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ORIGINAL INVESTIGATION

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Effects of phencyclidine on prepulse inhibition of acoustic startle response in the macaque

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Abstract *Rationale:* Prepulse inhibition (PPI) of the acoustic startle response (ASR) provides an index of neurophysiological dysfunction in schizophrenia and a method for analyzing underlying neurochemical mechanisms. In rodents, phencyclidine (PCP) and other *N*-methyl-D-aspartate receptor (NMDAR) antagonists induce schizophrenia-like PPI deficits. Similar effects have recently been observed in a New World monkey species, *Cebus apella*. *Objectives:* The present study evaluates the degree to which similar effects are observed in an Old World monkey, *M. fascicularis*. *Methods:* An initial study evaluated effects of interstimulus interval on PPI amplitude and latency. A subsequent study evaluated effects of PCP (0.25 mg/kg IM) on PPI of the ASR. *Results:* Prepulses reduced both the amplitude and latency of the ASR. PCP treatment prevented both effects without affecting amplitude or latency of the ASR itself. *Conclusions:* These results demonstrate that both amplitude reduction and latency facilitation are observed during PPI in the monkey and are disrupted by PCP.

Keywords *N*-Methyl-D-aspartate · Event-related potentials · Glutamate · Thought disorder · Schizophrenia

Introduction

Prepulse inhibition (PPI) of the acoustic startle reflex (ASR) is a widely used measure of sensorimotor gating dysfunction in schizophrenia (Braff and Geyer 1990; Geyer et al. 1990; Braff et al. 1992, 1999; Kumari et al. 2000; Parwani et al. 2000). Severity of PPI deficits correlate with severity of negative symptoms and, particularly, with thought disorder in at least some studies (Perry and Braff 1994; Braff et al. 1999; Perry et al. 1999). Further, deficits have been demonstrated in both acutely decompensated and stabilized patients with schizophrenia (Parwani et al. 2000), and in both unmedicated and medicated individuals (Braff et al. 1999), suggesting that it may constitute a trait marker of the disorder.

A particular advantage of the PPI paradigm is that rodents show startle inhibition similar to that observed in humans. Rodent studies can therefore be used to evaluate potential neurochemical mechanisms underlying PPI deficits in schizophrenia (Braff and Geyer 1990; Geyer et al. 1990; Swerdlow and Geyer 1998). However, rodent studies are somewhat limited by the facts that the exact phenomenon being studied differs between species (whole body versus eyeblink startle), and that response to pharmacological agents may, in some cases, also differ (Gouzoulis-Mayfrank et al. 1998; Vollenweider et al. 1999). A potential alternate approach to pharmacological dissection of PPI deficits in schizophrenia is the use of primate models. We have recently demonstrated PPI in a New World species, *Cebus apella*, suggesting that these monkeys may be used for pharmacological investigation of PPI along with rodents (Linn and Javitt 2000). The present study investigates PPI in an Old World species, *M. fascicularis* (cynomolgus).

Inhibition of startle response occurs when prepulses precede startle pulses by 30–500 ms, with maximal inhibition in both rodents and humans seen at prepulse-pulse interstimulus intervals (ISI) of 60–120 ms (Braff and Geyer 1990; Filion et al. 1993). In humans, prepulse stimuli also produce latency facilitation such that startle latency is shorter in prepulse than in pulse alone trials (Braff et al. 1999; Parwani et al. 2000). An additional goal of this study was to determine whether Old World monkeys show latency facilitation similar to that observed in humans.

A final goal of this study was to evaluate the effects of phencyclidine (PCP) on PPI in the macaque. PCP and related agents (e.g. ketamine) are potent drugs of abuse that induce schizophrenia-like symptoms in humans

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by blocking neurotransmission at *N*-methyl-D-aspartate (NMDA)-type glutamate receptors (Javitt and Zukin 1991). PCP (Mansbach and Geyer 1989; Bakshi and Geyer 1997), ketamine (Mansbach and Geyer 1991; Swerdlow et al. 1998) and other NMDA antagonists (al-Amin and Schwarzkopf 1996; Bakshi et al. 1999) disrupt PPI in rodents. However, in the one human study conducted to date, no effects of ketamine were observed (van Berckel et al. 1998). In our prior *Cebus* study, PCP was found to disrupt PPI at a dose that did not reduce responses to startle pulses alone. The present study evaluates whether similar effects of PCP are observed in a species phylogenetically closer to humans.

In this study, a single monkey was studied repeatedly. Although this introduces a potential order confound, PPI has been shown to be stable over repeated sessions in individual subjects (Abel et al. 1998; Cadenhead et al. 1999). Stability over repeated testing sessions was also observed in our prior *Cebus* study (Linn and Javitt 2000).

Materials and methods

Studies were performed in accordance with "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985). Recordings were obtained over repeated sessions from a single monkey (*M. fascicularis*) implanted with a head bar affixed to the skull to permit head fixation during recording sessions. There were no apparent alterations in the prepulse effect over time, permitting repeated testing of the same individual.

All testing was performed between 4 and 7 p.m. to minimize time of day effects. Experiments were conducted every third day. Pharmacological experiments were repeated at most every 6 days.

All recordings took place in an electrically shielded recording chamber. For recordings, the monkey was seated in a custom fitted primate chair (Primate Products, Tugunja, Calif., USA) and headphones (Sony Model MDR-V100) fitted with 8 cm padded collars covered the animal's ears without restraining them. Standard Grass subcutaneous needle electrodes were placed 1.5 cm above and 1 cm lateral to each eye. An implanted stainless steel occipital bone screw served as reference. Similar data were obtained from left and right eyes. Presented data are from left eye only. After being secured in the recording apparatus, the animal was allowed to acclimate for 5 min while 65 dB white noise was presented.

Stimuli were generated using a Neuroscan STIM system (Neuroscan, El Paso, Tex., USA). Background white noise was generated with a Model 1007A Noise Making Module (Nicolet Instruments, Madison, Wisc., USA). Stimuli and noise were mixed and amplified using a Realistic power amplified (Tandy Corporation, Forth Worth, Tex., USA) and calibrated using a sound pressure meter.

In all experiments, startle pulses consisted of 115 dB SPL white noise bursts of 30 ms duration presented against a 65 dB white noise background. The prepulse consisted of a 72 dB, 30 ms white noise burst. For parametric experiments, 120 trials were presented during an experiment. Each trial consisted of a startle stimulus alone, or a prepulse trial with a prepulse-pulse interval of 30, 50, 100 or 200 ms. Each of the five trials types was presented 24 times during the block in pseudorandom order. The interval between successive trials was varied from 12 to 30 s.

For pharmacological experiments, 40 trials were presented per block. In one-half of trials, startle stimuli were presented alone. In the remaining half, startle stimuli were preceded by prepulses with a prepulse-pulse interval of 50 ms. Recordings were obtained both prior to and following administration of PCP (0.25 mg/kg, IM) or saline. Post-drug recordings commenced 12 min following PCP administration. By this time, the monkey typically would no longer accept a juice reward.

EMG activity was amplified ×1000 with low and high filter settings of 0.15 Hz to 3 kHz using Grass Model 7 amplifiers (Astromed, Warwick, R.I., USA). Data were digitized and recorded continuously to computer disk along with digital timing tags using a Neuroscan SCAN system (Neuroscan). Epochs (0–120 ms) were constructed off-line, baseline corrected relative to the 0- to 20-ms latency period and rectified. Epochs containing artifact or not containing an obvious startle response were excluded. Remaining trials were averaged. Peak amplitudes and their corresponding latencies were scored in the 20- to 100-ms recording epoch, relative to 0–20 ms baseline.

PPI was determined based upon the relative amplitude and latency of peak response in the prepulse condition, compared to the amplitude and latency of response in the pulse alone condition. Effects of PCP (0.25 mg/kg IM) and saline were determined in separate experiments in which PPI was measured prior to and following drug administration (four experiments each). In one experiment (saline), post-drug data were not obtained for technical reasons. Pre-drug data from the PCP and saline sessions were not significantly different. For statistical analysis, therefore, pre-drug baseline data from these sessions were combined. Data were analyzed by one-way analysis of variance across baseline, saline and PCP conditions with follow-up protected *t*-tests. All statistics are two-tailed. Data are mean±SD.

Results

An initial series of studies evaluated PPI as a function of ISI. Prepulses were delivered at 30, 50, 100 or 200 ms before the startle stimulus. Maximal PPI was observed at an interval of 50–100 ms (Fig. 1). A significant effect was observed on latency, as well as amplitude, of response. Maximal latency facilitation was observed in the 100 ms ISI condition.

To investigate effects of PCP on PPI, recordings were conducted using a 50-ms interval. In each session, recordings were obtained prior to and following treatment with either PCP (0.25 mg/kg IM) or saline (Table 1). PCP administration did not significantly reduce amplitude of the ASR to the pulse alone (F=1.3, df=2,12, NS). However, PCP did significantly reduce PPI (F=12.3, df=2,12, P=0.001), with reductions being significant relative to both pretreatment baseline (t=4.47, df=10,

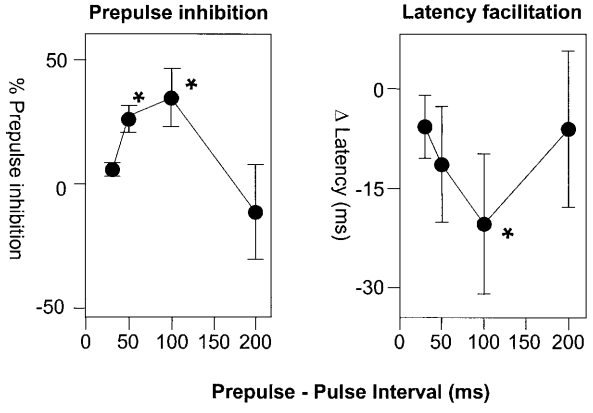

Fig. 1 Effect of prepulse–pulse interval (ISI) on prepulse inhibition and latency facilitation of the acoustic startle response

Table 1 Mean (±SD) amplitude and latency of the acoustic startle response to auditory stimuli (pulses) presented alone or following a prepulse stimulus. Values in *bold* are significantly different from saline control

Condition (number of experiments)	Amplitude			Latency		
	Pulse alone	Prepulse-pulse	% Prepulse inhibition	Pulse alone	Prepulse-pulse	Latency facilitation
Pre-treatment (*n*=8)	302.9±56.6	202.8±75.3	34.8±15.0	66.9±8.0	46.3±9.0	20.6±7.6
Post-treatment–saline (*n*=3)	288.4±58.7	163.6±87.3	45.7±17.9	77.2±56.4	59.6±3.9	17.6±9.2
Post-treatment–PCP (*n*=4)	246.7±57.9	260.4±77.3	**–5.3±13.8**	61.0±11.9	59.8±4.1	1.2±10.4

P=0.001) and saline (*t*=4.29, *df*=5, *P*=0.008). Further, whereas significant PPI was observed under both baseline (*t*=5.30, *df*=7, *P*=0.0003) and post-saline conditions (*t*=4.42, *df*=2, *P*=0.047), no significant PPI was observed following PCP administration (*t*=0.77, *df*=3, NS).

Similar effects of PCP were observed on latency facilitation. PCP treatment did not significantly affect latency of response to pulse alone trials (*F*=0.4, *df*=2,12, NS). However, it did significantly reduce the degree of prepulse-induced latency facilitation (*F*=6.9, *df*=2,12, *P*=0.01). Post-PCP values were significantly different from baseline values (*t*=3.70, *df*=10, *P*=0.004), although they were significantly different from post-saline values only at trend level (*t*=2.16, *df*=8, *P*=0.08). Significant latency facilitation was observed under baseline conditions (*t*=7.67, *df*=8, *P*=0.0001) and following saline infusion (*t*=4.46, *df*=4, *P*=0.01), but not following PCP administration (*t*=0.23, *df*=4, NS).

Discussion

The primary finding of this study is that similar PPI effects were observed in an Old World monkey as had previously been observed in New World monkeys. Further, as in Cebus monkeys, the ISI dependence of PPI in the macaque was very similar to the ISI dependence in humans (Braff and Geyer 1990). Finally, as opposed to rodent PPI, significant alterations were observed in both amplitude and latency of response. Both absolute response latencies and degree of latency facilitation were similar to those observed in human studies (Braff et al. 1999). Thus, while substantially more difficult to perform than rodent PPI experiments, monkey studies may more closely approximate the human condition and may therefore be used to complement the large literature that has accumulated concerning drug effects on rodent PPI.

PCP, at a dose that did not abolish the startle response to the pulse alone, significantly reduced the differential response to prepulse-pulse compared to pulse alone trials, indicating that effects of PCP in this paradigm may provide an effective target for development of drugs that could reverse cognitive deficits associated with both PCP abuse and schizophrenia. Interestingly, following PCP administration, both PPI of the ASR amplitude and latency facilitation of the startle response were abolished. In contrast, in schizophrenia latency facilitation remains intact, despite reduction of startle amplitude (Braff et al. 1999; Parwani et al. 2000). To the extent that the disruption of latency facilitation can be confirmed, it would represent a clear difference between PCP-induced changes and patterns observed in schizophrenia. It is also possible that differential effects would be observed after chronic, rather than acute, PCP dosing (Martinez et al. 1999). Thus, whether or not PCP disrupts latency facilitation in monkeys must remain an open question.

The dose of PCP used in this study caused significant behavioral sedation in the monkey. However, it is unlikely that the effects of PCP are due to generalized sedation, since both clonidine and diazepam produce sedation and attenuate startle response but do not attenuate PPI effects in humans (Abduljawad et al. 1997). An additional potential issue is that PCP might disrupt auditory thresholds in monkeys, so that monkeys might not be able to hear the prepulse even though they continue to respond to the pulse alone. However, PCP, at a dose similar to that used here, has been shown not to alter auditory thresholds in monkeys (Lukas et al. 1985). Moreover, ASR amplitude was unchanged in this study and auditory ERP response to repetitively presented stimuli was unchanged in a prior study (Javitt et al. 2000), suggesting that PCP treatment has minimal response on thresholds to individual stimuli. In contrast, it should be noted that ketamine, which is widely used in animal and human research, does elevate auditory thresholds (Lukas et al. 1985).

A limitation of this study is that it relies on data from a single animal. It was originally intended to study PPI in a second implanted animal. However, that animal showed insufficient ASR even in the absence of prepulses and so could not be used. In clinical studies, approximately 20% of subjects may fail to show ASRs that are sufficiently robust to permit meaningful analysis of the data and so must be excluded (e.g., Braff et al. 1999). This study shows that a similar phenomenon occurs in other primate species as well.

In conclusion, the present study demonstrates PPI of acoustic startle in a single macaque monkey studied repeatedly, along with PCP-induced disruption of PPI. Latency facilitation was observed along with amplitude reduction. Old World monkeys thus may serve as useful subjects for evaluation of neurochemical mechanisms underlying PPI deficits in schizophrenia.

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References

Abduljawad KA, Langley RW, Bradshaw CM, Szabadi E (1997) Effects of clonidine and diazepam on the acoustic startle response and on its inhibition by "prepulses" in man. J Psychopharmacol 11:29–34

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

al-Amin HA, Schwarzkopf SB (1996) Effects of the PCP analog dizocilpine on sensory gating: potential relevance to clinical subtypes of schizophrenia. Biol Psychiatry 40:744–754

Bakshi VP, Geyer MA (1997) Phencyclidine-induced deficits in prepulse inhibition of startle are blocked by prazosin, an alpha-1 noradrenergic antagonist. J Pharmacol Exp Ther 283: 666–674

Bakshi VP, Tricklebank M, Neijt HC, Lehmann-Masten V, Geyer MA (1999) Disruption of prepulse inhibition and increases in locomotor activity by competitive *N*-methyl-D-aspartate receptor antagonists in rats. J Pharmacol Exp Ther 288:643–652

Braff DL, Geyer MA (1990) Sensorimotor gating and schizophrenia. Human and animal model studies. Arch Gen Psychiatry 47:181–188

Braff DL, Grillon C, Geyer MA (1992) Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiatry 49:206–215

Braff DL, Swerdlow NR, Geyer MA (1999) Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. Am J Psychiatry 156:596–602

Cadenhead KS, Carasso BS, Swerdlow NR, Geyer MA, Braff DL (1999) Prepulse inhibition and habituation of the startle response are stable neurobiological measures in a normal male population. Biol Psychiatry 45:360–364

Filion DL, Dawson ME, Schell AM (1993) Modification of the acoustic startle-reflex eyeblink: a tool for investigating early and late attentional processes. Biol Psychol 35:185–200

Geyer MA, Swerdlow NR, Mansbach RS, Braff DL (1990) Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull 25:485–498

Gouzoulis-Mayfrank E, Heekeren K, Thelen B, Lindenblatt H, Kovar KA, Sass H, Geyer MA (1998) Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. Behav Pharmacol 9:561–566

Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148:1301–1308

Javitt DC, Jayachandra M, Lindsley RW, Specht CM, Schroeder CE (2000) Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP). Clin Neurophysiol 111:833–836

Kumari V, Soni W, Mathew VM, Sharma T (2000) Prepulse inhibition of the startle response in men with schizophrenia: effects of age of onset of illness, symptoms, and medication. Arch Gen Psychiatry 57:609–614

Linn G, Javitt DC (2000) Phencyclidine (PCP) induced deficits of prepulse inhibition in monkeys. Neuroreport 12:117–120

Lukas SE, Hienz RD, Brady JV (1985) The effects of phencyclidine and ketamine on sensory thresholds and reaction times in the baboon. Pharmacol Biochem Behav 23:743–747

Mansbach RS, Geyer MA (1989) Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. Neuropsychopharmacology 2:299–308

Mansbach RS, Geyer MA (1991) Parametric determinants in pre-stimulus modification of acoustic startle: interaction with ketamine. Psychopharmacology 105:162–8

Martinez ZA, Ellison GD, Geyer MA, Swerdlow NR (1999) Effects of sustained phencyclidine exposure on sensorimotor gating of startle in rats. Neuropsychopharmacology 21:28–39

Parwani A, Duncan EJ, Bartlett E, Madonick SH, Efferen TR, Rajan R, Sanfilipo M, Chappell PB, Chakravorty S, Gonzenbach S, Ko GN, Rotrosen JP (2000) Impaired prepulse inhibition of acoustic startle in schizophrenia. Biol Psychiatry 47:662–9

Perry W, Braff DL (1994) Information-processing deficits and thought disorder in schizophrenia. Am J Psychiatry 151:363–367

Perry W, Geyer MA, Braff DL (1999) Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. Arch Gen Psychiatry 56:277–281

Swerdlow NR, Geyer MA (1998) Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. Schizophr Bull 24:285–301

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

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

Vollenweider FX, Remensberger S, Hell D, Geyer MA (1999) Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. Psychopharmacology 143:365–372