovic et al. 2001) and MDMA (Morgan 2000), is readily available for human use (vs MDMA), and can be administered orally (vs i.v. for ketamine). Whether the PPI-increasing effects of amantadine on PPI (or its disruptive effects on PPIPSI) have predictive validity – i.e., are reversed by agents in a manner that predicts their clinical antipsychotic efficacy – is a question that warrants investigation.

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