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Parametric and pharmacological modulations of latent inhibition in mouse inbred strains

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ABSTRACT

Latent inhibition (LI) is a cross species selective attention phenomenon, which is disrupted by amphetamine and enhanced by antipsychotic drugs (APDs). Accumulating data of LI in gene-modified mice as well as in mouse inbred strains suggest genetic component of LI. Here we study modulation of LI in mouse inbred strains with *spontaneously* disrupted LI by parametric manipulations (number of pre-exposures and conditioning trials) and pharmacological treatments with antipsychotics and NMDA modulator, D-serine. C3H/He and CBA/J inbred mice showed disrupted LI under conditions with 40 pre-exposures (PE) and 2 trials of the conditioned stimulus–unconditioned stimulus (CS–US) due to either loss of the pre-exposure effect or a ceiling effect of poor learning, respectively. The increased number of pre-exposures and/or number of conditioning trials corrected expression of LI in these inbred mice. The disrupted LI was also reversed by haloperidol in both inbred strains at 1.2 mg/kg but not at 0.4 mg/kg, as well as by clozapine (at 3 mg/kg in C3H/He and at 9 mg/kg in CBA/J mice). D-serine potentiated LI in C3H/He mice at 600 mg/kg, but not in the CBA/J at both studied doses (600 and 1800 mg/kg). Desipramine (10 mg/kg) had no effect on LI in both inbred mouse strains. Our findings demonstrated some resemblance between the effects of parametric and pharmacological manipulations on LI, suggesting that APDs may affect the capacity of the brain processes environmental stimuli in LI. Taken together, LI may offer a translational strategy that allows prediction of drug efficacy for cognitive impairments in schizophrenia.

1. Introduction

The latent inhibition (LI) paradigm is based on the phenomenon of reduced conditioning after stimulus pre-exposure. It is used to measure *decremental* form of attention, the ability to ignore irrelevant stimuli. Deficits in attention and information processing are central features in schizophrenia, which may lead to stimulus overload, cognitive fragmentation and thought disorder common in this disorder (Freedman et al., 1991; Strauss et al., 1993; Perry et al., 1999; Ross et al., 2006). Abnormal LI is a marker of cognitive deficit related to schizophrenia (e.g. Baruch et al., 1988; Gray et al., 1992; Weiner, 2003; review Kumari and Ettinger, 2010). Disrupted LI has been reported in patients in the acute stage of schizophrenia (Gray et al., 1992; Rascle et al., 2001). Both typical and atypical antipsychotic drugs (APDs) restore amphetamine-induced disruption of LI (Warburton et al., 1994; Gosselin et al., 1996; Lipina and Roder, 2010a), and potentiate LI under conditions that normally do not yield robust LI (Christison et al., 1988; Dunn et al., 1993; Weiner et al., 1997; Weiner, 2003; Lipina et al., 2005; Lipina and Roder, 2010a).

LI can be demonstrated in a variety of classical and instrumental conditional procedures, (passive and active avoidance, conditional emotional response, taste and olfaction aversion, discrimination learning) and in many species (humans, monkey, sheep, pigeons, rodents, frogs and goldfishes) (Shishimi, 1985; Good and Macphail, 1994; review Lubow, 2005; Ferrari and Chivers, 2011). The mouse is a model to study processes related to the human brain functions is one of the most valuable resources in neuroscience, with approximately 98% of mouse genes having human counterparts (Tecott and Wehner, 2001). Mouse inbred strains (Gould and Wehner, 1999; Restivo et al., 2002; de Bruin et al., 2006) as well as gene-modified mice (review Lipina and Roder, 2010b) demonstrated a wide range of LI expression, suggesting the contribution of the genetic component in LI.

Interest to LI was spawned by the suggestion that its disruption may provide an animal model of schizophrenia. Further, LI was suggested to have two types of impairments: disruption and persistence (Weiner, 2003) as a "two-head" model, which reflects excessive and

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retarded switching between associations. According to the "switching model", the LI phenomenon involves the acquisition of two independent and conflicting contingencies in the pre-exposure (stimulus-no event) and conditioning (stimulus-reinforcement), which compete for expression during conditioning, when mismatch arises between conflicting predictions signaled by the conditioned stimulus (CS). The organism remembers that a stimulus is irrelevant, and then the "irrelevance" of the stimulus is expressed in the conditioning stage, organism continues to count it as irrelevant even if the stimulus has a significant outcome already. Thus, the model allowed switch locus of the *ability to ignore* from pre-exposure to conditioning. Notably, an *inability to ignore* could not be only due to the deficit in the ability to ignore the irrelevant stimulus in pre-exposure but also in the failure to continue to ignore it under changed reinforcement contingencies in conditioning. LI is a "window" phenomenon (Weiner, 2003) and can be obtained only under particular combinations of pre-exposure and conditioning parameters. For instance, reduced amount of pre-exposures, (or increase in the number of conditioning trials) would cause the cognitive switch to the stimulus-reinforcement contingency, and hence, disrupt LI. Parametric manipulations can affect switching, so manipulations which lead to excessive switching will prevent the expression of LI under conditions in which LI is normally observed and manipulations which retard switching will promote the expression of LI even under conditions in which normal organism fails to express LI.

Effects of parametric manipulations on LI have been demonstrated on C57BL/6 strain (Lipina et al., 2005; Bay-Richter et al., 2009; Singer et al., 2009). LI was disrupted by increasing the number of conditioning trials (Lipina et al., 2005) or facilitated by increased amount of pre-exposures (Bay-Richter et al., 2009; Singer et al., 2009). Among commonly used inbred strains, DBA/2 mice attracted most of the attention in regards to schizophrenia research due to its relevance to psychosis-related traits. This inbred line showed impaired Pre-pulse inhibition (PPI), as another behavioral endophenotype related to schizophrenia (Olivier et al., 2001; Tohmi et al., 2005) and responded to APDs (e.g. Kinney et al., 2003; Fox et al., 2005; Depoortère et al., 2005). In regards to LI in DBA/2 mice, the accumulating data in the literature are controversial. So, the earliest report of Gould and Wehner (1999) demonstrated LI in this line, estimating LI based on the conditioned emotional response (CER), whereas DBA/2 mice were not able to express LI assessed in passive avoidance (Baarendse et al., 2008) or active avoidance (Singer et al., 2009) paradigms. Given low performance of DBA/2 mice in the context tasks (e.g. Thinus-Blanc et al., 1996; Gerlai, 1998; Nguyen et al., 2000) are associated with weak long-term potentiation (LTP) in the hippocampus (Nguyen et al., 2000; Gerlai, 2002; review Schimanski and Nguyen, 2004), it could be suggested that poor associative memory could be modified by different task parameters and lead to the LI expression in CER paradigm.

Although the urgent need for cognition improving compounds in schizophrenia is widely accepted (Marder and Fenton, 2004; Gold, 2004; Heinrichs, 2005; Hagan and Jones, 2005), development of treatments has remained a major challenge, hindered by controversy regarding efficacy of available treatments and paucity of pre-clinical data. In recent years, therapeutic strategies have increasingly focused on enhancing NMDA receptor function as alternative treatment of cognitive impairments. Many clinical studies reported positive findings with compounds acting via the glycineB modulatory site (e.g., D-cycloserine, glycine, D-serine), (Goff et al., 1995, 1999; Tsai et al., 2004; Heresco-Levy, 2003, 2005; Javitt, 2002, 2008), although contradictory results were also reported (Buchanan et al., 2007; Goff et al., 2005). The usefulness of LI for preclinical research has been demonstrated by our finding of an identical pro-cognitive effect for NMDA enhancers in the mouse (Lipina et al., 2005), strengthening the predictive validity of the mouse LI model.

An assessment of the range of LI performance in inbred mice, its modulation by task parameters and drug treatments is of particular interest since it could help identify schizophrenia-related mouse inbred strain with expression of abnormal LI; further validate efficacy of anti- and pro-psychotic drugs and their mechanisms of action. As noted above, the demonstration of treatment-induced LI enhancement requires the use of task parameters that generate weak or marginal LI effect in controls (e.g. Feldon and Weiner, 1991; Dunn et al, 1993). Therefore, information about the influence of genetic variability on LI and its modulation by task parameters can be applied for pharmaco-behavioral research with usage of variety of gene-modified mice.

The main aim of the current study was to further characterize LI in mouse inbred strains. In the first experiment we sought to replicate strain differences reported by Gould and Wehner (1999) who measured LI in six inbred strains: C57BL/6J, 129S6, A/J, CBA/J (CBA), C3H/He (C3H) and in non-blind C3H mice—C3.BLiA-$+^{Pde6b}$ mice to rule out the effect of impaired vision on LI in mice. Next, we assessed modulation of LI expression by parametric manipulations (number of pre-exposures and conditioning trials) in inbred strains with *spontaneously* disrupted LI due to either disrupted ability to ignore irrelevant stimulus (C3H mice) or poor associative memory (CBA mice). The second part of the study sought to further validate the sensitivity of the mouse LI to the potentiating effects of APDs and D-serine. To determine specificity of APDs/D-serine effects in the LI model, we also probed the effect of antidepressant, desipramine. We found that the disrupted LI was reversed by both APDs at different doses. D-serine was able to ameliorate LI only in C3H but not in CBA mice and desipramine had no effect on LI in both strains. Taken together, LI may offer a translational strategy that allows prediction of drug efficacy for cognitive impairments in schizophrenia.

2. Materials and methods

2.1. Subjects

Male mice were purchased from the Jackson Laboratory (Bar Harbor, ME) and were 8–10 weeks old upon arrival. They were housed five per cage under a 12 h light/dark cycle (lights on at 07.00) with ad libitum food (Purina mouse chow) and were acclimatized for 1–2 weeks to the animal colony at the Samuel Lunenfeld Research Institute prior to the beginning of behavioral testing. Water deprivation was initiated 24 h before the training period and continued throughout the experiment. Water access was limited and was monitored by measuring weight loss (see below). Mice had additional access to the water daily in their home cages after the experiment for 1 h. Behavioral testing was conducted between 09.00 and 16.00 h. All animal procedures were approved by the Animal Management Committee of the Mount Sinai Hospital and were conducted in accordance to the requirements of the Province of Ontario Animals for Research Act 1971 and the Canadian Council on Animal Care.

2.2. Behavioral apparatus

LI was measured in three conditioning chambers (Med. Associates Inc., St. Albans, VT) each enclosed in a melamine, sound-attenuating chamber (ENV-022M) as described before (Lipina et al., 2005; Lipina and Roder, 2010a). The interior of the chamber was white with a speaker and a switch-control light bulb (ENV-221CL) mounted on the ceiling. Ventilation fans on the backs of the chests provided air exchange and background noise (68 dB). The chambers had clear Plexiglas walls (ENV-307W) and removable floors consisting of either metal rods (used on pre-exposure and conditioning days) or a flat piece of aluminum (used on pretraining, baseline drinking, and test days). They had a bottle with a metal tip (sipper tube). On the pre-exposure and conditioning days, access to the bottle was prevented by a guillotine door. Foot shock of 1 s duration and 0.37 mA intensity were administered via the metal rods of the grid floor wired to a shock generator (ENV-414) via a scrambler. The auditory stimulus was a 5 s 85-dB white

noise (ENV-324M). Licks were detected by a lickometer (ENV-350CM). When the mouse made contact with the floor of the chamber and the sipper tube (metal tip on regular bottle), a computer counted that as a lick. An IBM-PC compatible computer running MED Associates software (MED-PC) and connected to the chambers via an interface package (DIG-716P1 and ANL-926) controlled the administration of training and testing stimuli. All events were programmed by MED-PC software. The chambers were cleaned with 70% ethanol and Clidox between sessions.

2.3. Behavioral procedure

2.3.1. Training period

Prior to the beginning of each LI experiment, mice were weighed and water was removed from their home cages for 24 h. Mice were then maintained on water restriction with body weights maintained at no lower than 80% of initial body weight. Water restriction was used to reduce individual variability in motivation to drink. During training period, mice were trained to drink in the experimental chamber for 6 days, 15 min/day. Each daily session began with 5 min acclimatization without access to the sipper tube before the guillotine door was raised. Latency to the first lick and number of licks made during the 15 min were recorded. The LI procedure was conducted on days 6–9 and consisted of the following stages.

2.3.2. Pre-exposure

With the guillotine door closed, the pre-exposed mice received a predetermined number of a 5 s white noise presentations (20, 40 or 60 in different experiments as detailed below) with an inter-stimulus interval of 60 s. The non-pre-exposed mice were confined to the chamber for an identical period of time without receiving the stimuli.

2.3.3. Conditioning

With the guillotine door closed, all mice underwent fear conditioning to the noise stimulus by pairing the noise with the footshock 2 or 4 times (as detailed below for the specific experiments). The conditioning trials were given 5 min apart. Shock immediately followed noise termination. The first conditioning trial was given 5 min after the start of the session. After the last conditioning trial, mice were left in the experimental chamber for an additional 5 min.

2.3.4. Lick retraining

Mice were given a 15-min drinking session as during the training period. Data of mice that failed to complete 100 licks were dropped from the analysis.

2.3.5. Test

Each mouse was placed in the chamber with access to the sipper tube. When the mouse completed 75 licks the noise was presented and lasted until the mouse reached lick 101. The following times were recorded: Time to first lick, time to complete licks 50–75 (before noise onset; A period) and time to complete licks 76–101 (after noise onset; B period). Degree of lick suppression was calculated as a suppression ratio A/A + B. Lower suppression ratio indicates a stronger suppression of drinking. LI consists of lower suppression of drinking (higher suppression ratios) in the pre-exposed compared to the non-pre-exposed mice.

2.3.6. Drugs

Haloperidol (0.4 or 1.2 mg/kg; Tocris, USA) and clozapine (3 or 9 mg/kg; Tocris, USA) were dissolved in 0.9% NaCl containing 0.3% Tween-20 (Bio-Rad). D-serine (600 or 1800 mg/kg; Sigma, Canada) and desipramine (10 mg/kg; Tocris, USA) were dissolved in 0.9% NaCl. Drug doses were expressed as free-base. Haloperidol, clozapine and desipramine were injected intraperitoneally 30 min prior to the experimental session, and D-serine was injected subcutaneously 20 min prior to the experimental session. All drugs were administered in a volume of 10 ml/kg before pre-exposure and conditioning stages. Doses of haloperidol, clozapine, D-serine and desipramine were chosen based on the literature (Kumar and Garg, 2009; Lipina et al., 2005; Lipina and Roder, 2010a). Since LI in CBA mice was unaffected by the lower doses of clozapine and D-serine, we raised their dosage for this strain based on the literature (Olivier et al., 2001).

2.3.7. Statistical analysis

Times to complete licks 50–75 (A period) and suppression ratios were analyzed with two-way ANOVAs with main factors of pre-exposure and genotype (Experiment 1), parametric conditions (Experiments 2–3) or drug treatments (Experiments 4–6). Fisher's least significant difference (LSD) post-hoc comparisons were used to assess the differences between pre-exposed and non-pre-exposed groups within each condition.

3. Results

3.1. Experiment 1: LI in the inbred mouse strains

LI was tested in C57BL/6J (n = 9/8), 129/SvEvTac (n = 7/8), A/J (n = 6/6), CBA/J (CBA) (n = 6/6), C3H/He (C3H) (n = 7/7) and C3.BliA-+^{Pde6b} (C3A) (n = 7/7) strains using pre-exposure and conditioning parameters which can produce LI in the C57BL/6J strain, namely: 40 pre-exposures and 2 conditioning trials. The twelve experimental groups did not differ in their times to complete licks 50–75 before noise onset (all ps > 0.05; overall mean A period = 7.35 s). Fig. 1 presents the mean suppression ratios of the pre-exposed and non-pre-exposed groups in six inbred strains. ANOVA detected significant main effects of pre-exposure [$F(1, 78) = 25.3$, $p < 0.001$] and genotype [$F(5, 78) = 16.7$, $p < 0.001$] as well as pre-exposure × genotype interaction [$F(5, 78) = 6.7$, $p < 0.001$]. Post-hoc analysis found differences between the pre-exposed and the non-pre-exposed groups (i.e. expression of LI) in the C57BL/6J ($p < 0.001$) and 129/SvEvTac mice ($p < 0.01$), but not in the A/J, CBA, C3H and C3A mice (all ps > 0.05). Notably, that both blind C3H and non-blind C3A mice had disrupted LI, excluding vision as a factor which might affect LI in mice. Interestingly, absence of LI in C3H and C3A strains was due to strong suppression in the pre-exposed groups, which was as high as that of the non-pre-exposed groups, whereas in the A/J and CBA strains it was due to weak suppression in the non-pre-exposed groups. Although both A/J and CBA mice showed no LI in similar manner, we excluded A/J mice from follow up experiments due to their

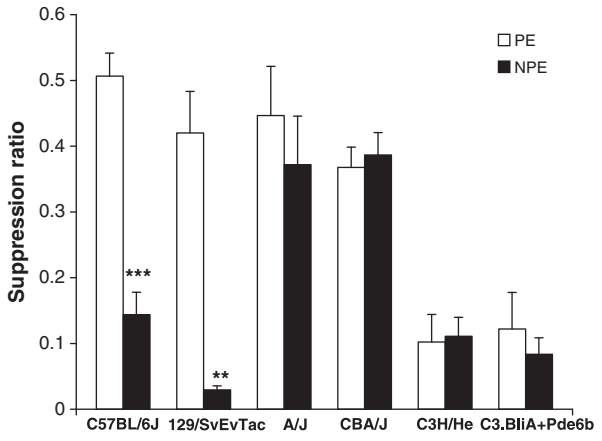

Fig. 1. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed (NPE) C57BL/6J, 129/SvEvTac, A/J, CBA/J, C3H/He and C3.BliA-+^{Pde6b} mice conditioned with two conditioning trials following 40 pre-exposures (n = 7–9 per group). **p < 0.01; *** p < 0.001—NPE in comparison with PE mice within each inbred strain.

poor water consumption during the training period (Supplementary Fig. 1A–B), which was also reported previously (Seburn, 2001).

3.2. Experiments 2–3: Parametric modulation of LI in the C3H and CBA mice

3.2.1. Correction of LI in the C3H strain by increased number of pre-exposure

The experiment included six experimental groups in a 2×3 design with main factors of pre-exposure (pre-exposed, non-pre-exposed) and parametric condition (40 pre-exposures and 2 conditioning trials; 60 pre-exposures and 2 conditioning trials; 60 pre-exposures and 4 conditioning trials). The six experimental groups did not differ in their times to complete licks 50–75 before noise onset (all ps>0.05; overall mean A period = 6.83 s). Fig. 2A shows the mean suppression ratios of the pre-exposed and non-pre-exposed C3H mice in the three conditions: 40PE + 2 CS–US (n = 7/7); 60 PE + 2 CS–US (n = 8/7) and 60 PE + 4 CS–US (n = 9/8). ANOVA yielded a significant main effect of pre-exposure [$F(1, 40) = 8.2$, $p<0.01$], parametric conditions [$F(2, 40) = 3.25$, $p<0.05$] and their interactions [$F(2, 40) = 7.6$, $p \leq 0.001$]. Post-hoc comparisons yielded a significant difference between the pre-exposed and non-pre-exposed C3H mice given 60 pre-exposures and 2 conditioning trials ($p<0.01$), but not in the other two conditions (both ps>0.05).

3.2.2. Correction of LI in the CBA strain by increased number of pre-exposure and conditioning trials

First, we sought to assess attentional processing in CBA inbred strain and probed how number of pre-exposures can alter LI in CBA mice under the same conditioning (2 CS–US). The experiment included six experimental groups in a 2×3 design with main factors of pre-exposure (pre-exposed, non-pre-exposed) and number of pre-exposures (20, 40, 60). The six experimental groups did not differ in their times to complete licks 50–75 before noise onset (all ps>0.05; overall mean A period = 10.8 s). Fig. 2B illustrates the mean suppression ratios of the pre-exposed and non-pre-exposed CBA mice under conditions with 20 PE + 2 CS–US trials (n = 6/6), 40 PE + 2 CS–US (n = 6/6) and 60 PE + 2 CS–US (n = 6/6). ANOVA did not detect significant effect of pre-exposure, number of pre-exposures or their interactions (all ps>0.05) on expression of LI in CBA mice. Regardless of number of pre-exposures, both pre-exposed and non-pre-exposed CBA mice did not express LI conditioned with 2 CS–US trials (all ps>0.05).

To overcome learning/memory deficit seen in CBA mice, next experiment applied stronger conditioning (4 CS–US) and probed if gradual increase of number of pre-exposures would lead to the expression of LI in this strain. The experiment included six experimental groups in a 2×3 design with main factors of pre-exposure (pre-exposed, non-pre-exposed) and number of pre-exposures (40, 60, 80). The six experimental groups did not differ in their time to complete licks 50–75 before noise onset (all ps>0.05; overall mean A period = 9.76 s). Fig. 2C presents the mean suppression ratios of the pre-exposed and non-pre-exposed CBA mice under conditions with 40 PE + 4 CS–US conditioning trials (n = 6/11); 60 PE + 4 CS–US (n = 6/9) and 80 PE + 4 CS–US (n = 6/7). ANOVA revealed a significant main effect of pre-exposures [$F(1, 39) = 119.7$, $p<0.001$], number of pre-exposures [$F(1, 39) = 5.46$, $p<0.01$], and pre-exposure x number of pre-exposures [$F(1, 39) = 7.6$, $p \leq 0.001$] interactions. Post-hoc comparisons detected LI in CBA mice under conditions with 60 pre-exposures + 4 conditioning trials and 80 pre-exposures + 4 conditioning trials (both ps<0.001) but not in conditions with 40 pre-exposures + 4 conditioning trials (p>0.05).

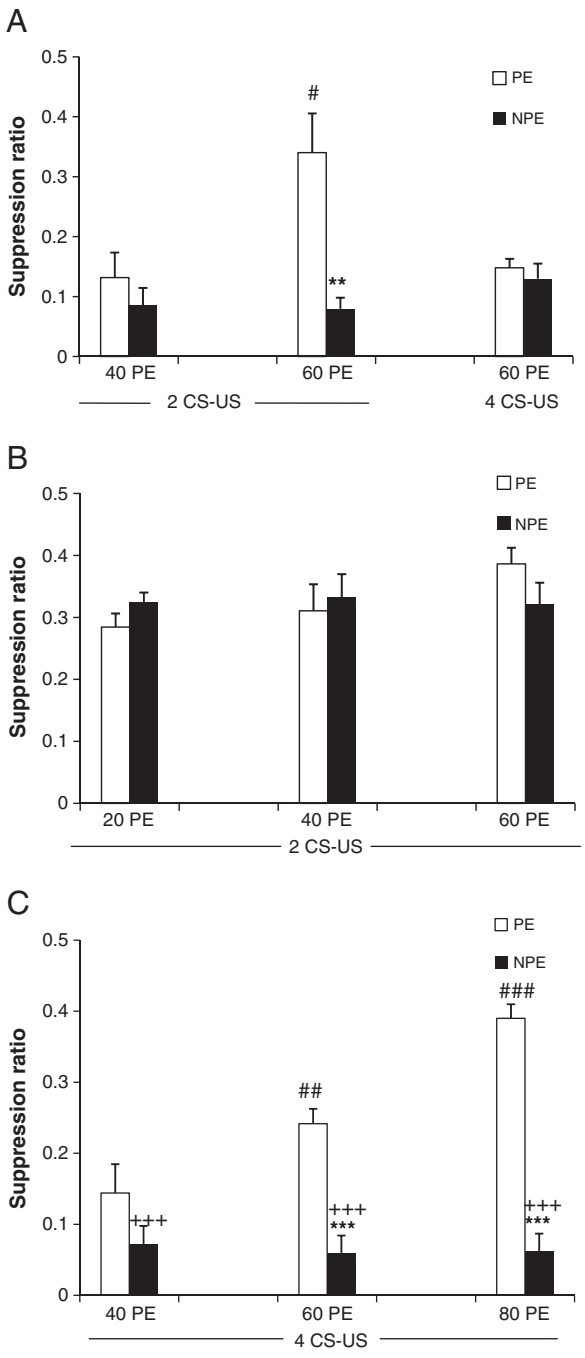

Fig. 2. Effects of parametric manipulations on LI in C3H (A) and CBA (B–C) mice. A. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed (NPE) C3H mice trained under three parametric conditions: 40 pre-exposures (PE) + 2 CS–US trials, 60 PE + 2 CS–US trials, or 60 PE + 4 CS–US trials (n = 7–8 per group). B. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed (NPE) CBA mice conditioned with 2 CS–US trials and given either 20 PE, 40 PE or 60 PE (n = 7–8 per group). C. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed CBA mice conditioned with 4 CS–US trials and given either 40 PE, 60 PE or 80 PE (n = 6–8 per group). ** p<0.01; *** p<0.001—in comparison with PE within each condition; # p<0.05—in comparison with PE mice under 40PE + 2 CS–US condition; ## p<0.01; ### p<0.001—in comparison with PE mice under 40PE + 4 CS–US condition.

3.3. Experiments 4–6: Pharmacological modulation of LI in the C3H and CBA inbred mice

3.3.1. Facilitation of LI in the C3H strain by clozapine, haloperidol and D-serine

The experiment included twelve experimental groups in a 2×6 design with main factors of pre-exposure (0, 40) and drug (vehicle, 3 mg/kg clozapine, 0.4 mg/kg haloperidol, 1.2 mg/kg haloperidol, 600 mg/kg D-serine and 10 mg/kg desipramine). The twelve experimental groups did not differ in their times to complete licks 50–75 before noise onset (all ps>0.05; overall mean A period = 8.3 s). Fig. 3 presents the mean suppression ratios of the pre-exposed and non-pre-exposed C3H mice injected with vehicle (n = 7/7), 3 mg/kg

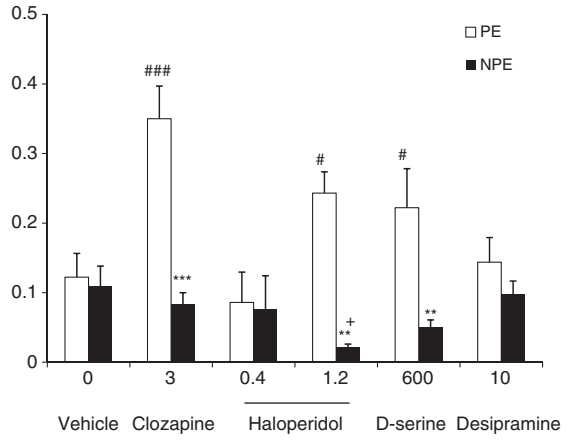

Fig. 3. Effects of APDs, D-serine and desipramine on LI in C3H mice. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed (NPE) C3H mice treated with saline, 3 mg/kg clozapine, 0.4 mg/kg haloperidol, 1.2 mg/kg haloperidol, 600 mg/kg D-serine or 10 mg/kg desipramine (n = 6–10 per group). Forty pre-exposures and two conditioning trials were used. ** p<0.01, *** p<0.001—in comparison with PE mice within each condition; # p<0.05; ### p<0.001—in comparison with vehicle-treated PE mice; + p<0.05—in comparison with vehicle-treated NPE mice.

clozapine (n = 7/7), 0.4 mg/kg haloperidol (n = 9/10), 1.2 mg/kg haloperidol (n = 6/6), 600 mg/kg D-serine (n = 8/8) or 10 mg/kg desipramine (n = 7/7). ANOVA yielded significant main effects of pre-exposure [F (1, 77) = 24.2, p<0.001], and drug [F (5, 77) = 2.43 p<0.05] as well as a significant pre-exposure × drug interaction [F (5, 77) = 3.4, p ≤ 0.01]. Post-hoc comparisons confirmed the presence of LI in mice injected with clozapine, 1.2 mg/kg haloperidol and D-serine (p<0.001, and ps<0.01, respectively), but not in any other experimental groups (all ps>0.05).

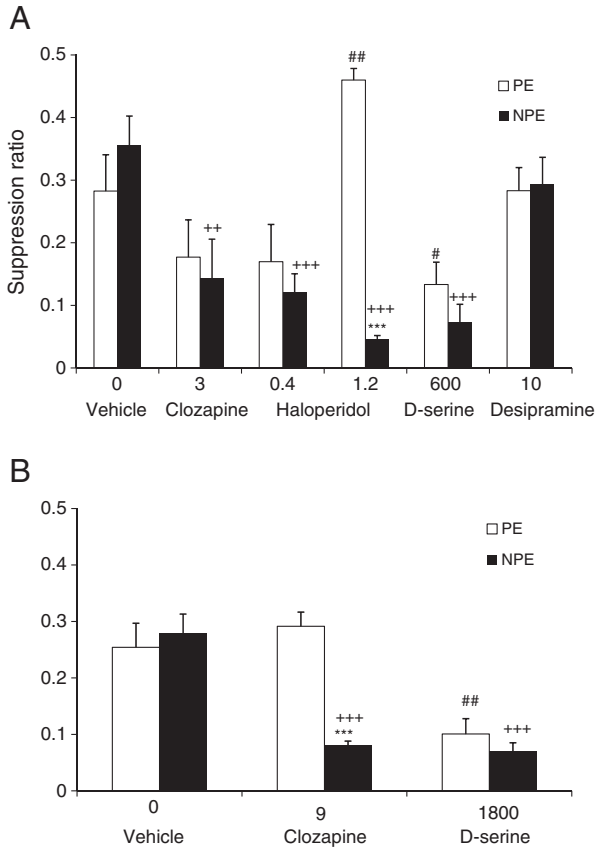

Fig. 4. Effects of APDs, D-serine and desipramine on LI in CBA mice. A. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed (NPE) CBA mice injected with vehicle, 3 mg/kg clozapine, 0.4 mg/kg haloperidol, 1.2 mg/kg haloperidol, 600 mg/kg D-serine or 10 mg/kg desipramine (n = 6–10 per group). B. Mean suppression ratios of the pre-exposed (PE) and non-pre-exposed (NPE) CBA mice injected with vehicle, 9 mg/kg clozapine, or 1800 mg/kg serine (n = 6–7 per group). Forty pre-exposures and two conditioning trials were used. *** p<0.001—in comparison with PE within each condition; # p<0.05; ## p<0.01—in comparison with vehicle-treated PE mice; ++ p<0.01; +++ p<0.001—in comparison with vehicle-treated NPE mice.

3.3.2. Facilitation of LI in the CBA strain by clozapine and haloperidol at high doses

The experiment included twelve experimental groups in a 2×6 design with main factors of pre-exposure (0, 40) and drug (vehicle, 3 mg/kg clozapine, 0.4 mg/kg haloperidol, 1.2 mg/kg haloperidol, 600 mg/kg D-serine and 10 mg/kg desipramine). The twelve experimental groups did not differ in their times to complete licks 50–75 before noise onset (all ps>0.05; overall mean A period = 9.7 s). Fig. 4A presents the mean suppression ratios of the pre-exposed and non-pre-exposed mice injected with vehicle (n = 6/6), 3 mg/kg clozapine (n = 6/6), 0.4 mg/kg haloperidol (n = 7/9), 1.2 mg/kg haloperidol (n = 8/8), 600 mg/kg D-serine (n = 10/8) and 10 mg/kg desipramine (n = 6/6). ANOVA yielded significant main effects of pre-exposure [F (1, 74) = 10.54, p<0.001], and drug treatment [F (5, 74) = 10.71, p<0.001] as well as their interaction [F (5, 74) = 9.25, p<0.001]. Post-hoc comparisons revealed LI only in the 1.2 mg/kg haloperidol-treated mice (p<0.001) but not in any other conditions (all ps>0.05).

Next, we assessed whether LI in CBA mice could be restored by the higher doses of clozapine and D-serine. The experiment included six experimental groups in a 2×3 design with main factors of pre-exposure (0, 40) and drug (vehicle, 9 mg/kg clozapine, 1800 mg/kg D-serine). The six experimental groups did not differ in their times to complete licks 50–75 before noise onset (all ps>0.05; overall mean A period = 8.3 s). Fig. 4B shows the mean suppression ratios of the pre-exposed and non-pre-exposed CBA mice injected with vehicle (n = 6/6), 9 mg/kg clozapine (n = 6/7) or 1800 mg/kg D-serine (n = 7/6). ANOVA yielded main effects of pre-exposure [F (1, 32) = 11.6, p = 0.002], and drug treatment [F (2, 32) = 19.6, p = 0.000003] as well as significant pre-exposure × drug interaction [F (2, 32) = 9.8, p = 0.0004]. Post-hoc comparisons confirmed presence of LI in clozapine-treated mice (p<0.001), but not in vehicle- or D-serine-treated mice (both ps>0.05).

4. Discussion

The results of the present study can be summarized as follows: 1. Inbred strains of mice can be differentiated phenotypically according to behavioral and pharmacological effects observed in the LI paradigm. 2. Since the disrupted LI in C3H and CBA strains reflects either lack of the pre-exposure effect or weak learning, respectively, the results revealed that APDs and parametric manipulations can elicit dual effect on attention and associative capacity in mice.

4.1. Strain differences in LI

The first experiment showed that with an experimental protocol yielding LI in the C57BL/6J strain (e.g., Gould and Wehner, 1999; Restivo et al., 2002; Lipina et al., 2005; de Bruin et al., 2006), namely, forty stimulus pre-exposures followed by two conditioning trials, expression of LI was dependent on genetic background. Weaker fear conditioning of the pre-exposed compared to the non-pre-exposed mice, was present in the C57BL/6J and 129/Svev strains, but there was no difference in the level of fear conditioning between the pre-exposed and the non-pre-exposed groups in the other studied inbred strains. These results are consistent with strain differences in LI reported by Gould and Wehner (1999), and provide further evidence that genetic factors contribute to the expression of LI.

Furthermore, as found by Gould and Wehner (1999), strain-dependent LI loss exhibited two distinct patterns. In the C3H and C3A strains, loss of LI was due to strong suppression in the pre-exposed

groups, which were as suppressed as their non-pre-exposed counterparts, the latter exhibiting intact associative learning. This is the "classical" attentional deficit captured by LI loss whereby the pre-exposed animals lose the capacity to ignore the irrelevant stimulus (or in other words, express the excessive switching towards stimulus-reinforcement contingency). Conversely, in the CBA and A/J mice the absence of LI was due to weak suppression in the non-pre-exposed groups, which performed as poorly as their pre-exposed counterparts. Deficient fear conditioning in non-pre-exposed CBA and A/J strains is consistent with previous data (Bolivar et al., 2001; Nie and Abel, 2001; Balogh and Wehner, 2003). Thus, LI loss in these inbred strains was due to an associative deficit in the non-pre-exposed group and hence, the study of LI in these strains will shed a light on our understanding of cognitive mechanisms of LI. Taken together, we sought to probe how parametric and pharmacological manipulations could target attentional and/or associative deficits in C3H and CBA inbred mice and as a result, modulate the expression of LI.

4.2. Parametric modulation of LI in the C3H and CBA strains

We found that different task parameters were needed to counteract attentional and associative-based LI loss. In the C3H strain, disrupted LI was due to the loss of efficacy of pre-exposure, raising the number of pre-exposures from 40 to 60 led to the emergence of LI, whereas raising the number of conditioning trials (from 2 to 4) counteracted effective pre-exposure (Fig. 2A). Furthermore, the effects of the parametric changes were exerted exclusively via the pre-exposed groups in C3H mice, reflecting attentional deficit, which may constitute a biological marker for schizophrenia (Cornblatt and Erlenmeyer-Kimling, 1984; Cornblat et al., 1989; Luck and Gold, 2008) and APDs can normalize attentional processes in humans (Braff and Light, 2004; Luck and Gold, 2008). The same pattern of the disrupted LI is typically observed following amphetamine administration in rodents (Weiner et al., 1988; Killcross and Robbins, 1993; Russig et al., 2002; Lipina and Roder, 2010a), which is reversed by treatment with APDs (Russig et al., 2002; Lipina and Roder, 2010a). Several genetically modified mice related to schizophrenia also expressed LI deficiency due to the attentional deficit (e.g. Miyakawa et al., 2003; Bruno et al., 2007; Clapcote et al., 2007; Lipina et al., 2007; Lipina and Roder, 2010b review). Interestingly, beyond the disrupted LI, C3H mice also exhibit some other schizophrenia-relevant endophenotypes. So, C3H inbred mice showed poor reversal learning and working memory (Bullock et al., 1997; Paylor and Crawley, 1997), coupled with increased level of dopamine (Yoshimoto and Komura, 1987), the endophenotypes associated with schizophrenia in humans (Arguello and Gogos, 2006; Coyle, 2006).

A different pattern of parametric modulation was obtained in the CBA strain (Fig. 2B–C). Manipulations by the amount of pre-exposures (decreasing by 20 PE or raising to 60 PE) had no effect on the expression of LI in CBA mice (conditioned with 2 CS–US trials), suggesting that poor learning/memory in this strain is a main dominant determining weak suppression in both pre-exposed and non-pre-exposed groups. However, increasing the number of conditioning trials (4 CS–US) caused the stronger suppression. This occurred in both the non-pre-exposed and pre-exposed mice given 40 PE, inducing a weak LI effect. However, raising the amount of pre-exposures up to 60 or 80 under strong conditioned environment allowed the emergence of pronounced/stable LI in the CBA strain. Although this outcome may appear paradoxical because learning to ignore a stimulus that predicts no consequence and learning that a stimulus is associated with reinforcement, appear as opposite processes, it is entirely consistent with the position that LI involves the acquisition of two independent associations in pre-exposure (CS-no event) and conditioning (CS-reinforcement) (Weiner, 1990, 2003), and that the acquisition of the inattentional response and the conditioned response is governed by the same processes (Lubow et al., 1981). Viewed from this perspective, CBA mice acquired both associations less efficiently under mild conditioning (2 CS–US) and required more pre-exposures and more conditioning trials to learn effectively, and as a result express LI.

4.3. Pharmacological modulation of LI by APDs and D-serine in the C3H and CBA strains

We have previously shown that the typical action of APDs in the mouse LI model, namely, facilitation of LI expression under parametric conditions that are insufficient for such expression in controls (Moser et al., 2000; Weiner, 2003), is obtained with APDs and NMDAR function enhancers in the C57BL/6J strain (Lipina et al., 2005; Lipina and Roder, 2010a). Here we have extended this line of investigation in several directions. First, we have confirmed the capacity of clozapine and haloperidol to potentiate LI in two additional strains, C3H and CBA. Overall our previous and present findings extend previous demonstrations in rats and humans (Williams et al., 1996, 1997; Millan et al., 1998; Weiner and Feldon, 1987; Weiner et al., 1997; McCartan et al., 2001) indicating that the sensitivity of weak LI to potentiation by APDs is a robust cross species phenomenon. Next, we have extended our previous finding of LI potentiation by D-serine in C57BL/6J mice (Lipina et al., 2005) to the C3H and CBA strains. In addition, we have shown that facilitation of LI in both inbred strains is specifically induced by APDs and D-serine but not by the antidepressant—desipramine, which is in agreement with previous findings showing no effect of imipramine and paroxetine on LI potentiation in rats (Weiner et al, 2003).

Importantly, the pattern of drug action differed among the strains depending on whether LI loss was due attentional or associative mechanisms. LI enhancement observed with all the three drugs in the C3H strain was mainly due to drug-induced reduction of suppression in the pre-exposed groups, confirming LI enhancement typically seen after APDs treatment in rats (e.g. Moser et al., 2000; Weiner, 2003) and C57BL/6J mice (Lipina et al., 2005; Lipina and Roder, 2010a).

A different mode of LI enhancement by APDs operated in the CBA strain. In this strain, LI enhancement by the effective doses of haloperidol and clozapine dominantly involved increased suppression in the non-pre-exposed groups, with mild effect also on the pre-exposed group. This effect of enhanced conditioning in APDs-treated non-pre-exposed animals is by itself novel; presumably, it could not be detected previously because APDs-induced LI enhancement is typically tested against *efficient* conditioning in the non-pre-exposed groups (such as the case in the C3H and C57BL/6J strains). However, it is important to emphasize that the enhancement of LI in CBA mice by APDs given at high doses was not due to improved conditioning per se; rather, it was due to the fact that these drugs (except D-serine) increased suppression of the non-pre-exposed groups *without* concomitantly increasing suppression in the pre-exposed groups. In fact, haloperidol dramatically *reduced* suppression in the pre-exposed group. Notable, that haloperidol given at high dose induced bidirectional mode of action on both inbred lines (decreasing suppression in pre-exposed and increasing suppression in non-pre-exposed animals). The importance of this distinct action in the pre-exposed and non-pre-exposed conditions is underscored that the ineffective drug treatments—D-serine and the lower doses of clozapine and haloperidol—drugs had the same effect of increasing suppression in the non-pre-exposed groups, but they concomitantly increased suppression in the pre-exposed groups, hence, no LI potentiation was manifested with these drugs/doses.

Thus, APDs particularly given at high doses, improved the performance of both the pre-exposed and non-pre-exposed CBA animals, restoring their capacity to ignore the stimulus in the pre-exposed and to associate the stimulus with reinforcement in the non-pre-exposed condition. APDs are not conventionally considered cognitive enhancers. However, there is some evidence that APDs, including haloperidol, improve learning in rats (Saha et al., 1991; Inoue et al, 1996; Cassaday et al., 2005; Nowakowska et al., 2006). Moreover,

improvement in cognition has been observed with APDs in several clinical studies (Rollnik et al., 2002; Mishara and Goldberg, 2004; Keefe et al., 2004, 2007; Harvey et al., 2005; Woodward et al., 2007; Mizrahi et al., 2007). Both APDs increase the level of dopamine (Moghaddam and Bunney, 1990), glutamate (Millan, 2005) and acetylcholine (Li et al., 2005) in the prefrontal cortex, which may explain their ability to improve cognition since an optimum level of these neurotransmitters in the prefrontal cortex is critical for cognitive functioning. Moreover, haloperidol and clozapine increase intracellular cAMP accumulation (Maxwell et al., 2004) which is associated with improved learning (Zhang et al., 2005), and correction of LI (Davis and Gould, 2005; Lipina and Roder, 2010a). The failure of D-serine to enhance LI in the CBA strain was surprising because glycineric agonists have been documented to enhance performance in a range of learning tasks (Ledgerwood et al., 2005; Duffy et al., 2008) and because here D-serine did normalize the performance in the pre-exposed condition in C3H strain and as we previously reported in C57BL/6J mice (Lipina et al., 2005). A thorough dose–response investigation is warranted to determine whether LI in the CBA strain would respond to D-serine. Very little is known about neurochemical peculiarities in CBA mice among other inbred strains, but e.g. lower density of D_2 receptors or decreased activity of tyrosine hydroxilase have been reported for this line as compared with C57BL/6J mice (Baker et al., 1980; Severson et al., 1981; Yoshimoto and Komura, 1987; Skrinskaya et al., 1992). Hence, systematic neurochemical analysis is needed, as it will provide insights into biochemical mechanisms of APDs and D-serine action in this inbred strain.

A comparison between effects, induced by the task parameters and pharmacological interventions, reveals some interesting similarities. Both types of manipulations potentiated specifically the stimulus pre-exposure effect in C3H strain, whereas enhanced both associative learning and the capacity to ignore irrelevant stimulus in CBA mice. So, ineffective pharmacological and parametric manipulations increased namely, suppression in both the pre-exposed and non-pre-exposed groups in CBA mice, so that the LI effect did not emerge. Whereas, haloperidol given at the high dose similarly to the effective parametric manipulations (80 PE and 4 CS–US) proportionally increased suppression in the non-pre-exposed group and improved the ability of pre-exposed CBA mice to ignore irrelevant CS that leads to the expression of LI. It remains to be determined whether identical overt effects on LI performance induced by APDs and parametric changes are elicited by the same or distinct neurobiological mechanisms. However, the correspondence in their behavioral influences suggests that APDs may modulate the functioning of neural systems that are responsible for strain specific LI disruption, and may change the manner in which these systems process stimulus salience and associative information. This, in turn may shed a light on how APDs modulate aberrant salience experience and associative deficit in schizophrenia (Kapur, 2003; Mizrahi et al., 2007).

While a systematic analysis of the effects of established and novel cognitive enhancers is required to fully validate the utility of genetically diverse mouse LI as a predictor of pro-cognitive effects, the use of mouse inbred strains with disrupted LI offers a non-pharmacological approach for screening cognitive enhancers which may be particularly promising for identifying treatments with new mechanisms of action. Moreover, naturally occurring differences in the efficacy of attentional and associative processes underlying LI in genetic mouse strains are powerful tools for revealing the molecular-genetic mechanisms of aberrant salience and associative processing and their pharmacological modulation. Thus, LI may offer a translational strategy that allows reliable prediction of cognitive benefit in schizophrenia.

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Appendix A. Supplementary data

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