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ORIGINAL INVESTIGATION

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Latent inhibition in 35-day-old rats is not an "adult" latent inhibition: implications for neurodevelopmental models of schizophrenia

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Abstract *Rationale:* Latent inhibition (LI) refers to retarded conditioning to a stimulus as a consequence of its inconsequential preexposure. Amphetamine-induced disruption of LI and its potentiation by antipsychotic drugs (APDs) in the adult rat are well-established models of schizophrenia and antipsychotic drug action, respectively. It is not clear whether LI can be similarly modulated at prepubertal age. *Objectives:* In view of the notion that schizophrenia is a neurodevelopmental disorder whose overt expression depends on postpubertal brain maturational processes, we investigated whether several manipulations known to modulate LI in adult rats, including systemic administration of amphetamine and the atypical APD clozapine, are capable of producing the same effects in prepubertal (35-day-old) rats. *Methods:* LI was measured in a thirst motivated conditioned emotional response (CER) procedure in which rats received 10 or 40 tone preexposures followed by 2 or 5 tone-footshock pairings. *Results:* Like in adults, LI was present with 40 preexposures and 2 conditioning trials. In contrast to findings in adults, LI was resistant to disruption by amphetamine at a dose (1 mg/kg) that significantly increased locomotor activity, as well as by reducing the number of preexposures to ten, increasing the number of conditioning trials to five, or changing the context between preexposure and conditioning. Clozapine (5 mg/kg) and the selective 5HT2A antagonist M100907 (0.3 mg/kg) administered in conditioning were without an effect on "persistent" LI with extended conditioning, but were capable of disrupting LI when administered in the preexposure stage, as found in adults. *Conclusion:* The results point to functionality within brain systems regulating LI acquisition but not those regulating LI expression in periadolescent rats, further suggesting that postpubertal maturation of the latter systems may underlie schizophrenia-mimicking LI disruption reported in adult rats following perinatal manipulations and possibly disrupted LI observed in schizophrenia.

Keywords Latent inhibition · Development · Schizophrenia · Periadolescence · Amphetamine · Clozapine · M100907

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Introduction

Latent inhibition (LI) refers to retarded conditioning to a stimulus that had been repeatedly preexposed without consequences compared to a novel stimulus. In the past two decades disrupted LI has been established as an animal model of schizophrenia with face, construct, and predictive validity, because: (1) LI is disrupted in rats and normal humans by the dopamine (DA) releaser amphetamine which produces and exacerbates psychotic symptoms, as well as in high-schizotypal humans, and in the acute stages of schizophrenia; (2) both typical and atypical antipsychotic drugs (APDs) reverse amphetamine-induced LI disruption in rats and potentiate LI in both rats and humans under parametric conditions that do not produce LI in controls; (3) the neural substrates of LI in the rat include the limbic system and the nucleus accumbens, in line with the temporolimbic and mesolimbic DA pathology implicated in schizophrenia (for reviews see, Gray et al. 1991; Moser et al. 2000; Weiner 1990, 2000, 2003; Weiner and Feldon 1997).

The LI disruptive effect of amphetamine and the LI potentiating effects of APDs have been demonstrated by numerous laboratories using adult rats (e.g., Killcross and Robbins 1993; Killcross et al. 1994a, 1994b; McAllister 1997; Moser et al. 1996; Trimble et al. 1997; Weiner et al. 1984, 1988, 1996, 1997). Although LI is present at as early as 10 days of age (Hoffmann and Spear 1989; for a range of prepubertal ages at which LI was seen, see Franchina et al. 1980; Hoffmann and Spear 1989; Nicolle et al. 1994; Rudy 1994), to the best of our knowledge

there are no published studies on the effects of these drugs on LI in prepubertal rats. Such information is of interest because in recent years, it has become widely accepted that schizophrenia is a neurodevelopmental disorder (Arnold 1999; Harrison 1999; Weinberger 1987, 1995), and this has been paralleled by efforts to develop animal neurodevelopmental models of schizophrenia (Lipska and Weinberger 2000), including those demonstrating that perinatal insults lead to LI loss in adulthood (Ellenbroek and Cools 1995; Grecksch et al. 1999; Shalev and Weiner 2001; Weiner et al. 1985, 1987b). Since a key feature of schizophrenia is a maturational delay between the neurodevelopmental aberration (presumably in utero) and its overt onset after puberty, an essential premise of the neurodevelopmental theory is that the emergence of psychotic symptoms is dependent on brain maturational processes that occur after puberty (Lieberman et al. 2001). Given that amphetamine-induced disruption of LI and its potentiation by APDs are the bona fide psychotic symptom and antipsychotic action, respectively, modeled by LI, it would be of interest to investigate whether these effects can be obtained in prepubertal rats. An inability of these drugs to modulate LI at prepubertal age presumably would indicate an immaturity within specific brain systems regulating LI, and by corollary, suggest that LI loss found in adults following various neurodevelopmental manipulations might be dependent on a postpubertal maturation of these same substrates.

We therefore sought to examine whether LI could be modulated by amphetamine and by the atypical APD clozapine in 35-day-old rats. This age was chosen because investigations within the framework of two neurodevelopmental models of schizophrenia that reproduce the maturational delay characteristic of this disorder, namely, those of a neonatal hippocampal lesion (Lipska et al. 1993), and prenatal immune activation (Zuckerman and Weiner 2003) have shown that several behavioral and neural assays considered to be relevant to schizophrenia are intact at this age but emerge as abnormal at adulthood (Al-Amin et al. 2001; Lipska et al. 1993; Wood et al. 1997; Zuckerman and Weiner 2003). LI was assessed in a thirst motivated conditioned emotional response (CER) procedure routinely used in our laboratory as well as in most studies concerned with the effects of lesions and drugs in the LI model of schizophrenia in adult rats (for a detailed discussion see Weiner 2001). In our CER procedure, LI is measured by comparing the suppression of drinking to a tone previously paired with a foot shock in rats that received nonreinforced exposure to the tone prior to conditioning (preexposed) and in rats for whom the tone is novel (nonpreexposed). Typically, in adult rats, we demonstrate the disruptive effect of amphetamine using 40 tone preexposures and 2 tone-shock conditioning trials which yield LI in controls (e.g., Weiner et al. 1988, 1996, 1997), and the potentiating effects of APDs using 40 preexposures and 5 conditioning trials or 10 preexposures and 2 conditioning trials, both of which disrupt LI in controls (e.g., Weiner et al. 1997, Shadach et al. 1999, 2000), and therefore identical parameters were used in the present study. Likewise, all the drug doses used here were shown by us to be behaviorally active in LI in adult rats under the conditions tested here (Gaisler-Salomon and Weiner 2003; Shadach et al. 1999, 2000; Weiner et al. 1988, 1996, 1997; Zuckerman et al. 2001).

Since in the first two experiments, LI was resistant to disruption by a low dose of amphetamine (1 mg/kg) shown by us to disrupt it in adult rats, as well as by a high dose (5 mg/kg) of this drug, the third experiment tested whether LI could be disrupted by the two parametric manipulations of lowering the number of preexposures or increasing the number of conditioning trials, and found that LI was present under both conditions. On this background, it was apparent that the conventional index of APD action in adults, namely, LI potentiation, could not be demonstrated in juveniles, because such a demonstration requires no LI in controls. However, we have recently demonstrated that atypical APDs, in addition to potentiating LI, have a capacity to disrupt LI (Gaisler-Salomon and Weiner 2003; Shadach et al. 2000; Weiner et al. 2003; Zuckerman et al. 2001). Briefly, the critical aspects allowing the differentiation between atypical APD-induced LI potentiation and disruption are the status of LI in controls and the stage of the LI procedure at which the drugs exert their effects. LI potentiation is manifested under parametric conditions that do not yield LI in no-drug controls, and this effect is produced at the conditioning stage (the drugs are ineffective when given in preexposure). LI disruption is manifested under parametric conditions that yield LI in no-drug controls, and this effect is exerted at the preexposure stage (the drugs are ineffective when given in conditioning). The conditioning-based potentiation is due to DA2 blockade which is shared by typical and atypical APDs (and indeed is the mirror effect of amphetamine-induced disruption of LI, which is exerted at conditioning and is due to DA hyperfunction). Conversely, preexposure-based LI disruption is not mediated by DA blockade because it is not produced by DA2 blockers like haloperidol, but is apparently due to the 5HT2A antagonism of atypical APDs, because precisely the same effect is produced by selective 5HT2A antagonists. While the major importance of the dual action of atypical APDs on LI lies in strengthening the predictive validity of the LI model by enabling the model to discriminate between typical and atypical APDs, in the present context our question was whether administration of an atypical APD and a selective 5HT2A antagonist in preexposure would succeed in disrupting the "persistent LI" seen in juveniles (for a discussion of the relevance of APD-induced LI disruption to the LI model of schizophrenia, see Weiner 2003). Therefore, in the fourth and fifth experiments, rats preexposed to 40 tones and conditioned with 5 tone-shock pairings were administered the atypical APD clozapine or the selective 5HT2A antagonist M100907 only in preexposure and only in conditioning, respectively. Finally, in experiment 6, we tested whether LI in 35-day-old rats would be resistant to disruption by an additional manipulation known to disrupt LI in adults,

namely, context change between preexposure and conditioning (Bouton 1993; Holt and Maren 1999; Lubow and Gewitz 1995; Westbrook et al. 2000). Since the context shift procedure used here was not used by us previously with adults, experiment 7 tested this procedure in adult rats.

In addition, since the most well established behavioral index of low doses of amphetamine is increased locomotor activity, we tested the effects of 1 mg/kg amphetamine on locomotor activity to assess whether this dose was behaviorally effective. Chronologically, this experiment was conducted after the first experiment which showed that amphetamine was ineffective in disrupting LI, but here we present it as experiment 8. Since it is commonly reported that periadolescent rats (30–40 days old) have lower responsiveness to amphetamine than adult rats (e.g., Bolanos et al. 1998), this experiment included adult controls.

Materials and methods

Subjects

Male Wistar rats (Tel Aviv University Medical School, Israel), 35 days old and weighing 85–115 g, or 3 months old and weighing 450–550 g, were housed four to a cage under reversed cycle lighting (lights on: 19:00–07:00) with free access to food and water, except for 1 week prior to and during the LI experiments. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

Apparatus and Procedure

Latent inhibition

Rats were tested in Campden Instruments rodent test chambers with a retractable bottle, each set in a ventilated sound-attenuating chest. When the bottle was not present, the hole was covered by a metal lid. Licks were detected by a Campden Instruments drinkometer circuit. The preexposed to-be-conditioned stimulus was a 10-s, 80-dB, 2.8-kHz tone produced by a Sonalert module. Shock was supplied by a Campden Instruments shock generator and scrambler set at 0.5-mA, 1-s duration. Equipment programming and data recording were computer controlled.

In experiments 1–5, LI was tested in four chambers. Rats were handled for about 2 min daily for 5 days prior to the beginning of the experiment. A 22-h water restriction schedule was initiated simultaneously with handling and continued throughout the experiment. On the next 5 days, rats were trained to drink in the experimental chamber for 20 min a day. Water in the test apparatus was given in addition to the daily ration of 2 h given in the home cages. The LI procedure was conducted on days 11–14 and consisted of the following stages: *Preexposure.* With the bottle removed, the preexposed (PE) rats received 10 or 40 tone presentations with an inter-stimulus interval of 40 s. The nonpreexposed (NPE) rats were confined to the chamber for an identical period of time without receiving the tones. *Conditioning.* With the bottle removed, each rat received 2 or 5 tone-shock pairings given 5 min apart. Shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the session. After the last pairing, rats were left in the experimental chamber for an additional 5 min. *Retraining.* Rats were given a 15-min drinking session as in initial training. *Test.* Each rat was placed in the chamber and allowed to drink from the bottle. When the rat completed 75 licks the tone was presented for 5 min. Time to complete 25 licks prior to tone onset (licks 51–75, A period) and time to complete 25 licks after tone onset (licks 76–100, B period) were recorded for each rat. Suppression of licking was measured using a suppression ratio, A/A+B. Nonpreexposed rats take longer to complete licks 76–100 than the preexposed rats, resulting in higher suppression ratios for the PE rats compared with the NPE rats (note that suppression ratio is inversely related to the amount of lick suppression), and this difference between the suppression ratios constitutes LI. Disrupted LI would be manifested in the disappearance of the difference in suppression between the PE and the NPE groups such that the PE group exhibits a similar level of suppression to that of the NPE group.

In experiments 6 and 7 (context shift), LI was tested in two sets of four chambers. One set was used as context A and the second set was used as context B. Each set of boxes was housed in a different room in the laboratory. In addition, the two contexts differed in the following respects: One set of boxes (A) had an odor produced by the addition of one drop of ilang ilang aromatic oil onto a cotton ball placed in the sound attenuating chest just outside of the test chamber, and the other (B) had an odor produced by cinnamon oil. In addition, in the latter boxes, the door was covered with a ribbed black and white tappet, and the grid floor was covered with plyboard. The LI procedure was as above with 40 preexposures and 2 tone-shock pairings. In the same context condition, preexposure was conducted in context A, and in the different context condition, preexposure was conducted in context B. Lick training, conditioning, rebaseline, and test were conducted for all rats in context A.

Spontaneous and amphetamine-induced activity

Rats were tested in plastic chambers (46×57×37 cm) covered by clear Perspex lids. An infrared sensor unit (Coulbourn Instruments) was installed in the center of the front wall 22 cm from the side walls and 12 cm above the grid floor. Animals' access to the sensor was prevented by a wired fence (10×10×6 cm). Blind areas of the sensor (the two corners of the triangles adjacent to the sensor, 17×17×25 cm) were blocked by clear Perspex walls. The movements detected by the sensor were transmitted through an 8-channel infrared motion interface to an infrared motion activity monitor controller/analyzer (Coulbourn Instruments). Data recording was computer controlled. Rats were individually placed in the activity chambers and allowed 30 min of free exploration, at the end of which they were returned to their home cage, injected with either amphetamine or saline, and replaced into the activity chambers for 60 min. The duration of movements performed by each rat was recorded in 6-min blocks.

Drugs

All drugs were administered IP in a volume of 1 ml/kg. d-Amphetamine sulfate (Sigma, Israel), dissolved in saline, was administered at a dose of 1 mg/kg or 5 mg/kg 15 min prior to the preexposure and conditioning stages in the LI procedure and at a dose of 1 mg/kg immediately before activity assessment. Clozapine (Novartis, Switzerland) and M100907 (Aventis, USA), dissolved in 1 N acetic acid (1.5 ml/10 mg) and diluted with saline (final pH of 5.5), were administered at a dose of 5 mg/kg and 0.3 mg/kg, respectively, 30 min prior to the preexposure or prior to the conditioning stage. No-drug controls received the corresponding vehicle.

Experimental design

Experiment 1 tested the effects of 1 mg/kg amphetamine on LI with 40 preexposures and two conditioning trials. Thirty juvenile rats were assigned to four experimental groups in a 2×2 factorial design with main factors of preexposure (0, 40) and drug (amphetamine, saline), (n=7–8 per group).

Experiment 2 tested the effects of 5 mg/kg amphetamine on LI with 40 preexposures and two conditioning trials. Twenty-four juvenile rats were assigned to four experimental groups in a 2×2 factorial design with main factors of preexposure (0, 40) and drug (amphetamine, saline), (n=6 per group).

Experiment 3 assessed LI using three parametric versions of the procedure: 40 preexposures and two conditioning trials, 40 preexposures and five conditioning trials, or 10 preexposures and two conditioning trials. Fifty juvenile rats were assigned to six experimental groups in a 2×3 factorial design with main factors of preexposure (PE, NPE) and parametric condition, (n=8–9 per group).

Experiments 4 and 5 tested the effects of clozapine or M100907 administration in preexposure (experiment 4) or in conditioning (experiment 5), on LI with 40 preexposures and five conditioning trials. In each experiment, forty two juvenile rats were assigned to six experimental groups in a 2×3 factorial design with main factors of preexposure (0, 40) and drug (saline, clozapine, M100907), (n=6–8 per group).

Experiment 6 compared LI in juvenile rats preexposed and conditioned in the same context and in rats preexposed and conditioned in different contexts. Thirty-one rats were assigned to four experimental groups in a 2×2 factorial design with main factors of preexposure (0, 40) and context (same, different), (n=7–8 per group).

Experiment 7 tested the effects of context shift in adult rats. Twenty-one rats were assigned to four experimental groups in a 2×2 factorial design with main factors of preexposure (0, 40) and context (same, different), (n=5–6 per group).

Experiment 8 assessed spontaneous and amphetamine-induced activity in 35-day-old and adult rats. Twenty-four rats were assigned to four experimental groups in a 2×2 factorial design with main factors of age (juvenile, adult) and drug (saline, amphetamine), (n=6 per group).

Statistical analysis

Suppression ratios were analyzed using two-way ANOVAs with main factors of preexposure and drug (experiments 1, 2, 4 and 5), parametric condition (experiment 3), or context (experiments 6 and 7). Significant interactions were followed by post hoc Tukey HSD comparisons assessing the difference between the PE and NPE groups within each condition. For the activity experiment, duration of movements was analyzed using a 2×2x(3)x(5) ANOVA with main factors of age (juvenile, adult) and drug (saline, amphetamine), and a repeated measurements factor of three 30-min periods (1–30 min before injection, 31–60 min after injection, 61–90 min after injection) and five 6-min blocks within each 30-min period.

Results

Experiment 1: the effects of 1 mg/kg amphetamine on LI with 40 preexposures and two conditioning trials

Figure 1 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed saline- or amphetamine-treated rats. As can be seen, LI, i.e., higher suppression ratios of the preexposed (PE) compared with the nonpreexposed (NPE) group, was present in both drug conditions, although amphetamine-treated rats showed overall higher suppression than saline-treated controls. ANOVA yielded significant main effects of preexposure, $F(1,26)=22.75$, $p< 0.0001$, and drug $F(1,26)=6.98$, $p< 0.014$, the latter reflecting stronger suppression of rats that received amphetamine.

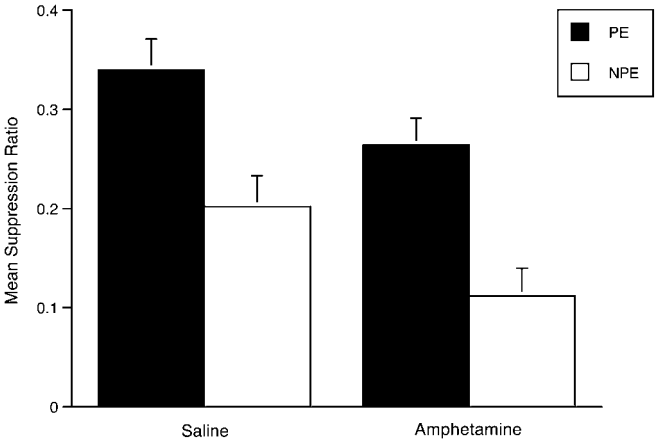

Fig. 1 Means ± SEM of suppression ratios of preexposed (PE) and nonpreexposed (NPE) juvenile rats injected with saline or amphetamine (1 mg/kg) in the preexposure and conditioning stages. Forty preexposures and two conditioning trials were used

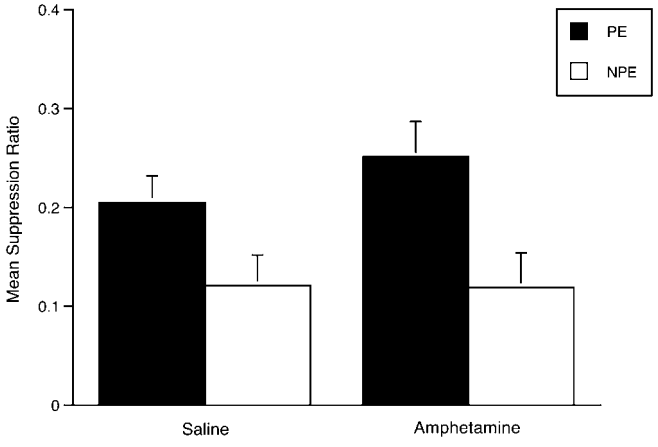

Fig. 2 Means ± SEM of suppression ratios of preexposed (PE) and nonpreexposed (NPE) juvenile rats injected with saline or amphetamine (5 mg/kg) in the preexposure and conditioning stages. Forty preexposures and two conditioning trials were used

Experiment 2: the effects of 5 mg/kg amphetamine on LI with 40 preexposures and two conditioning trials

Figure 2 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed saline- or amphetamine-treated rats. As can be seen, LI was present in both drug conditions (main effect of preexposure, $F(1,20)=10.91$, $p< 0.0035$).

Experiment 3: LI with low number of preexposures or high number of conditioning trials

Figure 3 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed groups in each of the three parametric conditions (40 preexposures and two conditioning trials, 40 preexposures and five conditioning trials, or 10 preexposures and two

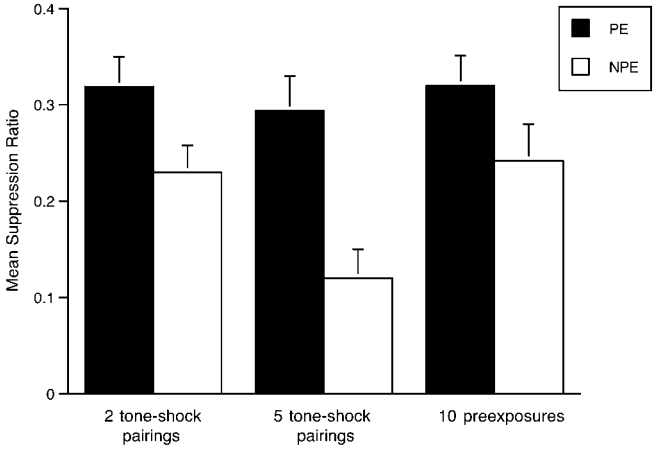

Fig. 3 Means ± SEM of suppression ratios of preexposed (PE) and nonpreexposed (NPE) juvenile rats under three parametric conditions in preexposure and conditioning: 40 preexposures and two conditioning trials, 40 preexposures and five conditioning trials and 10 preexposures and two conditioning trials

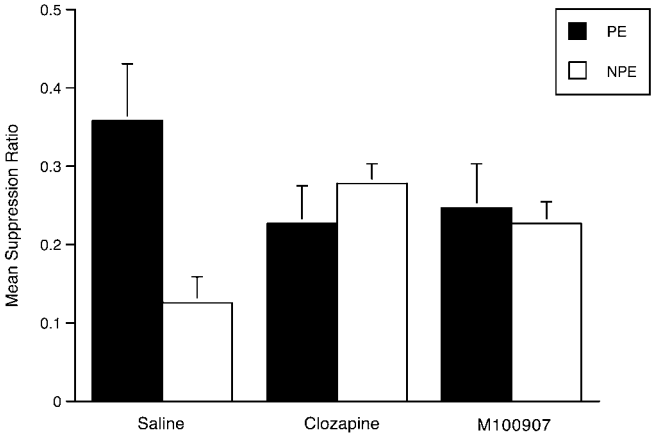

Fig. 4 Means ± SEM of suppression ratios of preexposed (PE) and nonpreexposed (NPE) juvenile rats injected with saline, clozapine (5 mg/kg), or M100907 (0.3 mg/kg). Forty preexposures and five conditioning trials were used, and the drugs were administered in the preexposure stage

conditioning trials). As can be seen, LI was present in all three conditions. ANOVA yielded significant main effects of preexposure, $F(1,44)=18.03$, $p< 0.0001$ and parametric condition $F(1,44)=3.22$, $p< 0.049$, the latter reflecting stronger suppression of rats that received five conditioning trials.

Experiment 4: the effects of clozapine- or M100907-administration in preexposure on LI with 40 preexposures and five conditioning trials

Figure 4 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed saline-, clozapine-, or M100907-treated rats. As can be seen, LI was present in rats that received saline in

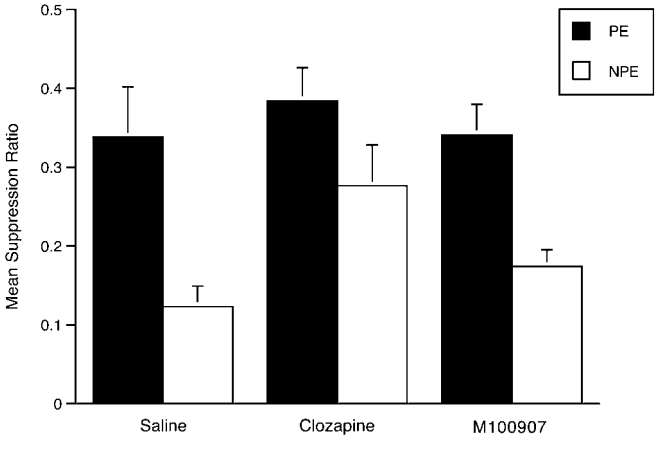

Fig. 5 Means ± SEM of suppression ratios of the preexposed (PE) and nonpreexposed (NPE) rats treated with saline, clozapine (5 mg/kg) or M100907 (0.3 mg/kg). Forty preexposures and five conditioning trials were used, and the drugs were administered in the conditioning stage

preexposure whereas rats that received clozapine or M100907 in preexposure did not show LI. This was supported by a significant preexposure x drug interaction, $F(2, 36)=5.11$, $p<0.011$, as well as by post hoc comparisons which confirmed the presence of LI in rats treated with saline ($p<0.015$), but not in rats treated with clozapine or with M100907 ($p>0.05$ in both cases).

Experiment 5: the effects of clozapine- or M100907-administration in conditioning on LI with 40 preexposures and five conditioning trials

Figure 5 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed saline-, clozapine-, or M100907-treated rats. As can be seen, LI was present in all the conditions (main effect of preexposure $F(1,36)=19.64$, $p<0.0001$).

Experiment 6: the effects of context shift on LI in juveniles

Figure 6 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed rats preexposed and conditioned in the same or different contexts. As can be seen, LI was present in both the same and different context conditions (main effect of preexposure, $F(1,27)=10.58$, $p<0.003$).

Experiment 7: the effects of context shift on LI in adults

Figure 7 presents the means and standard errors of suppression ratios of the preexposed and nonpreexposed groups in the same and in the different context conditions. As can be seen, LI was present in rats preexposed and

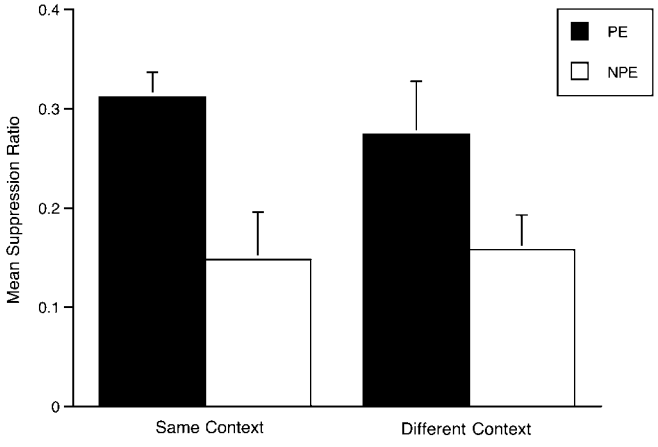

Fig. 6 Means ± SEM of suppression ratios of the preexposed (PE) and nonpreexposed (NPE) juvenile rats preexposed and conditioned in the same context or in different contexts

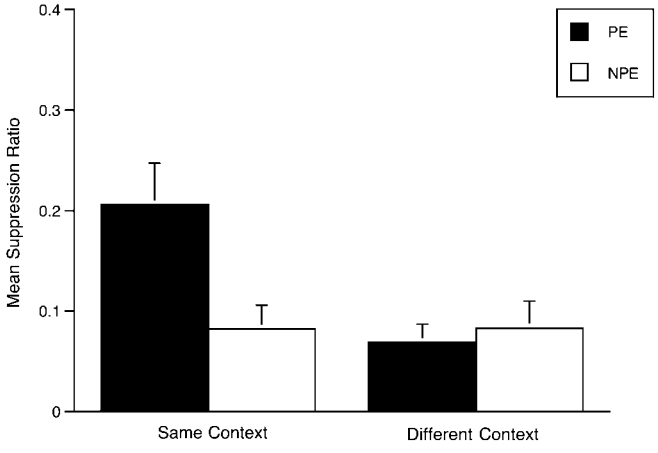

Fig. 7 Means ± SEM of suppression ratios of preexposed (PE) and nonpreexposed (NPE) adult rats preexposed and conditioned in the same context or in different contexts

conditioned in the same context, but not in rats that were preexposed and conditioned in different contexts. This was supported by a significant main effect of context, $F(1,17)=5.66$, $p<0.03$, a significant preexposure x context interaction, $F(1,17)=5.85$, $p<0.027$, as well as by post hoc comparisons which confirmed the presence of LI in the same ($p<0.036$), but not in the different ($p>0.05$) context condition.

Experiment 8: spontaneous and amphetamine-induced activity in juvenile and adult rats

Figure 8 presents the means and standard errors of duration of movements, in 6 min blocks, of juvenile and adult rats before and after saline or amphetamine injection. As can be seen, spontaneous activity levels (first 30 min period) were lower in juveniles than in adults but declined similarly in both groups. There were no differences between the two groups after saline injection. Amphetamine increased the duration of movements in both groups but the effect was more pronounced in adults than in juveniles. These outcomes were supported by significant main effects of age $F(1,20)=46.54$, $p<0.0001$, and drug $F(1,20)=82.85$, $p<0.0001$, as well as by significant interactions of age x period, $F(2,40)=6.85$, $p<0.003$, and age x period x drug $F(2,40)=4.63$, $p<0.0157$. In order to further analyze the latter interaction, separate 2-way ANOVAs (age x period) were conducted for each drug condition. The analysis yielded a significant age x period interaction within the amphetamine condition, $F(2,40)=10.408$, $p<0.0002$, but not within the saline condition, $p>0.05$.

Discussion

Thirty-five-day-old rats conditioned with two or five tone-shock pairings showed fear conditioning as assessed in the CER procedure. In addition, rats of this age which received 40 nonreinforced preexposures to the tone and were conditioned subsequently with two tone-shock pairings, showed reduced fear conditioning to the tone compared with their nonpreexposed controls, namely, exhibited LI. These results replicate our previous findings in adult rats, and are consistent with other studies that demonstrated fear conditioning (Hoffmann and Spear

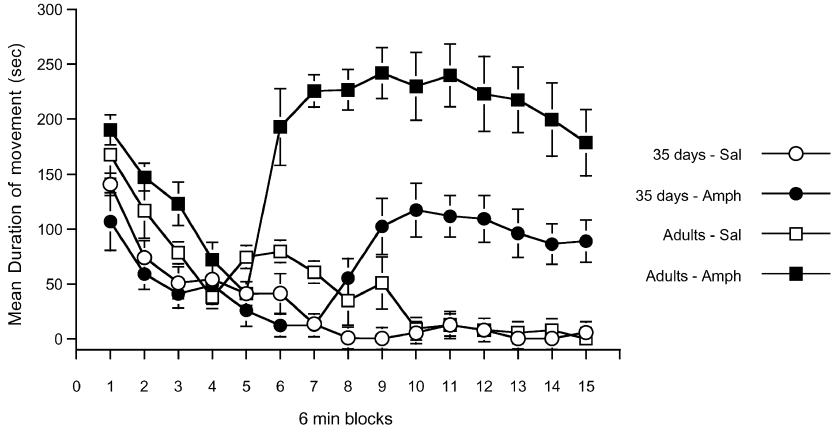

Fig. 8 Means ± SEM of duration of movements, in 6 min blocks, performed by 35-day-old and adult rats before drug administration (*blocks* 1–5) and after the administration of saline (Sal) or 1 mg/kg amphetamine (Amph; *blocks* 6–15)

1989; Rudy 1994; Spear and Smith 1978) and LI (Franchina et al. 1980; Nicolle et al. 1994) in juvenile rats. However, our results with amphetamine, low number of preexposures, high number of conditioning trials, and context shift, showed that LI exhibited by juvenile rats is not an "adult" LI. Thus, contrary to the well-documented capacity of low doses of amphetamine to disrupt LI in adult rats (e.g., Killcross et al. 1994a; McAllister 1997; Weiner et al. 1984, 1988), this drug failed to disrupt LI in juvenile rats. This was not due to an insufficient dosage since the same dose significantly increased locomotor activity in the same-age rats, and because LI was resistant to disruption also by a high dose of this drug. Moreover, 1 mg/kg amphetamine increased conditioned suppression in both the preexposed and the nonpreexposed rats but did not affect LI. Likewise, two parametric manipulations that have been shown by us to disrupt LI in the present procedure in adult rats (e.g., Shadach et al. 1999, 2000; Weiner et al. 1996, 1997), namely, decreasing the number of preexposures to 10 while leaving two conditioning trials, or increasing the number of conditioning trials to five following 40 nonreinforced tone preexposures, left LI intact in juveniles. Interestingly, an inspection of the suppression ratios in saline controls in the different experiments indicates that an increase from two to five conditioning trials increased conditioned suppression in the nonpreexposed rats, yet it did not have a parallel effect in the preexposed rats. In fact, this selective effect on the nonpreexposed groups had led, rather paradoxically, to a more pronounced LI effect (larger PE-NPE difference) in rats conditioned with five trials. Finally, while adult rats showed LI when preexposed and conditioned in the same context but not in different contexts, consistent with the well documented context-specificity of LI (Bouton 1993; Holt and Maren 1999; Lubow and Gewitz 1995; Westbrook et al. 2000), LI in juvenile rats was resistant to context shift: these rats exhibited LI in both the same- and different-context conditions.

The failure of amphetamine, the two parametric manipulations, and context shift, to disrupt LI in periadolescents may be taken to suggest that the brain systems mediating such disruptive effects are not functional at this age and by corollary, that LI disruption by these manipulations in adulthood reflects a postpubertal maturation of these systems. Disruption of LI in adult rats by amphetamine and by the two parametric manipulations used here, is dopamine mediated, because in all three cases, LI disruption is reversed by the administration of the DA-blocker haloperidol. In other words, adult rats treated with haloperidol, like periadolescents here, show LI with low number of preexposures and with high number of conditioning trials as well as when receiving systemic amphetamine. Moreover, the site at which reduced DA transmission produces these effects is the nucleus accumbens (NAC), because DA blockade or depletion within this structure blocks systemic amphetamine-induced LI disruption and produces LI with 10 preexposures (Gray et al. 1997; Joseph et al. 2000). In addition, it has been shown using microdialysis that the increased accumbal DA release seen in response to a nonpreexposed stimulus paired with shock was suppressed after preexposure to the stimulus (Young et al. 1993). Importantly, the behavioral effects of both systemic and intra-accumbal DA blockade as well as changes in NAC DA release, are confined to the conditioning stage of the LI procedure (Gray et al. 1997; Joseph et al. 2000; Shadach et al. 1999, 2000; Young et al. 1993), indicating that NAC DA mechanisms are not involved in the acquisition of the stimulus–no event association in the preexposure stage (acquisition of LI), but rather modulate the expression of this association in conditioning, when the preexposed stimulus is followed by reinforcement (expression of LI; Weiner 1990, 2000, 2003).

In view of the above, our results can be interpreted as reflecting reduced mesolimbic DA function in 35-day-old rats, consistent with other findings in the literature. Compared to adult rats, periadolescent rats (30–40 days old) were shown to have an attenuated responsiveness to acute administration of amphetamine, enhanced behavioral sensitization to repeated drug exposure, altered sensitivity to place conditioning, and problems in adjusting to alterations in reward contingencies, as well as lower DA synthesis and turnover in the NAC and a lower increase in DA levels after amphetamine as assessed by microdialysis, all suggestive of lower functional activity within the mesolimbic DA system in periadolescent rats (Andersen et al. 2001; Bolanos et al. 1998; Campbell et al. 2000; Cirulli and Laviola 2000; Infurna and Spear 1979; Laviola et al. 1999; Spear et al. 1980; Spear and Brake 1983; Spear 2000); indeed, it has been suggested that the neurochemical, behavioral, and pharmacological profile shown by periadolescent rodents resembles that of the adult animals with lesions of the mesolimbic DA system (Laviola et al. 1999; Spear and Brake 1983; Spear 2000).

While "persistent" LI exhibited by 35-day-old rats is consistent with functional hyporesponsivity of the mesolimbic DA system, it should be born in mind that amphetamine was effective in increasing locomotor activity in juveniles, as was also observed in other studies (Bolanos et al. 1998; Laviola et al. 1999). This suggests that the mesolimbic DA system is at least partially functional with respect to its role in locomotion, but not so with respect to its role in LI. Since in adult rats, NAC-mediated modulation of LI expression is controlled by its temporolimbic inputs (Gray et al. 1991; Schmajuk et al. 2001; Weiner 1990, 2000, 2003; Weiner and Feldon 1997), the absence of adult-like LI modulation in juveniles may also reflect nonfunctionality of these NAC inputs. This was supported by the failure of context shift to disrupt LI in juveniles. Context-shift-induced LI disruption in adult rats depends on the integrity of the hippocampus, because adult rats sustaining cell lesions or inactivation of the hippocampus, like juveniles here, display LI following context change between preexposure and conditioning (Holt and Maren 1999; Honey and Good 1993). Thus, the absence of adult-like context-dependent

LI modulation in juveniles may reflect nonfunctionality of the hippocampal inputs to the NAC. This could be because the processing of information by the hippocampus has not attained its adult level of complexity, or because of reduced glutamatergic function (Frantz and Van Hartesveldt 1999a, 1999b; Spear 2000). Interestingly, we have recently found that adult rats with cell lesions of another major limbic input to the NAC, the basolateral amygdala (BLA), persist in showing LI with five conditioning trials (Schiller and Weiner, submitted), suggesting that LI with extended conditioning seen in juveniles, may reflect nonfunctionality of BLA inputs to the NAC.

As detailed in the Introduction, atypical APDs such as clozapine exert in adults a dual pattern of effects on LI which enables detection of their "typical" action (conditioning-based LI potentiation under conditions which do not produce LI in controls), as well as a dissociation from typical APDs by their "atypical" action (preexposure-based LI disruption under conditions which produce LI in controls). Clozapine-induced potentiation of LI could not be demonstrated in 35-day-old rats because the manifestation of LI potentiation requires an absence of LI in the no-drug controls; accordingly, clozapine administered in conditioning had no effect on LI. Although this result mimics that obtained in adults, it does not allow the conclusion regarding whether the absence of clozapine effect in juveniles reflects a genuine inability of clozapine to modulate LI or is an artifact of a robust LI in no-drug controls. In contrast to clozapine's ineffectiveness in conditioning, this drug disrupted LI when given in preexposure, and the same disruptive effect was obtained with M100907, as found with both drugs in adult rats (Shadach et al. 2000; Zuckerman et al. 2001). Although the mechanism underlying the preexposure-based LI disruption by clozapine remains to be elucidated, it is certainly not mediated by its DA-blocking action because, as noted above, DA mechanisms are not operative in the preexposure stage (Weiner 2003; Weiner et al. 1984, 1987a). Since the same effect is produced by selective 5HT2A receptor antagonists, this action of clozapine is likely to be due its 5HT2A antagonistic action (Shadach et al. 2000). Although the role of serotonergic mechanisms in LI is not established, most of the existing data indicate that serotonergic manipulations exert their effect on LI via the preexposure stage (Moser et al. 2000; Weiner 2003; Shadach et al. 2000), i.e., they affect the acquisition of LI. Our results suggest that the preexposure-based serotonergic modulation of LI, at least that mediated via 5HT2A receptors, is operative at 35 days of age and is not dependent on processes of later maturation. However, the present conclusions, being based on a single-dose analysis, are limited, and further studies with additional doses of these compounds as well as with additional serotonergic compounds are necessary for their substantiation.

In summary, a comparison of our previous and present findings with LI in adults with the present findings in juveniles, reveals that under identical testing parameters in the CER procedure, the status of LI in the two age groups differs: only with 40 preexposures followed by two conditioning trials both juveniles and adults show LI; decreasing the number of preexposures to 10 while leaving two conditioning trials or leaving 40 preexposures while increasing the number of conditioning trials to five, disrupts LI in adults whereas juveniles show LI with both sets of parameters; likewise, changing the context between preexposure and conditioning disrupts LI in adults but spares LI in juveniles. In addition, matching for equivalent LI in both age groups (40 preexposures with two conditioning trials in adults, and 40 preexposures with two or five conditioning trials in juveniles), 1 mg/kg amphetamine acts differently, disrupting LI in adults but not in juveniles, whereas 5 mg/kg clozapine exerts the same actions: it has no effect when given in conditioning and disrupts LI when given in preexposure, and the latter applies also to 0.3 mg/kg M100907 (we have no data in adults on the effects of M100907 in conditioning, but the 5HT2A antagonist ritanserin has no effect).

Presence of LI in 35-day-old rats under all the no-drug conditions tested and following amphetamine administration, as well as disruption of LI by drugs acting via the preexposure stage, indicates that the brain substrates subserving the acquisition of the stimulus–no event association in preexposure (as manifested in poor fear conditioning in the preexposed rats) are functional, and responsive to at least some drug manipulations in a manner found in adults. Likewise, the brain substrates subserving the acquisition of the stimulus-reinforcement association (as manifested in normal fear conditioning in the nonpreexposed rats) are functional. However, the LI phenomenon exhibited by 35-day-old rats differs from that exhibited by normal adult rats, because juveniles express the preexposure effect (show LI) under conditions which prevent the expression of the preexposure effect (disrupt LI) in normal adult rats. As emphasized by us previously (Weiner 1990, 2003; Weiner and Feldon 1997), in normal adult rats, LI is a "window" phenomenon, expressed under limited and specific conditions of preexposure and conditioning, and changes in these conditions, e.g., a reduction in the number of stimulus preexposures, an increase in the number of conditioning trials, or a context shift, cause the organism to switch responding according to the stimulus-reinforcement contingency prevailing in conditioning and thus not to show LI. The same occurs following the administration of amphetamine, a drug known to enhance behavioral switching (Oades 1985; Robbins and Sahakian 1983). Our results suggest that it is precisely such a "window" characteristic that is lacking in prepubertal rats; thus, the capacity to acquire the stimulus–no event association as well as the stimulus-reinforcement association is normal in these rats, but the ability to switch responding to the stimulus-reinforcement association under conditions triggering such a shift in adult rats is lacking. The latter points to an immaturity in the brain mechanisms responsible for restricting the expression of the preexposure effect to specific conditions (e.g., low but not high

number of conditioning trials, or same but not different context in preexposure and conditioning). It is important to emphasize that the latter mechanisms are those that make the LI phenomenon in adult rats flexible and adaptive to environmental changes, by enabling LI disruption when environmental changes demand so (Weiner 2003).

Thus, LI may have a unique developmental course whereby it evolves from a robust and an inflexible phenomenon to one that is highly responsive to situational demands, and this development is apparently underlaid by the postpubertal maturation of brain systems that regulate LI expression. The latter are likely to include the NAC and its limbic sources of input, in particular, the hippocampus and the BLA, because investigations in adult rats have shown that these are key regions regulating LI expression (Schmajuk et al. 2001; Weiner 2003; Weiner and Feldon 1997). By corollary, a maturation-dependent dysfunction in these same systems might be responsible for the postpubertal disruption of LI observed following various perinatal manipulations and possibly, for disrupted LI observed in schizophrenia. This is consistent with the neurodevelopmental view of schizophrenia which posits that this disorder involves a disruption of late-maturing, highly evolved cortical functions that fully manifests itself only in adult life as well as with the mesolimbic DA and temporolimbic pathology implicated in schizophrenia.

Finally, given that amphetamine-induced LI disruption in rats, which is the bona fide symptom of psychosis in the model, is dependent on postpubertal changes in the brain, it can be suggested that a postpubertal maturation of these same mechanisms underlies the manifestation of psychosis. Indeed, the inability of amphetamine to disrupt LI in periadolescent rats is consistent with and may provide an animal analogue of the remarkable phenomenon whereby drugs producing psychosis in adults, including amphetamine and PCP, do not produce psychosis in children (Barkley 1977; Ellison 1995; Ney 1967; Olney et al. 1999).

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