Psychopharmacology (2003) 169:340–353
DOI 10.1007/s00213-002-1254-4

ORIGINAL INVESTIGATION

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Prepulse inhibition during withdrawal from an escalating dosage schedule of amphetamine

Received: 6 March 2002 / Accepted: 21 August 2002 / Published online: 12 November 2002

Abstract *Rationale:* Psychomotor stimulants can induce psychotic states in humans that closely resemble those observed in patients with idiopathic schizophrenia. Attentional and sensorimotor gating impairments are observed in schizophrenic patients using the latent inhibition (LI) and prepulse inhibition (PPI) behavioral assays, respectively. Our previous studies demonstrated that after 4 days of withdrawal from a period of amphetamine (AMPH) administration, animals exhibited disrupted LI but normal PPI. *Objective:* The aim of the present study was to test PPI in AMPH-withdrawn rats under experimental conditions similar to those used to best demonstrate locomotor sensitization following AMPH withdrawal. *Methods:* We examined the effects on PPI of (1) pairing drug injections with PPI test-associated cues, (2) administration of a low-dose dopamine agonist challenge and (3) testing following longer withdrawal periods (23, 30, 60 days). *Results:* Although none of these conditions revealed a disruption of PPI in AMPH-withdrawn rats, we did observe that the acoustic startle response was reduced during a restricted time period following AMPH withdrawal. Similar to our previous findings, AMPH-withdrawn animals showed disrupted LI on day 16 of withdrawal and locomotor sensitization to a challenge injection of AMPH after 62 days of withdrawal. *Conclusion:* We conclude that the effects of repeated AMPH on PPI are not modulated by the same experimental parameters known to be important for eliciting locomotor sensitization and that withdrawal from the schedule of AMPH administration used in this study models only specific cognitive dysfunctions linked to schizophrenic symptoms, since LI was disrupted but PPI was not affected.

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Keywords Startle · Schizophrenia · Latent inhibition · Sensitization · Rat

Introduction

Administration of amphetamine (AMPH) can induce symptoms of psychosis in humans. This outcome is most frequently associated with a chronic high-dose escalating pattern of stimulant abuse (Davis and Schlemmer 1980; Angrist 1994). Given that stimulant-induced psychosis in humans closely resembles the psychosis observed in patients with idiopathic schizophrenia (Ellinwood 1967; Griffith et al. 1972; Snyder 1973), it has been suggested that similar neural adaptations could be responsible for the development of these two phenomena. It is well known that repeated exposure to psychostimulants, like AMPH or cocaine, induces psychomotor sensitization in experimental animals. This phenomenon is indicated by a progressive behavioral augmentation of responses (increased locomotion, stereotypies) to drug challenge, as well as an enhanced release of nucleus accumbens dopamine (DA) following challenge AMPH administration (Robinson and Becker 1986; Segal and Kuczenski 1994). It has therefore been proposed that studies of the neural bases of psychomotor stimulant sensitization might yield insights into the biological mechanisms responsible for the onset of schizophrenia (Kokkinidis and Anismann 1980; Robinson and Becker 1986; Lieberman et al. 1990).

Specifically, Lieberman and colleagues have suggested that a process of endogenous sensitization, in which schizophrenic patients exhibit enhanced DA release in response to AMPH challenge, is a key element in the pathology of the disease (Lieberman et al. 1990; Lieberman et al. 1997). Recent positron emission tomography (PET) imaging studies examining competition for receptor occupancy between endogenously released DA and D2 receptor radioligand binding have established that not only do schizophrenic patients show enhanced striatal DA release in response to AMPH administration (i.e., a sensitized response) but the DA response is positively

correlated with the severity of their positive symptoms (reviewed in Laruelle 2000). Thus, there is convincing evidence for the involvement of sensitization processes in the expression of the schizophrenic phenotype. A number of studies have also established that, during the acute phase of withdrawal from high-dose AMPH, animals often exhibit depressive-like symptoms – in particular, anhedonia as it is indexed by decreased sensitivity to rewarding brain stimulation (Lin et al. 1999; Koob and Le Moal 2001). However, the state of anhedonia during AMPH withdrawal is typically very transient, persisting for up to only 3–5 days following the last administration. In comparison, behavioral sensitization can persist even after prolonged periods of abstinence, a time course which is perhaps more consistent with the long-term adaptations typically associated with chronic mental illness.

Two animal models believed to reflect cognitive/attentional deficits typical of schizophrenic patients are latent inhibition (LI) of classically conditioned responding and prepulse inhibition (PPI) of the startle response (Weiner and Feldon 1997; Swerdlow et al. 2000). Both LI and PPI are disrupted in schizophrenic patients, and these deficits can be restored by neuroleptic treatment (Baruch et al. 1988; Gray et al. 1992, 1995; Weiner and Feldon 1997; Braff et al. 2001). LI refers to the observation that repeated exposure to a stimulus without consequence comes to impede the formation of subsequent associations with that stimulus (Lubow 1973). Our previous studies have shown that LI is disrupted in rats pretreated with escalating doses of AMPH during the first two weeks of withdrawal (Murphy et al. 2001b). Moreover, the antipsychotic drugs haloperidol and clozapine restored LI in AMPH-withdrawn rats (Russig et al. 2002). Thus, the LI results during AMPH withdrawal are consistent with the hypothesis, based on neuroimaging studies, that sensitized levels of DA are associated with an animal model of schizophrenic deficits.

PPI is the phenomenon whereby moderate-intensity prepulse stimuli attenuate startle responses to subsequent intense stimulation (Graham 1975; Braff et al. 1978; Hoffman and Ison 1980). This phenomenon is thought to result from the activation of central inhibitory mechanisms that gate behavioral responses to ensuing stimuli (Swerdlow et al. 1992; Taylor et al. 1995). Acute administration of psychomotor stimulants such as AMPH, apomorphine (APO) or selective D_2 DA agonists disrupts PPI, such that startle responses are less influenced by the prepulse presentations (Mansbach et al. 1988; Peng et al. 1990; Bakshi et al. 1995; Caine et al. 1995; Taylor et al. 1995; Sills 1999). It is believed that PPI disruption may index the sensorimotor gating deficit observed in schizophrenic patients (Braff et al. 1978; Braff and Geyer 1990) and that, consequently, the assessment of psychomotor stimulant effects on PPI may be a valid animal model of sensorimotor gating disturbances in schizophrenia (Braff et al. 1992; Swerdlow et al. 1992, 1994). However, previous studies from our laboratory showed no effect of the escalating dose AMPH treatment on PPI tested on day 4 of withdrawal (Murphy et al. 2001b). Given the similarities in brain areas and cognitive functions implicated in LI and PPI (Weiner and Feldon 1997; Swerdlow et al. 2000) and the clear disruptive effects of withdrawal from this escalating dose AMPH schedule on LI, it is somewhat surprising that AMPH withdrawal does not also affect PPI. The purpose of the present investigation was to further explore this issue of PPI disruptibility during AMPH withdrawal, by specifically examining the effects on PPI of experimental conditions that are known to maximize locomotor sensitization effects.

The role of contextual cues in psychostimulant-related behavior has been extensively studied in sensitization experiments (Robinson et al. 1998; Ohmori et al. 2000). It has been shown that under certain experimental circumstances, sensitization to psychostimulants is only detected when repeated drug administrations were previously paired with specific contextual cues (Hinson and Poulos 1981; Drew and Glick 1988; Badiani et al. 1995; Robinson et al. 1998). There is also direct evidence that drug-conditioned cues disrupt sensorimotor gating. A study with abstinent smokers indicated that a presentation of smoking-associated stimuli reduced PPI (Hutchison et al. 1999). Moreover, other studies have shown that PPI was reduced during withdrawal from repeated DA agonist treatment when drug administrations were repeatedly paired with PPI testing (Zhang et al. 1998; Martin-Iverson 1999) whereas repeated psychostimulant treatment that was not paired with PPI testing failed to result in PPI reduction (Mansbach et al. 1988; Druhan et al. 1998; Martinez et al. 1999; Byrnes et al. 2000; Adams et al. 2001). These studies suggest that PPI reduction following repeated psychostimulant administration may, like locomotor sensitization, be context dependent such that AMPH withdrawal-induced deficits in the PPI paradigm might only be detected if a drug-related cue were present during test. This hypothesis was tested in the present study by measuring PPI in AMPH-withdrawn animals that previously received drug injections paired with an environment similar to that experienced during PPI testing.

Locomotor sensitization is always measured following the administration of a DA agonist challenge. Swerdlow et al. (1995) previously demonstrated PPI disruption in rats with lesions of the hippocampus and prefrontal cortex following the administration of very low doses of the direct DA agonist APO, whereas lesioned animals receiving vehicle injections did not show reduced PPI. In the present study, we sought to determine whether a PPI disruption during AMPH withdrawal might be similarly revealed following low-dose APO and AMPH challenge injections.

Finally, it has been reported that sensitization of locomotor behavior becomes more pronounced following longer withdrawal periods (Paulson et al. 1991; Paulson and Robinson 1995). That is, effects of AMPH pretreatment that are not apparent during the first few days of withdrawal have been found to emerge 1–2 weeks later. Therefore, one objective of the present study was to

investigate the time course of AMPH withdrawal effects on PPI, to determine whether PPI disruption may become evident only after an extended withdrawal period, similar to behavioral sensitization.

The present study was designed to test the hypothesis that effects of withdrawal from an escalating dosage schedule of AMPH administration on PPI might be revealed by experimental conditions similar to those used to best demonstrate locomotor sensitization. These include administration of a DA agonist challenge, pairing of drug administration with cues also associated with the PPI testing protocol and testing after withdrawal intervals longer than that used in a previous study (4 days). In addition, to enable a direct comparison of LI and PPI results in the same animals, we tested these animals for LI following 16 days of withdrawal. Selected animals were also tested for locomotor sensitization to a challenge AMPH injection following 2 months of withdrawal.

Materials and methods

Animals

We used three batches of rats, 48 animals for experiment 1, 32 animals for experiment 2, and 32 animals for experiments 3 and 4 (Table 1). Male Wistar rats (Zur: WIST [HanIbm]; 250–350 g) obtained from our in-house specific-pathogen-free (SPF) breeding facility were used as subjects in these experiments. Animals were housed individually in Macrolon type-III cages (48×27×20 cm) under reversed-cycle lighting (lights on 2100–0900 hours) in a temperature- (21±1°C) and humidity- (55±5%) controlled animal facility. Food (Kliba 3430, Klibamühlen, Kaiseraugst, Switzerland) and water were available ad libitum. All experiments were carried out during the dark phase of the light/dark cycle and in agreement with Swiss Cantonal regulations for animal experimentation.

Drugs and pretreatment procedure

D-Amphetamine sulfate (Sigma Chemical Company, St. Louis, Mo., USA) was dissolved in a 0.9% NaCl solution to obtain concentrations of 0.5, 1, 2, 3, 4 and 5 mg/ml AMPH (calculated as the salt). Vehicle-treated groups received 0.9% NaCl solution. A solution of 0.03 mg/kg APO was made by dissolving APO in 0.9% NaCl with 0.1% ascorbic acid. All solutions were freshly prepared and given in a volume of 1 ml/kg. AMPH and saline (SAL) were injected intraperitoneally during the drug pretreatment period and as a challenge administration, whereas APO and SAL administered just prior to PPI testing were injected subcutaneously. During the escalating-dose pretreatment schedule, animals received three injections per day for six consecutive days, beginning with a 1 mg/kg dose and ending with doses of 5 mg/kg AMPH on the sixth day of the cycle. The control group received injections of SAL (0.9%) according to the same schedule. The dosing parameters are summarized in Table 2.

Table 2 Escalating dose amphetamine injection schedule (drug doses in mg/kg)

	0900 hours	1500 hours	2100 hours
Day 1	1	2	3
Day 2	4	5	5
Days 3–6	5	5	5

Apparatus

PPI apparatus

Testing was conducted in four ventilated startle chambers (SR-LAB, San Diego Instruments, San Diego, Calif.), each containing a transparent Plexiglas tube (diameter 8.2 cm, length 20 cm) mounted on a Plexiglas frame. Noise bursts were presented via a speaker mounted 24 cm above the tube. Motion inside the tube was detected by a piezoelectric accelerometer below the frame. The amplitude of the whole body startle to an acoustic pulse was defined as the average of one-hundred and fifty 1-ms accelerometer readings collected from pulse onset.

Two-way avoidance apparatus

Testing was conducted in four identical shuttle boxes (Coulbourn Instruments, Allentown, Pa.; model E10–16TC), each set in a ventilated, sound- and light-attenuating shell (model E10–20). The internal dimensions of each chamber were 35×17×21.5 cm. The grid floor of each chamber was divided into two identical compartments by an aluminum hurdle (17-cm long, 4-cm high). The barrier was very thin to prevent animals from balancing on it, thus avoiding shock. Foot shocks were supplied to the grid floor by a constant direct current source (model E 13–14) and a scanner (model E 13–13) set at 0.5-mA intensity. During the experimental session, each chamber was illuminated by a diffuse light source (house light), mounted 19 cm above the grid floor in the center of

Table 1 Treatment conditions and withdrawal periods for animals used in experiments 1–4. *inj* injection, *PPI* prepulse inhibition, *LI* latent inhibition, *SAL* saline, *AMPH* amphetamine

Pretreatment		Withdrawal day and test							
		Day 4	Day 5	Day 16	Day 23	Day 24	Day 30	Day 60	Day 62
Experiment 1	SAL	PPI SAL inj. + PPI	SAL/APO inj. + PPI	LI test					
	AMPH	PPI SAL inj. + PPI							
	SAL/tube	SAL inj. + PPI							
	AMPH/tube	SAL inj. + PPI							
Experiment 2	SAL				PPI	SAL/AMPH inj. + PPI			
	AMPH								
Experiments 3 and 4	SAL						PPI	PPI	Locomotor sensitization
	AMPH								

the side walls. The conditioned stimulus (CS) was a tone of 85 dB produced by a speaker (model E 12–02) placed behind the shuttle box on the floor of the shell.

Apparatus for detection of locomotor activity

Sixteen stations were used. Each station was a 25-cm wide × 40-cm long × 40-cm high compartment contained within an individual sound-attenuating wooden cabinet. One end wall of the compartment, the device wall, consisted of wooden panels, whereas the remaining walls were clear plastic. The device wall contained a water bottle spout and an opening that provided access to powdered chow in a feeding bin. A large drop-down door in the front wall of the compartment allowed easy access to the animal. The floor of each compartment was a black removable pan holding a thin layer of dark, absorbent, autoclaved earth. The ceiling was open. A 4-W lamp (Lampi, model number 5304), outside the compartment but within the cabinet, was used to produce a light/dark cycle. Each lamp was connected to an appliance timer (Migros type NL24MI). A fan mounted on the wall of a cabinet provided ventilation. A camera, centered approximately 49 cm above the compartment floor, was mounted in the ceiling of each cabinet. The field of vision of the camera included the entire area of the compartment in which an animal could move, and images from this camera were used to quantify activity. The stations were located in a well-ventilated, temperature-, humidity- and sound-controlled room that was used only for this experiment. The room could be illuminated with red ceiling lights. The cameras from all the stations were connected to a 16-channel multiplexer (Sony model YS-DX216CE) located in an adjoining room, and the multiplexer was connected, in turn, to a Dell Computer (OptiPlex GXpro with a Pentium Pro Processor) running image analysis software. The software was a custom-written Visual Basic Program (P. Schmid, Laboratory of Behavioral Neuroscience ETH Zurich) that was based on a NIH Image Analysis script. The software "grabbed" an image from each station every second and compared this image pixel by pixel with an image obtained the second before. Each white Wistar rat was monitored against a darker background. The percentage of pixels that went from dark to light or from light to dark from one second to the next was quantified. This percentage provided a measure of the magnitude of an animal's displacement or "activity". One-second activity values ranged from 0% (no movement) to approximately 7.5%. The multiplexed images from the 16 stations could be taped simultaneously on a single videotape with a video recorder (Sony model SVT-1000P), and the 16 images could be viewed simultaneously on a single monitor.

Behavioral testing procedures

PPI procedure

A background noise level of 68 dB(A) was maintained throughout each test session. A test session started with 5 min of acclimatization, after which four startle pulses [30 ms, 120 dB(A)] were presented. These four initial startle pulses served to achieve a relatively stable level of startle reactivity for the remainder of the test session, as the most rapid habituation of the startle reflex occurs within the first few startle pulse presentations (Koch 1999). To measure PPI, six blocks of 11 trials were then presented. The 11 trials of each block included: two "pulse-alone" trials, one "prepulse followed by pulse" and one "prepulse-alone" trial for each of four prepulse intensities and one "no-stimulus" trial. The prepulses were broadband bursts of 20-ms duration and an intensity of either 72, 76, 80 or 84 dB(A). Between prepulse offset and pulse onset, there was a time interval of 80 ms. The different trial types were presented pseudo-randomly with an inter-trial interval of 10–20 s (average 15 s). Each complete test session lasted about 23 min. The percentage PPI (%PPI) induced by each prepulse intensity was calculated as: [100–(100×startle amplitude on "prepulse followed by pulse" trial)/(startle amplitude on "pulse-alone" trial)].

Active avoidance procedure

The LI procedure in the two-way active avoidance paradigm was carried out over 3 days. Animals received two consecutive daily sessions of preexposure to both the tone and the apparatus or only to the apparatus, and a conditioning session on the third day.

Days 1–2: preexposure to the apparatus or apparatus/tone CS. The preexposure sessions took place on day 14 and day 15 of withdrawal. Each non-preexposed (NPE) animal was placed in the shuttle box with the house light on for a period of 50 min. Each preexposed (PE) rat received 50 presentations of the tone (mean variable inter-stimulus interval =50 s [range 10–90 s], duration 10 s). A general evaluation of each animal's activity level was supplied by recording the total number of crossings during the preexposure sessions.

Day 3: conditioning to the CS. On day 16 of withdrawal, all animals were tested for conditioned active avoidance. Each animal was placed into the shuttle box and received 100 avoidance trials on a variable interval schedule of 50 s, ranging from 10 s to 90 s. Each avoidance trial began with a 10-s tone followed by a 2-s, 0.5 mA shock, the tone remaining on with the shock. If the rat crossed the barrier to the opposite compartment during the tone, the stimulus was terminated and no shock was delivered (avoidance response). A crossing response during the shock terminated the tone and the shock (escape response). If the rat failed to cross during the entire tone-shock trial, the tone and the shock terminated after 12 s (unfinished trial). As an additional measure of activity, we analyzed the total number of inter-trial crossings.

Sensitization procedure

AMPH-induced locomotion was assessed in 16 test boxes and testing was carried out in three stages. In the first stage, each rat was placed in the apparatus (withdrawal day 61) and allowed to remain there undisturbed for 14 h. On withdrawal day 62, rats were removed from the apparatus and injected with 0.9% saline and again placed into the apparatus for the second stage, consisting of 1 h free exploration. Rats were then injected with 0.5 mg/kg AMPH and returned to the apparatus for 6 h free exploration. Activity levels were monitored for the entire duration of each of the three stages.

Experiment 1: effects of drug-conditioned cues and AMPH withdrawal on PPI and LI

1.1. Forty-eight Wistar rats were separated into six experimental groups (n=8 per group) in this experiment (Table 1). During the drug pretreatment period, eight SAL and eight AMPH-treated animals (SAL/tube and AMPH/tube groups) were placed directly following each injection into transparent plexiglas tubes (diameter 10.5 cm, length 28 cm) which were similar to PPI restraint tubes, but larger in size. The tubes were placed within normal home cages that did not contain sawdust. Following each 20-min exposure to the tube, animals were returned to their home cages. The remaining 32 animals were returned to their home cages immediately following each injection of SAL (n=16) or AMPH (n=16). Preliminary results suggested that an injection of saline prior to testing reduced PPI; therefore, we compared the effects of AMPH withdrawal on PPI in animals which did (SAL/SAL and AMPH/SAL groups) and did not (SAL and AMPH groups) receive a saline injection prior to test. On day 4 of withdrawal from AMPH, all animals were tested for PPI in four squads randomized for drug pretreatment and the different cue conditions. The SAL/SAL and the AMPH/SAL as well as the SAL/tube and the AMPH/tube animals received a SAL injection (i.p.) 5 min before PPI testing was conducted.

1.2. All of the animals from experiment 1.1 were used for the APO challenge PPI test on day 5 of withdrawal. Half of the animals in each drug/cue condition received 0.03 mg/kg APO (s.c.) and the other half received a SAL injection (s.c.) 5 min prior to placement in the PPI apparatus (n=4 per group).
1.3. All animals were subsequently tested for LI in a two-way active avoidance paradigm as described above. The two preexposure sessions took place on day 14 and day 15 of withdrawal, and the test session was conducted on day 16 of withdrawal. PE and NPE groups were counterbalanced for all previous treatments and testing conditions (n=12 per group).

Experiment 2: effects of AMPH withdrawal on the acoustic startle response and PPI at 23–24 days of withdrawal, with and without a 0.5-mg/kg AMPH challenge injection

2.1. Two groups of 16 animals each were pretreated with either AMPH or SAL. Following each injection, all animals were returned to their home cages. The effects of AMPH and SAL pretreatment on PPI and the acoustic startle response were assessed following 23 days of withdrawal. Animals did not receive any injection treatments on the test day.
2.2. On withdrawal day 24, half of the animals of each pretreatment group used in experiment 2.1 received an AMPH challenge injection of 0.5 mg/kg (i.p.) 5 min before beginning PPI/acoustic startle response testing (SAL/AMPH and AMPH/AMPH groups, n=8 per group). The remaining half of the animals received a SAL injection 5 min before the test (SAL/SAL and AMPH/SAL groups, n=8 per group).

Experiment 3: effects of 30 days and 60 days withdrawal from an escalating dosage schedule of AMPH on the acoustic startle response and PPI

Two additional groups of 16 animals each were pretreated with either AMPH or SAL. Following each injection, all animals were returned to their home cages. All rats were tested for the acoustic startle response and PPI, first on day 30 and then again on day 60 of withdrawal. Animals did not receive any injection treatments on the test days.

Experiment 4: AMPH sensitization of locomotor activity

At 61–62 days of withdrawal, 16 animals (8 SAL, 8 AMPH) from experiment 3 were tested for locomotor sensitization. Locomotor activity was measured during a baseline period of 14 h, over a 1-h period following a SAL injection, and over a 6-h period following a challenge injection of 0.5 mg/kg AMPH.

Data collection and analysis

For all experiments post-hoc comparisons were conducted using Fisher's protected least-significant difference test. Significant differences were accepted at P<0.05. All statistical analyses were performed with the StatView software program (Abacus Concepts, Inc., Berkeley, Calif., 1992).

Experiment 1

The startle amplitude of the PPI test on day 4 of withdrawal was analyzed using a 3×2×16 analysis of variance (ANOVA) design consisting of the factors of drug-related cue condition (none, SAL injection, tube and SAL injection) and drug pretreatment (SAL, AMPH) and a repeated-measurements factor of 16 pulse-alone presentations. Mean %PPI was analyzed using a 3×2×4 ANOVA design consisting of the same between-subjects factors and a repeated-measurements factor of four prepulse intensities. The ANOVAs used for the PPI test on withdrawal day 5 included an additional between-subjects factor of APO (SAL, APO) treatment. For the two preexposure sessions in the active avoidance shuttle box, the total number of crossings was analyzed using a 2×2×2 ANOVA with two between-subjects factors of drug pretreatment (AMPH, SAL) and preexposure (NPE, PE), and with two preexposure days as a within-subjects factor. For the active avoidance conditioning session, the 100 avoidance trials were separated into ten blocks of ten trials each. Percentage avoidance responses were analyzed using a 2×2×10 ANOVA consisting of between-subjects main factors of drug pretreatment and preexposure and a repeated-measurements factor of ten-trial blocks. Total numbers of inter-trial crossings were analyzed as an index of activity level using the between-subjects main factors of drug pretreatment and preexposure

Experiment 2

Analysis of the acoustic startle response and PPI on withdrawal day 23 was similar to experiment 1 but with only one between-subjects factor of drug treatment (SAL, AMPH). The analysis of acoustic startle and PPI on withdrawal day 24 also included a between-subjects factor of drug challenge (AMPH, SAL).

Experiment 3

Acoustic startle response and PPI on withdrawal day 30 and day 60 were analyzed similarly to in experiment 1 with a between-subjects factor of drug pretreatment (AMPH, SAL).

Experiment 4

Locomotor activity data were analyzed using three separate two-way ANOVAs for the no-drug baseline, saline and AMPH periods, each consisting of a between-subjects factor of drug pretreatment (SAL, AMPH) and a repeated-measurements factor of 28 blocks of 30 min (baseline period), 6 blocks of 10 min (SAL period) or 36 blocks of 10 min (AMPH period).

Results

Experiment 1: effects of drug-conditioned cues and AMPH withdrawal on PPI and LI

Experiment 1.1: effects of 4 days AMPH withdrawal and drug-conditioned cues on the acoustic startle response and PPI

A significant habituation of the startle response was seen over the 16 pulse-alone presentations in all groups (main effect of trials: $F_{15,630}$=8.42, P<0.0001). However, there were no significant effects of either drug pretreatment or cue condition (Fig. 1A, B, C). The mean %PPI as a function of prepulse intensity in the six conditions is also shown in Fig. 1D, E, F. The ANOVA yielded a significant main effect of prepulse intensity ($F_{3,126}$=83.77, P<0.0001), reflecting a gradual increase in PPI as a function of the intensity of the prepulse stimulus. However, there were no significant main effects or interactions involving the factors of drug pretreatment or cue condition on %PPI.

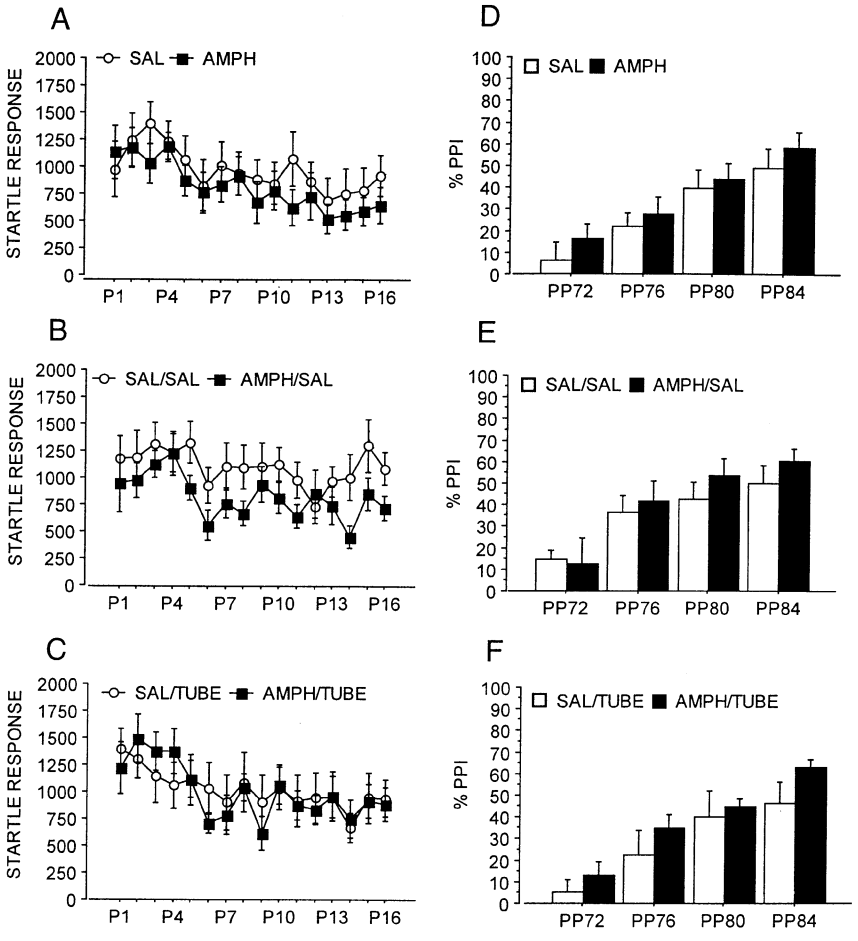

Fig. 1. **A**–**C** Startle responses during 16 pulse-alone trials. **D**–**F** Percentage prepulse inhibition (%PPI) measured in rats previously treated with amphetamine (AMPH) or saline (SAL) and assigned to one of six experimental conditions. Animals represented in **A**, **B**, **D** and **E** were returned to the home cage after each injection during the pretreatment phase and received either no injection treatment on the test day (**A**, **D**; AMPH and SAL groups) or a saline injection before testing (**B**, **E**; AMPH/SAL and SAL/SAL groups). Animals represented in **C** and **F** received AMPH and SAL injections during the pretreatment phase that were paired with placement into restraint tubes similar to those used during PPI/startle testing and also received a saline injection before testing (AMPH/tube and SAL/tube groups). %PPI was measured using a range of prepulse intensities (72, 76, 80 or 84 dB). Testing was conducted on day 4 of withdrawal. Values are means±SEM. n=8 per group

Experiment 1.2: effects of 5 days AMPH withdrawal, drug-conditioned cues and a 0.03-mg/kg APO challenge injection on the acoustic startle response and PPI

In experiment 1.1, no differences in PPI or acoustic startle were seen between those groups that received an injection prior to testing (SAL/SAL and AMPH/SAL groups) and those that did not (SAL and AMPH groups). Because all animals were to receive a SAL or APO injection before the PPI test in experiment 1.2, we collapsed the injected and non-injected control groups of experiment 1.1 to form a new no-cue treatment category. We analyzed the data in a 2×2×2 ANOVA design, including the factors of drug pretreatment (SAL, AMPH), cue treatment (no treatment, tube) and challenge treatment (SAL, APO).

Independent of any drug pretreatment or cue treatment, the animals again showed habituation of the startle response over the 16 pulse-alone presentations ($F_{15,600}$=11.72, P<0.0001, Fig. 2A–D) but no other significant main effects or interactions. The mean %PPI for all experimental groups is summarized in Fig. 2E–H. PPI was clearly evident in all groups and characterized by an increased amount of inhibition as a function of the intensity of the prepulse stimulus (main effect of prepulse intensity: $F_{3,120}$=39.10, P<0.0001). The analysis also revealed a significant main effect of cue treatment ($F_{1,40}$=4.54, P<0.05), reflecting increased PPI in the tube animals relative to the no-cue animals. Administration of 0.03 mg/kg APO reduced PPI overall (main effect of APO treatment: $F_{1,40}$=22.82, P<0.0001). No other significant main effects or interactions were detected. Thus, APO was not more effective in reducing PPI in AMPH-pretreated groups than in SAL-pretreated groups.

Experiment 1.3: effects of 16 days AMPH withdrawal on LI in the two-way active avoidance paradigm

PE and NPE groups were counterbalanced for all previous treatments. There were no significant main effects or interactions including the factors of cue condition or prior APO treatment on behaviors measured during either the preexposure or conditioning sessions; therefore, the data were analyzed in a 2×2 design including only the factors of drug pretreatment (SAL, AMPH) and preexposure (NPE, PE).

Preexposure sessions. A comparison of the total number of crossings during the two preexposure sessions revealed a near-significant tendency for greater activity on the first preexposure day relative to the second day ($F_{1,44}$=3.16, P=0.08; 35.5±2.3 for session 1 versus 31.8±2.0 for

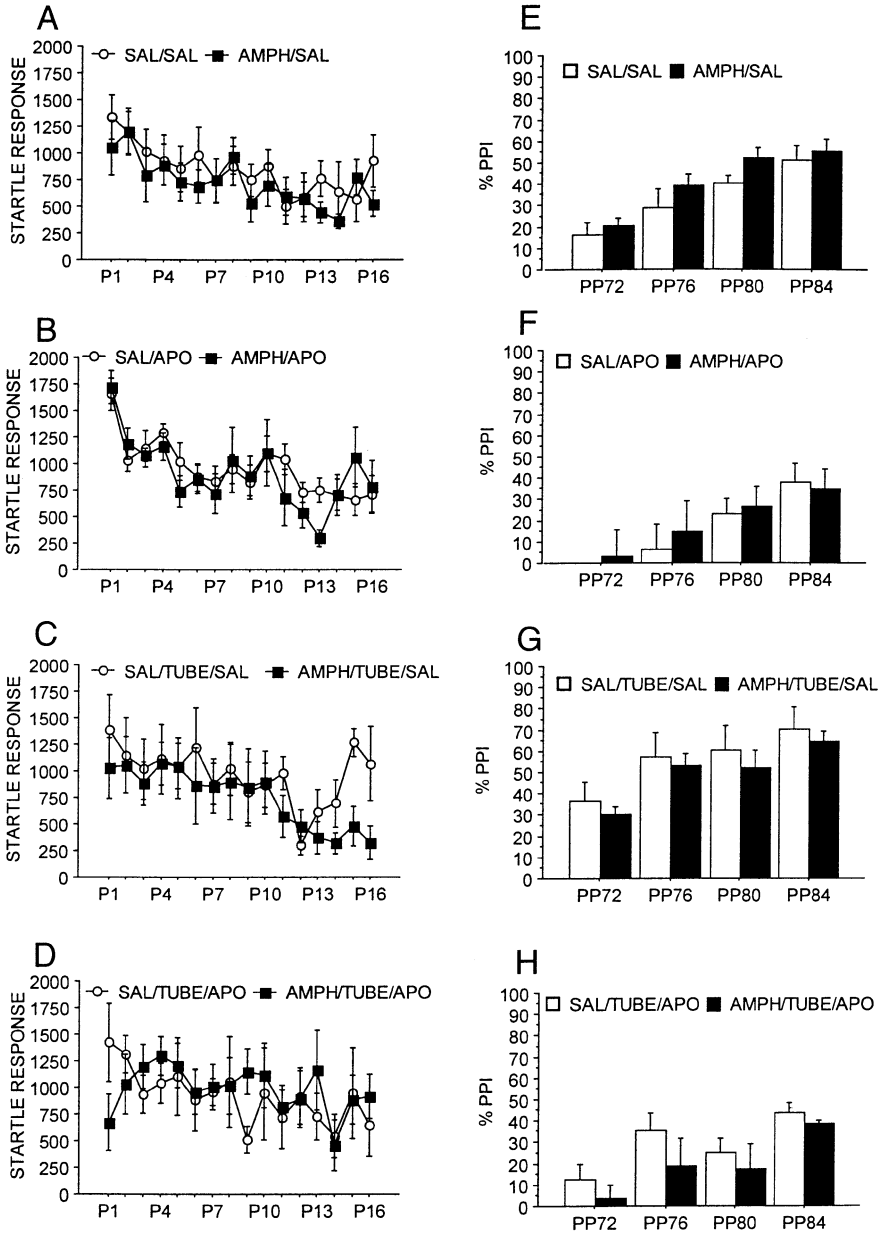

Fig. 2. **A**–**D** Startle responses during 16 pulse-alone trials. **E**–**H** Percentage prepulse inhibition (%PPI) measured in rats previously treated with amphetamine (AMPH) or saline (SAL) and assigned to one of four experimental conditions. Animals represented in **A**, **B**, **E** and **F** were returned to the home cage after each injection during the pretreatment phase and received either an injection of SAL (**A**, **E**; SAL/SAL and AMPH/SAL groups; *n*=8 per group) or apomorphine (APO; **B**, **F**; SAL/APO and AMPH/APO groups; *n*=8 per group) before testing. Animals represented in **C**, **D**, **G** and **H** received AMPH and SAL injections during the pretreatment phase that were paired with placement into restraint tubes similar to those used during PPI/startle testing, and received either an injection of SAL (**C**, **G**; SAL/tube/SAL and AMPH/tube/SAL groups; *n*=4 per group) or APO (**D**, **H**; SAL/tube/APO and AMPH/tube/APO groups; *n*=4 per group) before testing. %PPI was measured using a range of prepulse intensities (72, 76, 80, or 84 dB). Testing was conducted on day 5 of withdrawal. Values are means±SEM

session 2), suggesting habituation to the apparatus. There were no significant outcomes involving the factors of drug treatment or preexposure (data not shown).

Conditioning session. PE rats made generally fewer avoidance responses than NPE animals, as reflected by a significant main effect of preexposure ($F_{1,44}$=7.86, P<0.01). Our analysis also revealed a highly significant effect of blocks ($F_{9,396}$=54.12, P<0.0001) and a significant interaction of preexposure × drug × blocks ($F_{9,396}$=2.19, P<0.05). As can be seen in Fig. 3, all groups acquired the avoidance response; however, LI (i.e., significantly reduced avoidance performance in PE relative to NPE rats) was only seen in the SAL groups (Fisher's post-hoc: SAL NPE versus SAL PE, P=0.017; AMPH NPE versus AMPH PE, P=0.187). LI was disrupted in the AMPH-pretreated rats primarily due to increased avoidance responses in the PE group. Finally, an analysis performed on the total number of inter-trial crossings made by animals during the test session revealed no significant main effects or interactions involving the factors of drug pretreatment or preexposure (data not shown).

Experiment 2: effects of AMPH withdrawal on the acoustic startle response and PPI at 23–24 days of withdrawal, with and without a 0.5-mg/kg AMPH challenge injection

Experiment 2.1: effects of 23 days AMPH withdrawal on the acoustic startle response and PPI. All groups showed

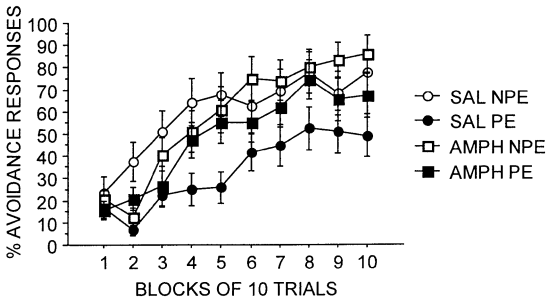

Fig. 3 Percentage of avoidance responses made during a 100-trial test of conditioned two-way active avoidance acquisition in rats previously treated with either amphetamine (AMPH) or saline (SAL) and preexposed to either the apparatus (NPE) or to the tone and the apparatus (PE). Rats were tested 16 days after their last injection. Values are means±SEM. n=12 per group

habituation of the startle response over the 16 pulse-alone presentations (main effect of trials: $F_{15,450}$=7.71, P<0.0001; Fig. 4A). AMPH-pretreated animals exhibited a reduced acoustic startle response compared with the SAL control animals, as reflected by a significant main effect of drug treatment ($F_{1,30}$=6.49, P<0.05). ANOVA of the PPI results yielded a significant main effect of prepulse intensity ($F_{3,90}$=63.43, P<0.0001; Fig. 4D), reflecting a gradual increase in PPI as a function of intensity of the prepulse stimulus. However, there were no significant main effects or interactions including the factor of drug pretreatment on PPI.

Experiment 2.2: effects of 24 days AMPH withdrawal and a 0.5-mg/kg AMPH challenge injection on the acoustic startle response and PPI. A highly significant main effect of 16 trials ($F_{15,420}$=8.55, P<0.0001) reflected a habituation of the startle response over the 16 pulse-alone presentations (Fig. 4B, C). There were no significant main effects or interactions including the factors of drug treatment or challenge treatment. PPI again increased

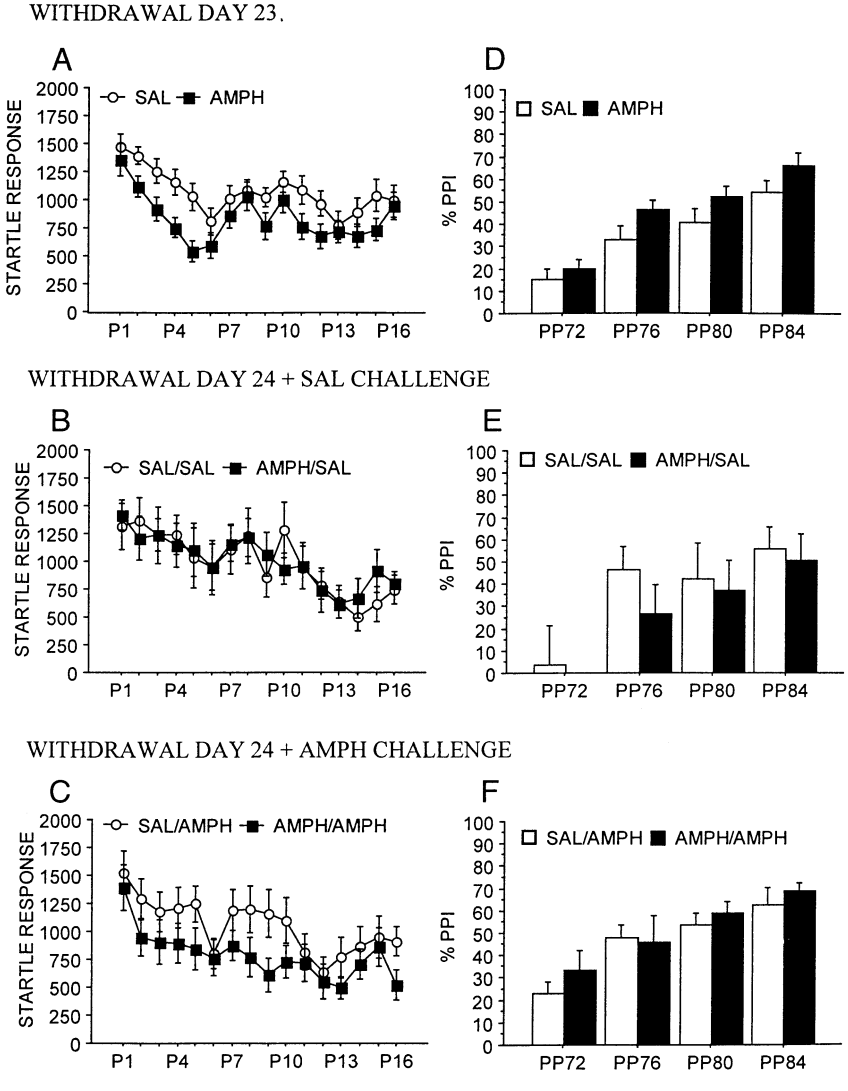

Fig. 4 **A–C** Startle responses during 16 pulse-alone trials. **D–F** Percentage prepulse inhibition (%PPI) in rats previously treated with amphetamine (AMPH) or saline (SAL). Animals were tested on withdrawal day 23 (**A**, **D**; n=16 per group) and then again on day 24 after a challenge injection of either SAL (**B**, **E**; n=8 per group) or 0.5 mg/kg AMPH (**D**, **F**; n=8 per group). %PPI was measured using a range of prepulse intensities (72, 76, 80 or 84 dB). Values are means±SEM

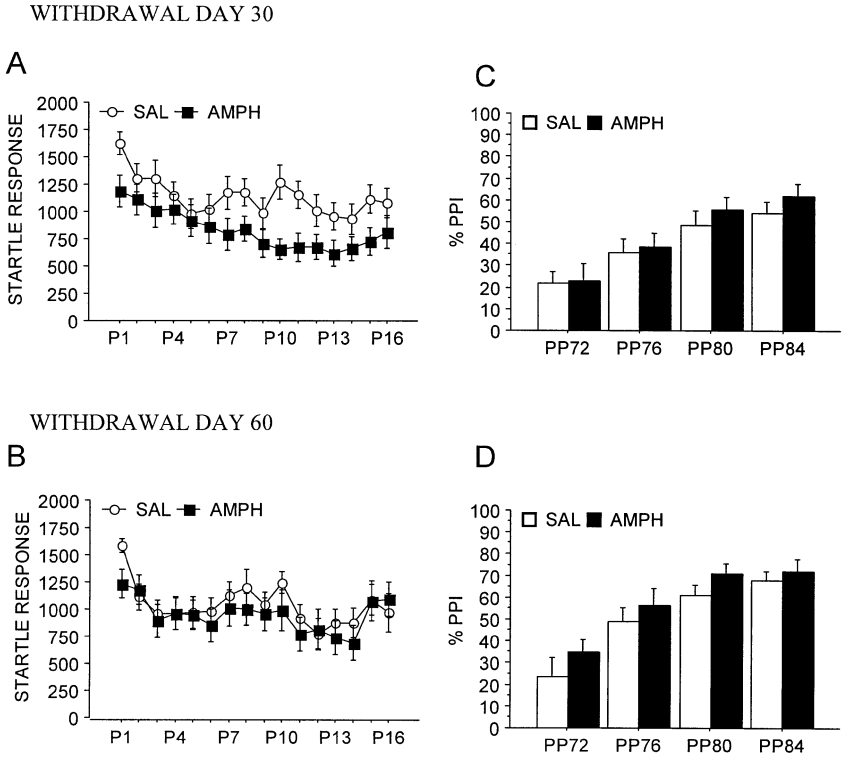

Fig. 5 **A**, **B** Startle responses during 16 pulse-alone trials. **C**, **D** Percentage prepulse inhibition (%PPI) in rats previously treated with amphetamine (AMPH) or saline (SAL). Animals were tested 30 days (**A**, **C**) and 60 days (**B**, **D**) after their last injection. %PPI was measured using a range of prepulse intensities (72, 76, 80 or 84 dB). Values are means±SEM. n=16 per group

gradually as a function of prepulse intensity (main effect of prepulse intensity: $F_{3,84}$=32.16, P<0.0001). No significant main effects or interactions were detected for the factors of drug pretreatment or challenge treatment on PPI (Fig. 4E, F).

Experiment 3: effects of 30 days and 60 days AMPH withdrawal on the acoustic startle response and PPI

Withdrawal day 30. Habituation to the acoustic startle response over the 16 pulse-alone presentations was seen in both AMPH- and SAL-treated animals (main effect of trials: $F_{15,450}$=4.65, P<0.0001, Fig. 5A). The startle response was reduced following 30 days of AMPH withdrawal, as reflected by a main effect of drug pretreatment ($F_{1,30}$=6.14, P<0.05). %PPI increased gradually as a function of prepulse intensity (main effect of prepulse intensity: $F_{3,90}$=49.51, P<0.0001). However, PPI did not differ between AMPH- and SAL-pretreated animals, as supported by an absence of significant main effects or interactions including the factor of drug pretreatment (Fig. 5C).

Withdrawal day 60. During the 16 pulse-alone presentations, the acoustic startle response again appeared to habituate over trials in both AMPH-pretreated and SAL control rats, as reflected by a significant main effect of trials ($F_{15,450}$=4.49, P<0.0001). In contrast to our findings at 30 days of withdrawal, however, AMPH and SAL groups showed similar degrees of startle responding (Fig. 5B). %PPI increased as a function of prepulse intensity, as supported by a significant main factor of prepulse intensity ($F_{3,90}$=42.57, P<0.0001). Similar to our results at 30 days of withdrawal, PPI did not differ between AMPH and SAL groups, as supported by an absence of significant main effects or interactions including the factor of drug pretreatment (Fig. 5D).

Experiment 4: AMPH sensitization of locomotor activity

Sixteen of the animals from experiment 3 were tested on days 61–62 of AMPH withdrawal for baseline levels of locomotor activity and for locomotor responding to a challenge injection of 0.5 mg/kg AMPH. Baseline locomotor activity decreased over the 28 half-hour bins ($F_{27,378}$=40.30, P<0.0001) with no significant differences between SAL- and AMPH-pretreated rats (not all data are shown). This outcome reflected habituation to the apparatus. As can be seen in Fig. 6, the last hour of the habituation period was analyzed in blocks of 10 min, and no significant effect of drug pretreatment was detected. Animals showed an elevation of activity followed by a rapid decrease in response to saline administration (main effect of blocks: $F_{5,70}$=31.83, P<0.0001; Fig. 6), with no differences detected between SAL- and AMPH-pretreated rats. Both AMPH and SAL groups showed an augmentation of locomotor activity in response to a 0.5-mg/kg AMPH challenge administration (Fig. 6). However, AMPH-pretreated animals exhibited significantly enhanced locomotor activity during the first 40 min in comparison with the SAL control group. This outcome

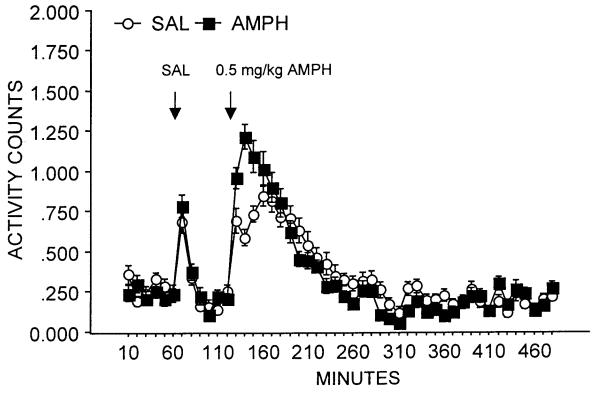

Fig. 6 Locomotor activity measured during an initial 16-h habituation period (only the last hour shown), a 1-h period following an injection of saline vehicle and a 6-h period following a challenge injection of 0.5 mg/kg amphetamine. Testing was conducted 61–62 days after the last injection in animals that had been pretreated with either amphetamine (AMPH) or saline (SAL). Values are means±SEM. n=8 per group

was supported by a significant interaction of drug pretreatment × 10-min bins during this period ($F_{35,490}$=1.86, P<0.01).

Discussion

The present study was designed to test the effects of AMPH withdrawal on PPI using experimental conditions known to be optimal for demonstrating behavioral sensitization. Therefore, we measured PPI and the acoustic startle response (1) after 4 days of withdrawal in the presence and absence of a drug-conditioned context, (2) following low-dose challenge injections of the DA agonists APO and AMPH, and (3) at longer withdrawal intervals. We found no effect of AMPH withdrawal on PPI irrespective of these experimental conditions. However, the acoustic startle response of AMPH-treated rats was reduced on day 23 and day 30, but not on day 4 and day 60 of withdrawal. Finally, consistent with our previous findings (Murphy et al. 2001b; Russig et al. 2002), AMPH-pretreated rats showed deficits in LI following 16 days of withdrawal and pronounced sensitization of locomotor activity to an AMPH challenge injection after 2 months of withdrawal.

Given that disrupted LI is an animal model of the positive symptoms of schizophrenia, the LI reduction found after a period of AMPH administration in this study is consistent with the hypothesis that endogenous sensitization of DA contributes to the expression of positive schizophrenic symptoms. Importantly, the disruption of LI in AMPH-withdrawn animals was almost entirely due to the increased avoidance responses of the AMPH PE relative to the SAL PE animals. We previously showed that LI was disrupted following 4 days and 13 days of withdrawal, and reduced but apparently beginning to normalize after 28 days of withdrawal from the AMPH schedule used in this study (Murphy et al. 2001b). Moreover, the LI disruption induced by AMPH withdrawal was restored by acute treatment with either haloperidol or clozapine prior to avoidance conditioning (Russig et al. 2002). In the present study, we have shown that LI is significantly reduced after 16 days of withdrawal as well, representing a modest extension of the time course during which this effect is observed. Given the reduced LI previously reported in schizophrenic patients (Baruch et al. 1988; Gray et al. 1992, 1995), the ability of repeated psychostimulant administration to produce symptoms of psychosis (Davis and Schlemmer 1980; Angrist 1994), and the antipsychotic efficacy of haloperidol and clozapine, we can speculate that AMPH withdrawal-mediated disruptions of LI may reflect cognitive processes that are linked to positive psychotic symptoms.

We originally hypothesized that PPI might be similarly eliminated during AMPH withdrawal. PPI disruption immediately following a single AMPH administration has been demonstrated in a number of studies (Mansbach et al. 1988; Bakshi et al. 1995; Sills 1999; Geyer et al. 2001); however, previous investigations have failed to show sensitization to the disruptive effects of repeated AMPH on PPI, whether testing was conducted with or without a challenge AMPH injection (Mansbach et al. 1988; Druhan et al.1998). In other studies, repeated cocaine treatment similarly had no effect on PPI during withdrawal and in fact prevented PPI disruption following a challenge administration of the drug (Martinez et al. 1999; Byrnes et al. 2000; Adams et al. 2001). In contrast, PPI was reduced by repeated DA agonist treatment when the injections were paired with PPI testing (Zhang et al. 1998; Martin-Iverson 1999), suggesting that PPI reductions following repeated psychostimulant administration might be revealed only in the presence of a drug-associated context. Schulz and co-workers (2001) similarly demonstrated that repeated dizocilpine (MK-801) produced a sensitized disruption of PPI only when repeatedly administered in the context of startle response testing, and Gordon and Rosen (1999) showed that the acoustic startle response is enhanced during cocaine withdrawal only if cocaine injections had been paired with prior exposure to the startle test environment. In the present study, however, PPI was not disrupted during AMPH withdrawal, either in animals presented with a SAL injection cue prior to testing or in animals in which a restraint tube context had been paired with AMPH injections during pretreatment. The acoustic startle response during the 16 pulse-alone trials was likewise not affected by the SAL injection or restraint tube-AMPH pairings. Our study differed from previous ones reporting PPI reductions after repeated DA agonist treatment (Zhang et al. 1998; Martin-Iverson 1999) in that we exposed the rats during the pretreatment phase only to an environment that was similar to the PPI tubes, whereas the prior investigations paired DA agonist administrations with both the context of PPI testing and exposure to prepulses and startling stimuli. Our negative results in this

regard suggest that the reported influence of drug-paired startle testing in sensitizing PPI reductions is not strictly a contextual association phenomenon. Rather, these effects may result from processes more akin to fear-potentiated startle (Davis 1986), whereby perhaps associations with the sympathomimetic and/or anxiogenic properties of DA agonists lead to either a potentiated or less-disruptible startle response (i.e., reduced PPI).

Swerdlow and colleagues (1995) previously demonstrated that PPI was reduced following an APO injection in hippocampal lesioned rats which otherwise show no PPI deficit. We similarly anticipated that administration of low-dose APO and AMPH challenges prior to PPI testing might uncover evidence of dysfunctional sensorimotor gating. Indeed, in the present study, a single low dose of 0.03 mg/kg APO disrupted PPI as has been shown previously (Pouzet et al. 1999, Weiss et al. 1999, Geyer et al. 2001). However, the effects of APO were similar in SAL- and AMPH-pretreated rats, regardless of whether or not animals had received injections paired with a PPI tube context during the pretreatment phase. In addition, administration of a 0.5-mg/kg AMPH challenge, a dose which is not normally sufficient to reduce PPI (Kinney et al. 1999; Feldon, unpublished observations), also did not reveal a PPI disruption in AMPH-treated animals following 24 days of withdrawal. As discussed above, these results are consistent with those of previous investigations in which startle testing was not paired with repeated DA agonist administration (Mansbach et al. 1988; Druhan et al. 1998). It is interesting to note that tube-PE animals showed enhanced PPI during the APO challenge test compared with the no-cue animals. This result indicates that the tube-pretreatment was not totally ineffective in influencing PPI; however, the enhancement effect of the tube condition was not seen on day 4 (first PPI test) and was not influenced by either drug pretreatment or administration of an APO challenge injection. The reason for this PPI enhancement effect is unclear at this time; however, it is conceivable that after the initial PPI test, tube animals' increased familiarity with the PPI test environment resulted in more selective attention to the prepulse stimuli rather than to the context of the restraint tube, thus increasing animals' sensorimotor gating abilities.

We also found that extending the time course of PPI testing out to withdrawal day 60 did not reveal any disruption due to AMPH withdrawal. However, the acoustic startle response was significantly reduced on withdrawal day 23 and day 30 in AMPH-pretreated animals. In contrast, the acoustic startle response on day 4 was not significantly reduced in AMPH-pretreated animals, consistent with previous findings (Murphy et al. 2001b), and after 2 months the effect was again absent, indicating that the startle reduction effect occurs within a restricted time window. Withdrawal from another psychostimulant drug, cocaine, also induces a reduction of the acoustic startle response in rats (Gordon and Rosen 1999; Adams et al. 2001) and chronic cocaine users similarly exhibit marked impairments in the acoustic startle response (Efferen et al. 2000).

Since it is known that fear and anxiety increase the startle reflex (Davis 1986) and a pleasant context conversely attenuates startle amplitude (Lang et al. 1990; Koch 1999), it has been suggested that the startle response measurement could be a useful index of an animal's emotional state (Marsh et al. 1973; Koch and Schnitzler 1997). It seems unlikely that a positive hedonic state develops that could be responsible for the reduction in startle during AMPH withdrawal, given numerous reports of negative affect during psychostimulant withdrawal (Lin et al. 1999; Koob and Le Moal 2001). In fact, we recently showed that animals receiving the schedule of AMPH administration used in the present study showed an enhanced conditioned fear response on day 4 of withdrawal (Pezze et al.2002). The time course of this increase in conditioned fear is likely to be a short-lived effect, given that the symptoms of anxiety seen in both psychostimulant-withdrawn rats and newly-abstinent human addicts are typically transient (Gawin 1991; Basso et al. 1999). Therefore, if a transiently increased state of anxiety independently potentiated the acoustic startle response during the first week of withdrawal, it may have effectively masked any reduction in startle present at that time. It is possible then that the true time course of startle reduction during AMPH withdrawal includes the entire first month of withdrawal. The return of a normal startle response on withdrawal day 60 suggests that normalization of and/or compensation for the etiology of reduced startle has taken place at this time. Given the fact that the magnitude of the startle response in the absence of a CS or a prepulse is sometimes viewed as a non-specific behavioral parameter and that reduced startle during AMPH withdrawal was only observed in two of four time points in this study, and was not clearly seen on day 24 even in the same animals that showed the reduction on day 23, it is difficult to gauge the true significance of this effect at this time. Future studies will be needed to determine the robustness of the startle reduction during AMPH withdrawal as well as its biological underpinnings.

We predictably found evidence of locomotor sensitization to a 0.5-mg/kg AMPH challenge following 2 months of AMPH withdrawal; in a previous study, we similarly demonstrated locomotor sensitization to a 1.0-mg/kg AMPH challenge after 30 days of withdrawal from the same AMPH injection schedule (Russig et al. 2001). Increased DA release in the nucleus accumbens after an AMPH challenge has been repeatedly found in sensitized rats (Robinson and Becker 1986; but see Segal and Kuczenski 1992) and numerous studies have shown that both LI and PPI are disrupted by DA agonists (Swerdlow et al. 1992; Weiner and Feldon 1997; Geyer et al. 2001). However, basal levels of nucleus accumbens DA are reportedly reduced or unchanged during AMPH withdrawal (Rossetti et al. 1992; Segal and Kuczenski 1992; Crippens et al. 1993). Our laboratory has in fact shown that rats withdrawn from the AMPH schedule used in the

present study showed no differences in basal DA levels, but decreased DA efflux in the shell, and increased DA efflux in the core of the nucleus accumbens during the expression of a conditioned fear response (Pezze et al. 2002). If an enhanced nucleus accumbens core DA response contributes in some manner to the disruption of LI in AMPH-withdrawn rats, then apparently it is not enough of a stimulus to elicit disrupted PPI in these animals as well. However, reduced nucleus accumbens shell DA responsiveness may contribute to startle reduction during AMPH withdrawal. In support of this idea, blockade of DA receptors by acute administration of risperidone or clozapine has been shown to decrease startle amplitude (Johansson et al. 1995; Depoortere et al. 1997). Of course, other neurotransmitter systems may also be involved in modulating the startle response during AMPH withdrawal. In particular, there is strong evidence for glutamatergic, noradrenergic and corticotropin-releasing factor regulation of the acoustic startle response (Davis 1986; Koch 1999).

Conclusions

To summarize, we report here that withdrawal from an escalating dosage schedule of AMPH disrupted LI but left PPI intact. Manipulations of the PPI testing environment that were intended to simulate the experimental conditions considered optimal for demonstrating behavioral sensitization (contextual associations, presence of a DA agonist challenge, later withdrawal time points for testing) likewise did not reveal any increased sensitivity of AMPH-withdrawn animals to PPI disruption. Such a dissociation between LI and PPI has been shown previously following other behavioral and pharmacological treatments (Wilkinson et al. 1994; Feldon et al. 2000; Murphy et al. 2001a). The existence of this dissociation may be due at least in part to the suggested involvement of different brain regions in the mediation of LI and PPI. LI has been linked primarily to activity within the nucleus accumbens and hippocampus, whereas the regulation of PPI is believed to occur in brain nuclei that extend from the prefrontal cortex to the pontine tegmentum (Weiner and Feldon 1997; Koch and Schnitzler 1997). Nevertheless, the attenuation of the startle response, which we report here during AMPH withdrawal, is similar to cocaine withdrawal effects on startle that have been reported previously in both humans and in rodents (Gordon and Rosen 1999; Efferen et al. 2000; Adams et al. 2001). Further investigations will be needed to clarify the neuronal mechanisms underlying this effect as well as the functional significance of this reduction in startle to an animal's emotional state.

Acknowledgements This study was supported by the Swiss Federal Institute of Technology (ETH-Zurich, Switzerland). We would like to thank the staff of the animal facility for their care and maintenance of the animals used in this study, Mr. Peter Schmid for his valuable technical assistance, and Mrs. Jane Fotheringham for her editorial help.

References

Adams JU, Efferen TR, Duncan EJ, Rotrosen J (2001) Prepulse inhibition of the acoustic startle response in cocaine-withdrawn rats. Pharmacol Biochem Behav 68:753–759

Angrist B (1994) Amphetamine psychosis: clinical variations of the syndrome. In: Cho AK, Segal DS (eds) Amphetamine and its analogs. Academic Press, San Diego, pp 387–414

Badiani A, Browman KE, Robinson TE (1995) Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res 674:291–298

Bakshi VP, MA, Taaid NN, Swerdlow NR (1995) A comparison of the effects of amphetamine, strychnine and caffeine on prepulse inhibition and latent inhibition. Behav Pharmacol 6:801–809

Baruch I, Hemsley DR, Gray JA (1988) Differential performance of acute and chronic schizophrenics in a latent inhibition task. J Nerv Ment Dis 176:598–606

Basso AM, Spina M, Rivier J, Vale W, Koob GF (1999) Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. Psychopharmacology 145:21–30

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

Braff DL, Stone C, Callaway E, Geyer MA, Glick I, Bali L (1978) Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology 15:339–343

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, Geyer MA, Swerdlow NR (2001) Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology 156:234–258

Byrnes JJ, Hammer RP (2000) The disruptive effect of cocaine on prepulse inhibition is prevented by repeated administration in rats. Neuropsychopharmacology 22:551–554

Caine SB, Geyer MA, Swerdlow NR (1995) Effects of D3/D2 dopamine receptor agonists and antagonists on prepulse inhibition of acoustic startle in the rat. Neuropsychopharmacology 12:139–145

Crippens D, Camp DM, Robinson TE (1993) Basal extracellular dopamine in the nucleus accumbens during amphetamine withdrawal: a "no net flux" microdialysis study. Neurosci Lett 164:145–148

Davis JM, Schlemmer Jr FP (1980) The amphetamine psychosis. In: Caldwell J (ed) Amphetamines and related stimulants: chemical, biological, clinical and social aspects. CRC Press, Boca Raton, pp 161–173

Davis M (1986) Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. Behav Neurosci 100:814–824

Depoortere R, Perrault G, Sanger DJ (1997) Potentiation of prepulse inhibition of the startle reflex in rats: pharmacological evaluation of the procedure as a model for detecting antipsychotic activity. Psychopharmacology 132:366–374

Drew KL, Glick SD (1988) Environment-dependent sensitization to amphetamine-induced circling behavior. Pharmacol Biochem Behav 31:705–708

Druhan JP, Geyer MA, Valentino RJ (1998) Lack of sensitization to the effects of d-amphetamine and apomorphine on sensorimotor gating in rats. Psychopharmacology 135:296–304

Efferen TR, Duncan EJ, Szilagyi S, Chakravorty S, Adams JU, Gonzenbach S, Angrist B, Butler PD, Rotrosen J (2000) Diminished acoustic startle in chronic cocaine users. Neuropsychopharmacology 22:89–96

Ellinwood EH (1967) Amphetamine psychosis: I. Description of the individuals and process. J Nerv Ment Dis 144:273–283

Feldon J, Lehmann J, Pryce C, Weiss I (2000) Rat latent inhibition and prepulse inhibition are sensitive to different manipulations

of the social environment: a comprehensive study of the environmental approach to neurodevelopmental models of schizophrenia. In: Myslobodsky, Weiner I (eds) Contemporary issues in modelling psychopathology. Kluwer, Boston, pp 231–245

Gawin FH (1991) Cocaine addiction: psychology and neurophysiology. Science 251:1580–1586

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156:117–154

Gordon MK, Rosen JB (1999) Lasting effect of repeated cocaine administration on acoustic and fear-potentiated startle in rats. Psychopharmacology 144:1–7

Graham FK (1975) The more or less startling effects of weak prestimulation. Psychophysiology 12:238–248

Gray NS, Hemsley DR, Gray JA (1992) Abolition of latent inhibition in acute, but not chronic, schizophrenics. Neurol Psychiatry Brain Res 1:83–89

Gray NS, Pilowsky LS, Gray JA, Kerwin RW (1995) Latent inhibition in drug naive schizophrenics: relationship to duration of illness and dopamine D_2 binding using SPET. Schizophr Res 17:95–107

Griffith JD, Cavanaugh J, Held J, Oates JA (1972) Dextroamphetamine: evaluation of psychomimetic properties in man. Arch Gen Psychiatry 26:97–100

Hinson RE, Poulos CX (1981) Sensitization to the behavioral effects of cocaine: modification by Pavlovian conditioning. Pharmacol Biochem Behav 15:559–562

Hoffman HS, Ison JR (1980) Reflex modulation in the domain of startle: I Some empirical findings and their implications for how the nervous system processes sensory input. Psychol Rev 87:175–189

Hutchison KE, Niaura R, Swift R (1999) Smoking cues decrease prepulse inhibition of the startle response and increase subjective craving in humans. Exp Clin Psychopharmacol 7:250–256

Johansson C, Jackson DM, Zhang J, Svensson L (1995) Prepulse inhibition of acoustic startle, a measure of sensorimotor gating: effects of antipsychotics and other agents in rats. Pharmacol Biochem Behav 52:649–654

Kinney GG, Wilkinson LO, Saywell KL, Tricklebank MD (1999) Rat strain differences in the ability to disrupt sensorimotor gating are limited to the dopaminergic system, specific to prepulse inhibition, and unrelated to changes in startle amplitude or nucleus accumbens dopamine receptor sensitivity. J Neurosci 19:5644–5653

Koch M (1999) The neurobiology of startle. Prog Neurobiol 59:107–128

Koch M, Schnitzler HU (1997) The acoustic startle response in rats – circuits mediating evocation, inhibition and potentiation. Behav Brain Res 89:35–49

Kokkinidis L, Anisman H (1980) Amphetamine models of paranoid schizophrenia: an overview and elaboration of animal experimentation. Psychol Bull 88:551–579

Koob GF, Le Moal M (2001) Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24:97–129

Lang PJ, Bradley MM, Cuthbert BN (1990) Emotion, attention, and the startle reflex. Psychol Rev 97:377–395

Laruelle M (2000) The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. Brain Res Rev 31:371–384

Lieberman JA, Kinon BJ, Loebel AD (1990) Dopaminergic mechanisms in ideopathic and drug-induced psychoses. Schizophr Bull 16:97–109

Lieberman JA, Sheitman BB, Kinon BJ (1997) Neurochemical sensitization in the pathophysiology of schizophrenia: deficits and dysfunction in neuronal regulation and plasticity. Neuropsychopharmacology 17:205–229

Lin D, Koob GF, Markou A (1999) Differential effects of withdrawal from chronic amphetamine or fluoxetine administration on brain stimulation reward in the rat – interactions between the two drugs. Psychopharmacology 145:283–294

Lubow RE (1973) Latent inhibition. Psychol Bull 79:398–407

Mansbach RS, Geyer MA, Braff DL (1988) Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 94:507–514

Marsh R, Hoffman HS, Stitt CL (1973) Temporal integration in the acoustic startle reflex of the rat. J Comp Physiol Psychol 82:507–511

Martin-Iverson MT (1999) Does sensitization occur to prepulse inhibition of the startle reflex effects of repeated apomorphine treatments in rats? J Psychopharmacol 13:261–273

Martinez ZA, Ellison GD, Geyer MA, Swerdlow NR (1999) Effects of sustained cocaine exposure on sensorimotor gating of startle in rats. Psychopharmacology 142:253–260

Murphy CA, Di Iorio L, Feldon J (2001a) Effects of psychostimulant withdrawal on latent inhibition of conditioned active avoidance and prepulse inhibition of the acoustic startle response. Psychopharmacology 156:155–164

Murphy CA, Fend M, Russig H, Feldon J (2001b) Latent inhibition, but not prepulse inhibition, is reduced during withdrawal from an escalating dosage schedule of amphetamine. Behav Neurosci 115:1247–1256

Ohmori T, Abekawa T, Ito K, Koyama T (2000) Context determines the type of sensitized behaviour: a brief review and a hypothesis on the role of environment in behavioural sensitization. Behav Pharmacol 11:211–221

Paulson PE, Robinson TE (1995) Amphetamine-induced time-dependent sensitization of dopamine neurotransmission in the dorsal and ventral striatum: a microdialysis study in behaving rats. Synapse 19:56–65

Paulson PE, Camp DM, Robinson TE (1991) Time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during amphetamine withdrawal in rats. Psychopharmacology 103:480–492

Peng RY, Mansbach RS, Braff DL, Geyer MA (1990) A D2 dopamine receptor agonist disrupts sensorimotor gating in rats. Implications for dopaminergic abnormalities in schizophrenia. Neuropsychopharmacology 3:211–218

Pezze MA, Feldon J, Murphy (2002) Increased conditioned fear response and altered balance of dopamine in the shell and the core of the nucleus accumbens during amphetamine withdrawal. Neuropharmacology 42:633–643

Pouzet B, Feldon J, Veenman CL, Yee BK, Richmond M, Nicholas J, Rawlins P, Weiner I (1999) The effects of hippocampal and fimbria-fornix lesions on prepulse inhibition. Behav Neurosci 113:968–981

Richter RM, Weiss F (1999) In vivo CRF release in rat amygdala is increased during cocaine withdrawal in self-administering rats. Synapse 32:254–261

Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res 396:157–198

Robinson TE, Browman KE, Crombag HS, Badiani A (1998) Modulation of the induction or expression of psychostimulant sensitization by the circumstances surrounding drug administration. Neurosci Biobehav Rev 22:347–354

Rossetti ZL, Hmaidan Y, Gessa GL (1992) Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur J Pharmacol 221:227–234

Russig H, Murphy CA, Pezze MA, Feldon J (2001) Withdrawal from intermittent and escalating dosage schedules of amphetamine produces sensitization, but is not associated with depressive symptoms in rats. Behav Pharmacol 12 [Suppl] 1:87

Russig H, Murphy CA, Feldon J (2002) Clozapine and haloperidol reinstate latent inhibition following its disruption during amphetamine withdrawal. Neuropsychopharmacology 6:765–777

Schulz B, Fendt M, Pedersen V, Koch M (2001) Sensitization of prepulse inhibition deficits by repeated administration of dizocilpine. Psychopharmacology 156:177–181

Segal DS, Kuczenski R (1992) In vivo microdialysis reveals a diminished amphetamine-induced DA response corresponding to behavioral sensitization produced by repeated amphetamine pretreatment. Brain Res 571:330–337

Segal DS, Kuczenski R (1994) Behavioral pharmacology of amphetamine. In: Cho AK, Segal DS (eds) Amphetamine and its analogs: psychopharmacology, toxicology and abuse. Academic, San Diego, pp 115–150

Sills TL (1999) Amphetamine dose dependently disrupts prepulse inhibition of the acoustic startle response in rats within a narrow time window. Brain Res Bull 48:445–448

Snyder SH (1973) Amphetamine psychosis: a "model" schizophrenia mediated by catecholamines. Am J Psychiatry 130:61–67

Swerdlow NR, Braff DL, Geyer MA, Caine SB (1992) The neural substrates of sensorimotor gating of the startle reflex: a review of recent findings and their implications. J Psychopharmacol 6:176–190

Swerdlow NR, Braff DL, Taaid N, Geyer MA (1994) Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch Gen Psychiatry 51:139–154

Swerdlow NR, Lipska BK, Weinberger DR, Braff DL, Jaskiw GE, Geyer MA (1995) Increased sensitivity to the sensorimotor gating-disruptive effects of apomorphine after lesions of medial prefrontal cortex or ventral hippocampus in adult rats. Psychopharmacology 122:27–34

Swerdlow NR, Braff DL, Geyer MA (2000) Animal models of deficient sensorimotor gating: what we know, what we think we know, and what we hope to know soon. Behav Pharmacol 11:185–204

Taylor MK, Ison JR, Schwarzkopf SB (1995) Effects of single and repeated exposure to apomorphine on the acoustic startle reflex and its inhibition by a visual prepulse. Psychopharmacology 120:117–127

Weiner I, Feldon J (1997) The switching model of latent inhibition: an update of neural substrates. Behav Brain Res 88:11–25

Weiss IC, Feldon J, Domeney AM (1999) Circadian time does not modify the prepulse inhibition response or its attenuation by apomorphine. Pharmacol Biochem Behav 64:501–505

Wilkinson LS, Killcross SS, Humby T, Hall FS, Geyer MA, Robbins TW (1994) Social isolation in the rat produces developmentally specific deficits in prepulse inhibition of the acoustic startle response without disrupting latent inhibition. Neuropsychopharmacology 10:61–72

Zhang J, Engel JA, Soderpalm B, Svensson L (1998) Repeated administration of amphetamine induces sensitization to its disruptive effect on prepulse inhibition in the rat. Psychopharmacology 135:401–406