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Pro-Cognitive and Antipsychotic Efficacy of the α7 Nicotinic Partial Agonist SSR180711 in Pharmacological and Neurodevelopmental Latent Inhibition Models of Schizophrenia

Segev Barak[1], Michal Arad[1], Amaya De Levie[1], Mark D Black[2], Guy Griebel[3] and Ina Weiner*,[1]

[1]Department of Psychology, Tel Aviv University, Tel Aviv, Israel; [2]Sanofi-Aventis, CNS Department, Bridgewater, NJ, USA; [3]Sanofi-Aventis, CNS Department, Bagneux, France

Schizophrenia symptoms can be segregated into positive, negative and cognitive, which exhibit differential sensitivity to drug treatments. Accumulating evidence points to efficacy of α7 nicotinic receptor (nAChR) agonists for cognitive deficits in schizophrenia but their activity against positive symptoms is thought to be minimal. The present study examined potential pro-cognitive and antipsychotic activity of the novel selective α7 nAChR partial agonist SSR180711 using the latent inhibition (LI) model. LI is the reduced efficacy of a previously non-reinforced stimulus to gain behavioral control when paired with reinforcement, compared with a novel stimulus. Here, no-drug controls displayed LI if non-reinforced pre-exposure to a tone was followed by weak but not strong conditioning (2 vs 5 tone-shock pairings). MK801 (0.05 mg/kg, i.p.) -treated rats as well as rats neonatally treated with nitric oxide synthase inhibitor L-NoArg (10 mg/kg, s.c.) on postnatal days 4–5, persisted in displaying LI with strong conditioning, whereas amphetamine (1 mg/kg) -treated rats failed to show LI with weak conditioning. SSR180711 (0.3, 1, 3 mg/kg, i.p.) was able to alleviate abnormally persistent LI produced by acute MK801 and neonatal L-NoArg; these models are believed to model cognitive aspects of schizophrenia and activity here was consistent with previous findings with α7-nAChR agonists. In addition, unexpectedly, SSR180711 (1, 3 mg/kg, i.p.) potentiated LI with strong conditioning in no-drug controls and reversed amphetamine-induced LI disruption, two effects considered predictive of activity against positive symptoms of schizophrenia. These findings suggest that SSR180711 may be beneficial not only for the treatment of cognitive symptoms in schizophrenia, as reported multiple times previously, but also positive symptoms.

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INTRODUCTION

Schizophrenia can be segregated into positive, negative and cognitive symptoms. Antipsychotic drugs (APDs), although effective in ameliorating positive symptoms, have limited efficacy in improving negative/cognitive symptoms (Buchanan et al, 2007; Miyamoto et al, 2005). In recent years, therapeutic strategies have focused on enhancing the function of the cholinergic system, because of its central role in cognition and evidence of cholinergic dysfunction in schizophrenia (Friedman, 2004; Raedler et al, 2007; Sarter et al, 2005).

*Correspondence: Professor I Weiner, Department of Psychology, Tel-Aviv University, Ramat-Aviv 39040, Tel-Aviv 69978, Israel, Tel: +972 3 6408993, Fax: +972 3 6409547, E-mail: weiner@post.tau.ac.il

Among cholinergic function enhancers, α7 nicotinic acetylcholine (ACh) receptors (nAChRs) agonists have emerged as particularly promising (Martin et al, 2004). A growing body of data demonstrates that α7-nAChR agonists facilitate cognitive function in a variety of learning and memory tasks in rodents and humans (eg Levin et al, 1999; Olincy and Stevens, 2007). Of particular relevance to attentional and sensory gating deficits in schizophrenia (Adler et al, 1998; Heinrichs, 2005; Lubow, 2005), α7-nAChR agonists alleviate both types of deficits in humans and animals (Hajos et al, 2005; Olincy et al, 2006; Timmermann et al, 2007; Wishka et al, 2006). A role for the α7-nAChR in these processes is supported by findings that α7-nAChR knock-out mice show attentional and gating impairments (Adams et al, 2008; Hoyle et al, 2006; Young et al, 2004, 2007). Finally, there is a diminished expression of α7-nAChR in the hippocampus and frontal cortex in schizophrenia (Freedman et al, 1995; Guan et al, 1999). These findings have converged to identify α7-nAChR

agonists as lead candidates for improving cognition in schizophrenia (MATRICS project (http://www.matrics.ucla.edu)). To date, very little if any activity would be predicted for these agents on positive symptoms of schizophrenia.

SSR180711 (4-bromophenyl-1,4-diazabicyclo[3.2.2]nonane-4-carboxylate-hydrochloride) is a novel α7-nAChR partial agonist (Ki of 22 4 and 14 1 nM for rat and human receptors, respectively), with no significant binding and/or functional activity at other human nAChRs. At low doses boosting α7-nAChR signaling without causing desensitization of the receptor, SSR180711 was shown to produce several electrophysiological, neurochemical and behavioral effects predictive of activity against cognitive impairments of schizophrenia, (Biton et al, 2007; Hashimoto et al, 2005; Pichat et al, 2007). Here, pro-cognitive and antipsychotic activities of SSR180711 were evaluated in the latent inhibition (LI) model of schizophrenia.

Pro-cognitive effects of SSR180711 were evaluated in acute pharmacological and neurodevelopmental LI models. The former used acute administration of the NMDA receptor antagonist MK801. As NMDA receptor antagonists induce a wide spectrum of schizophrenia-like symptoms in healthy humans including cognitive deficits (eg impairments in attention, working and declarative memory and mental flexibility; Krystal et al, 1994, 2003), NMDA antagonist-induced behavioral deficits in animals (eg impaired attentional gating, novel object recognition, perseveration in reversal learning) are considered to model cognitive deficits in schizophrenia (Geyer et al, 2001; Javitt and Zukin, 1991; Krystal et al, 2003; Moghaddam and Jackson, 2003).

LI is the retarded conditioning to a stimulus consequent upon its repeated non-reinforced pre-exposure. Because non-reinforced pre-exposure retards any associative learning in which the pre-exposed stimulus is subsequently engaged, the common interpretation is that such pre-exposure reduces the salience of, or attention to, the pre-exposed stimulus (Rescorla, 2002), which under specific conditions can reduce the efficacy with which the stimulus acquires behavioral control when paired with reinforcement (Bouton, 1993; Gray et al, 1991; Lubow, 2005; Weiner, 1990, 2003). In this manner, LI allows the organism to ignore irrelevant stimuli and to selectively attend to important/relevant stimuli. As deficits in selective attention reflected among others in an inability to discriminate between relevant and irrelevant stimuli are a core cognitive dysfunction of schizophrenia (Anscombe, 1987; Green et al, 1992; Hajos, 2006; Kapur, 2003; Luck and Gold, 2008; Wiedl et al, 2004), LI abnormalities in rodents are considered to model selective attention deficits associated with schizophrenia (Kilts, 2001; Lipska and Weinberger, 2000; Lubow, 2005; Powell and Miyakawa, 2006; Smith et al, 2007; Weiner, 1990, 2003).

MK801 produces an abnormally persistent LI that becomes manifest under conditions preventing the expression of LI in no-drug controls. In other words, MK801-treated rats perseverate in ignoring the pre-exposed stimulus under conditions in which normal animals shift to treating it as relevant, and this models attentional perseveration, or impaired set shifting, associated with the negative symptoms of schizophrenia (Gaisler-Salomon and

Weiner, 2003). MK801-induced attentional perseveration is reversed by atypical APDs and glycinergic NMDA-enhancers but not typical APDs (Black et al, 2008; Gaisler-Salomon et al, 2008; Gaisler-Salomon and Weiner, 2003; Lipina et al, 2005), consistent with the differential efficacy of these treatments for negative/cognitive symptoms (Harvey et al, 2005; Heresco-Levy et al, 2005). As SSR180711 was shown to reverse NMDA blockade-induced cognitive deficits (impaired novelty discrimination and object recognition as well as memory deficits in the Morris water maze; Hashimoto et al, 2008; Pichat et al, 2007) here we expected that it would reverse MK801-induced persistent LI.

In our neurodevelopmental model, inhibition of nitric oxide (NO) production was produced during very early postnatal period (Black et al, 1999, 2002), presumably modeling disrupted NO function in schizophrenia (Bernstein et al, 2005). This developmental interference with NO function was found to produce several schizophrenia-like abnormalities in adulthood (Black et al, 1999, 2002), including abnormally persistent LI which was reversed by atypical but not typical APDs and NMDA-enhancers (Black et al, 2008; De Levie A et al, unpublished observations). Here we tested whether SSR180711 would reverse neurodevelopmentally induced persistent LI.

To date, it is unknown whether α7 agonists possess activity against positive symptoms, and this was the last question we investigated in the LI model using the psychosis-inducing dopamine-releaser amphetamine. Contrary to MK801, amphetamine disrupts LI in rodents and this is paralleled by LI loss in amphetamine-treated healthy humans and acutely psychotic schizophrenia patients (Rascle et al, 2001; Thornton et al, 1996; Weiner et al, 1984, 1988). Amphetamine-induced LI disruption in rodents is reversed by both typical and atypical APDs, consistent with their efficacy against positive symptoms (Moser et al, 2000; Weiner, 2003). In addition, both classes of APDs potentiate LI in naive animals under conditions that do not yield robust LI in no-drug controls. The latter effect is obtained also in humans (McCartan et al, 2001; Williams et al, 1997), and is the most widely used index of antipsychotic activity in the LI model (Moser et al, 2000; Weiner, 2003). To date, it is unknown whether α7 agonists possess activity against positive symptoms. Here, we evaluated whether SSR180711 would be active in these two LI models predictive of activity against positive symptoms.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 350–510 g were used. Rats were housed four per cage under reversed cycle lighting (lights on: 0700–1900) with ad lib access to food and water except for the duration of the LI experiments (see apparatus and procedure). All experimental protocols conformed to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University, Israel, and to the guidelines of the NIH (animal welfare assurance number A5010-01, expires on 30 September 2011). All efforts were made to minimize the number of animals used and their suffering.

Neonatal Treatment

Wistar rats (Tel-Aviv University Medical School) were mated at an age of 3 months. At birth, litters were culled to 10, composed of five male and five female rats whenever possible. The day of birth was defined as postnatal day 0. On postnatal days 3, 4, and 5 rat pups were given a subcutaneous injection in a volume of 1 ml/kg of either 10 mg/kg N^{ω}-nitro-L-arginine (L-NoArg, Sigma, Israel), a competitive inhibitor of nitric oxide synthase (NOS) with selectivity for the neuronal and endothelial isoforms of the enzyme (Furfine et al, 1993), or vehicle. L-NoArg was dissolved in 1N HCL, diluted with 10 mM phosphate-buffered saline and titrated with 2 M Tris 7.5 pH buffer to a final pH of 5.5. On day 21, the pups were weaned and housed four to a cage by sex and litter, and maintained undisturbed till 3 months of age. At adulthood, male rats that were treated neonatally with L-NoArg or vehicle were assigned to the experimental groups, with the provision that in each experimental group there was no more than one rat from the same litter. The neonatal treatment did not affect viability or weight of rats on postnatal days 1, 3, 10, or in adulthood.

Apparatus and Procedure

LI was measured in a thirst-motivated conditioned emotional response procedure. Rats were tested in rodent test chambers with a retractable bottle (Campden Instruments, Loughborough, UK), each enclosed in a ventilated sound-attenuating chest. When the bottle was not present, the hole was covered with a metal lid. The pre-exposed to-be-conditioned stimulus was a 10 s, 80 dB, and 2.8 kHz tone produced by a Sonalert module (model SC 628). Shock was supplied through the floor by a Campden Instruments shock generator and shock scrambler set at 0.5 mA intensity and 1 s duration. Licks were detected by a Campden Instruments drinkometer. Equipment programming and data recording were computer controlled.

Ten days prior to the beginning of the LI procedure, rats were put on a 23 h water restriction schedule and handled for about 2 min daily for 5 days. On the next 5 days, rats were trained to drink in the experimental chamber, 20 min on the first day, and 15 min on the remaining 4 days. Water in the test apparatus was given in addition to the daily ration of 1 h given in the home cages. The LI procedure was conducted on days 11–14 and consisted of four stages given 24 h apart.

Pre-exposure. With the bottle removed, the pre-exposed (PE) rats received 40 tone presentations with an inter-stimulus interval of 40 s. The non-pre-exposed (NPE) rats were confined to the chamber for an identical period of time without receiving the tone.

Conditioning. With the bottle removed, rats received two (weak conditioning, experiment 3) or five (strong conditioning, experiments 1 and 2) tone-shock pairings given 5 min apart. Shock immediately followed tone termination. Strong conditioning was used in experiments (1 and 2) using MK801 and neonatal NOS inhibition, because this level of conditioning prevents LI in non-treated controls and thus allows the demonstration of treatment-induced abnormally persistent LI. Conversely, weak conditioning was used in the experiment (3) using amphetamine, because this level of conditioning yields LI in non-treated controls and thus allows the demonstration of treatment-induced LI disruption.

Rebaseline. Rats were given a 15 min drinking session as an initial training. Data of rats that failed to complete 600 licks were dropped from the analysis.

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. The following times were recorded: Time to first lick, time to complete licks 1–50, time to complete licks 51–75 (before tone onset) and time to complete licks 76–100 (after tone onset). Times to complete licks 76–100 were submitted to logarithmic transformation to allow parametric ANOVA. Longer log times indicate stronger suppression of drinking. LI is defined as significantly shorter log times to complete licks 76–100 of the PE compared NPE rats.

Drugs

All drugs were administered intraperitoneally. MK801 (dizocilpine; Merck Research Laboratories, USA) was diluted in saline and administered at a dose of 0.05 mg/kg (Gaisler-Salomon and Weiner, 2003), in a volume of 1 ml/kg 30 min before conditioning. D-amphetamine (Sigma; Switzerland) was diluted in saline and administered at a dose of 1 mg/kg, in a volume of 1 ml/kg 30 min prior to pre-exposure and conditioning. SSR180711 (Sanofi-Aventis, France) was dissolved in saline and administered at doses of 0.3, 1 or 3 mg/kg 30 min in a volume of 3 ml/kg prior to pre-exposure and conditioning stages. No-drug controls received the corresponding vehicle.

Statistical Analysis

Times to complete licks 50–75 and mean log times to complete licks 76–100 were analyzed using three-way ANOVAs with main factors of pre-exposure, treatment and pre-treatment. LSD *post hoc* comparisons were used to assess the difference between the PE and NPE groups within each treatment condition.

Experimental Design

Experiment 1 tested the effects of SSR180711 on MK801-induced persistent LI. The experiment included sixteen experimental groups in a $2 \times 2 \times 4$ design with main factors of pre-exposure (PE, NPE), treatment (vehicle, MK801), and pre-treatment (0, 0.3, 1, 3 mg/kg SSR180711). Experiment 2 tested the effects of SSR180711 on neonatal NOS inhibition-induced persistent LI. The experiment included 16 experimental groups in a $2 \times 2 \times 4$ design with main factors of pre-exposure (PE, NPE), neonatal treatment (vehicle, L-NoArg), and adult treatment (0, 0.3, 1, 3 mg/kg SSR180711). As both of these experiments used strong conditioning, the effects of SSR180711 on the non-treated controls allowed the demonstration of SSR180711-induced
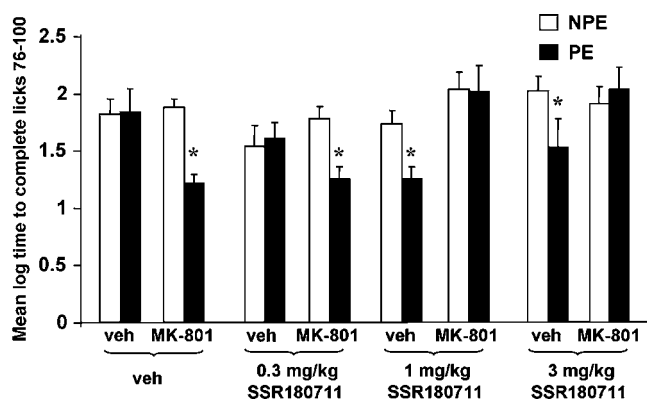
LI potentiation. Consequently, no separate experiments were conducted to measure this index of antipsychotic activity of SSR180711. Experiment 3 tested the effects of SSR180711 on amphetamine-induced disrupted LI. Only the two higher doses of SSR180711 were tested here because only these doses potentiated LI in non-treated rats in experiments 1 and 2. The experiment included 12 experimental groups in a $2 \times 2 \times 3$ design with main factors of pre-exposure (PE, NPE), treatment (vehicle, amphetamine), and pre-treatment (0, 1, 3 mg/kg SSR18071).

RESULTS

Experiment 1: Effects of SSR180711 on MK801-Induced Persistent LI and LI with Strong Conditioning

The experiment included 113 rats (n per group = 6–8). Data of one rat were dropped from the analysis. The 16 experimental groups did not differ in their times to complete licks 51–75 before tone onset (all p's > 0.05; overall mean A period = 8.23 s). Figure 1 presents the mean log times to complete licks 76–100 (after tone onset) of the pre-exposed and non-pre-exposed rats in the different experimental conditions. As expected, vehicle-injected rats did not show LI, whereas MK801-treated rats showed LI inspite of extended conditioning. MK801-induced abnormally persistent LI was reversed by 1 and 3 mg/kg SSR180711, but not by 0.3 mg/kg SSR180711. In addition, the two higher doses of SSR180711 potentiated LI in vehicle-treated rats.

Three-way ANOVA with main factors of pre-exposure (0, 40), treatment (vehicle, MK801) and pre-treatment (0, 0.3, 1, 3 mg/kg SSR180711), yielded significant main effects of pre-exposure ($F_{(1,96)} = 14.41$, $p < 0.005$) and pre-treatment ($F_{(1,96)} = 3.24$, $p < 0.03$), as well as significant interactions of treatment × pre-treatment ($F_{(3,96)} = 5.01$, $p < 0.003$), and pre-exposure × treatment × pre-treatment ($F_{(3,96)} = 4.92$,

$p < 0.005$). *Post hoc* comparisons revealed a significant difference between the pre-exposed and non-pre-exposed groups in the MK801-vehicle condition ($p < 0.001$), the MK801 + 0.3 mg/kg SSR180711, the vehicle + 1 mg/kg SSR180711, and the vehicle + 3 mg/kg SSR180711 conditions (p's < 0.05), but not in all the other conditions.

Experiment 2: Effects of SSR180711 on Neonatal L-NoArg-Induced Persistent LI and LI with Strong Conditioning

The experiment included 143 rats (n per group = 8–9). The 16 experimental groups did not differ in their times to complete licks 51–75 before tone onset (all p's > 0.05; overall mean A period = 9.11 s). Figure 2 presents the means and s.e. of the log times to complete licks 76–100 (after tone onset) of the pre-exposed and non-pre-exposed rats in the different experimental conditions. As can be seen, LI was absent in neonatally vehicle-treated rats whereas neonatally treated L-NoArg rats showed LI. The three doses of SSR180711 successfully reversed the abnormally persistent LI in the neonatal L-NoArg-rats, so that these rats did not show LI like the neonatal vehicle-treated rats. In addition, 1 and 3 mg/kg but not 0.3 mg/kg potentiated LI when administered to neonatally vehicle-treated rats in a manner consistent with that seen in vehicle-treated rats in experiment 1. Three-way ANOVA with main factors of pre-exposure (PE, NPE), neonatal treatment (vehicle, L-NoArg) and adult treatment (0, 0.3, 1, 3 mg/kg SSR180711), yielded significant main effects of pre-exposure [$F(1, 127) = 26.64$, $p < 0.0001$] and neonatal treatment [$F(1, 127) = 5.17$, $p < 0.05$], as well as significant interactions of neonatal treatment × adult treatment [$F(3, 127) = 2.98$, $p < 0.005$], and pre-exposure × neonatal treatment × adult treatment [$F(3, 127) = 3.361$, $p < 0.05$]. *Post hoc* comparisons revealed a significant difference between the pre-exposed and non-pre-exposed groups (LI) in the neonatal L-NoArg-rats
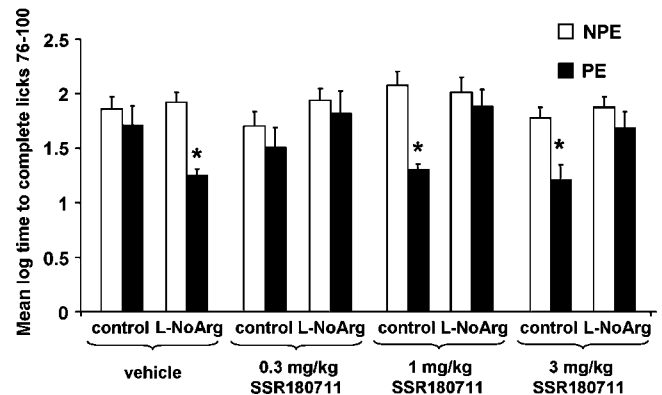

Figure 1 Effects of SSR180711 on MK801-induced persistent LI and LI with strong conditioning. Means and SE of the log times to complete licks 76–100 (after tone onset) of the pre-exposed (PE) and non-pre-exposed (NPE) rats treated with MK801 or vehicle (veh), and pre-treated with SSR180711 at doses of 0.3, 1 or 3 mg/kg, or vehicle. Forty pre-exposures and five conditioning trials were used. SSR180711 was administered i.p. prior to the pre-exposure and conditioning stages; MK801 was administered i.p. prior to the conditioning stage. Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI.
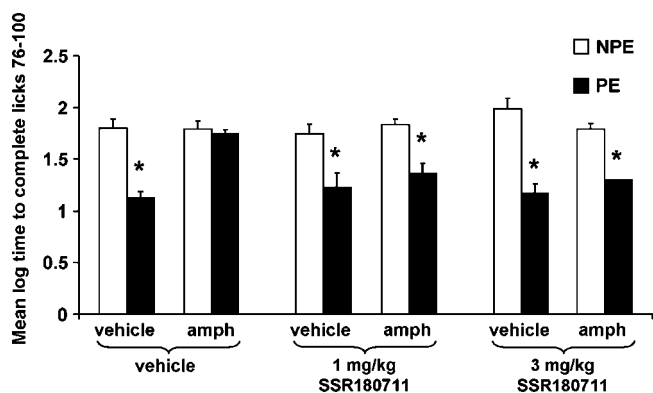

Figure 2 Effects of SSR180711 on neonatal L-NoArg-induced persistent LI and LI with strong conditioning. Means and SE of the log times to complete licks 76–100 (after tone onset) of the pre-exposed (PE) and non-pre-exposed (NPE) rats neonatally treated with L-NoArg or vehicle (control), injected with SSR180711 at doses of 0.3, 1 or 3 mg/kg, or vehicle. Forty pre-exposures and five conditioning trials were used. SSR180711 was administered i.p. in the pre-exposure and conditioning stages. Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI.

Figure 3 Effects of SSR180711 on amphetamine-induced LI disruption. Means and SE of the log times to complete licks 76–100 (after tone onset) of the pre-exposed (PE) and non-pre-exposed (NPE) rats treated with amphetamine (amph) or vehicle, and pre-treated with SSR180711 at doses of 1 or 3 mg/kg, or vehicle. Forty pre-exposures and two conditioning trials were used. Both SSR180711 and amphetamine were administered i.p. prior to the pre-exposure and conditioning stages. Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI.

injected with vehicle ($p < 0.001$), and in the neonatal vehicle rats injected with 1 mg/kg ($p < 0.0001$) and 3 mg/kg ($p < 0.005$), but not in all the other conditions.

Experiment 3: Effects of SSR180711 on Amphetamine-Induced LI Disruption

The experiment included 113 rats (n per group = 9–10). Data of one rat were dropped from the analysis. The 12 experimental groups did not differ in their times to complete licks 51–75 before tone onset (all p's > 0.05; overall mean A period = 8.33 s). Figure 3 presents the mean log times to complete licks 76–100 (after tone onset) of pre-exposed and non-pre-exposed rats in the different experimental conditions. As expected, vehicle-injected rats show LI, whereas amphetamine disrupted LI. Both doses of SSR18711 reversed amphetamine-induced disruption of LI. Three-way ANOVA with main factors of pre-exposure (PE, NPE), treatment (vehicle, amphetamine) and pre-treatment (0, 1, 3 mg/kg SSR180711), yielded significant main effects of pre-exposure ($F_{(1, 100)} = 105.78$, $p < 0.0001$) and treatment ($F_{(1, 100)} = 6.86$, $p < 0.015$), as well as significant interactions of treatment × pre-exposure ($F_{(2, 100)} = 10.96$, $p < 0.002$), treatment × pre-treatment ($F_{(2, 100)} = 4.08$, $p < 0.02$) and pre-exposure × treatment × pre-treatment ($F_{(2, 100)} = 3.10$, $p < 0.05$). *Post hoc* comparisons revealed a significant difference between the pre-exposed and non-pre-exposed groups in the vehicle–vehicle, vehicle-1 mg/kg SSR180711, vehicle-3 mg/kg SSR180711, amphetamine-1 mg/kg SSR180711 and in the amphetamine-3 mg/kg SSR180711 conditions (p's < 0.01), but not in the vehicle–amphetamine conditions.

DISCUSSION

The aim of the present experiments was to profile the novel α7 partial agonist SSR180711 in non-pharmacological, acute pharmacological and neurodevelopmental models of LI. We show that SSR180711 was able to alleviate abnormally persistent LI produced by acute MK801 and neonatal NOS blockade; these models are believed to model cognitive aspects of schizophrenia and the activity here was consistent with previous findings with α7-nAChR agonists (Arendash *et al*, 1995; Hashimoto *et al*, 2008; Levin *et al*, 1999; Meyer *et al*, 1998; Olincy and Stevens, 2007; Pichat *et al*, 2007; Timmermann *et al*, 2007; Wishka *et al*, 2006). Rather unexpectedly SSR180711 potentiated LI in normal rats and reversed amphetamine-induced LI disruption, two models considered predictive of activity against positive symptoms of schizophrenia (Gray *et al*, 1991; Kilts, 2001; Lipska, 2004; Lipska and Weinberger, 2000; Moser *et al*, 2000; Powell and Miyakawa, 2006; Smith *et al*, 2007; Weiner, 1990, 2003) . These findings suggest that SSR180711 may be beneficial not only for the treatment of cognitive symptoms in schizophrenia, as reported previously, but also positive symptoms.

Reversal of Abnormally Persistent LI: Putative Efficacy for Negative/Cognitive Symptoms

As repeatedly shown by us in the present LI procedure (eg Barak and Weiner, 2008; Gaisler-Salomon and Weiner, 2003), normal rats pre-exposed to 40 tones showed LI if subsequently trained with 2 tone-shock pairings (weak conditioning), but increasing the number of pairings to five counteracted the effect of pre-exposure so that pre-exposed rats conditioned as efficiently as their non-pre-exposed counterparts. In contrast, under the latter conditions, MK801 administration led to the emergence of LI. Thus, although pre-exposed rats treated with vehicle switched in the conditioning stage to respond according to the stimulus-reinforcement contingency, MK-801-treated pre-exposed rats perseverated in responding according to the stimulus-no event contingency acquired in pre-exposure in spite of the repeated pairings of the stimulus with reinforcement. This outcome is consistent with findings showing that NMDA receptor blockade induces behavioral and cognitive inflexibility, and specifically, impairs the capacity to flexibly alter responding based upon changed relationships between stimuli and outcomes (Carlsson and Carlsson, 1990; Jentsch and Taylor, 2001; Moghaddam *et al*, 1997; Svensson, 2000; van der Meulen *et al*, 2003). In this study, MK801-induced cognitive inflexibility was ameliorated by SSR180711.

Reversal of MK801-induced persistent LI by SSR180711 is consistent with previous findings that this agent reversed cognitive deficits induced by the administration of the NMDA antagonists MK801 and phencyclidine (PCP), in mice and rats (Hashimoto *et al*, 2008; Pichat *et al*, 2007). It is also in line with the efficacy of other nicotinic agonists in antagonizing the behavioral effects of NMDA blockade (Mastropaolo *et al*, 2004; Rezvani and Levin, 2003; Tizabi *et al*, 1998), although nicotine failed to reverse PCP-induced deficit in prepulse inhibition (PPI), a model of impaired sensorimotor gating in schizophrenia (Suemaru *et al*, 2004), and augmented MK801-induced impairment of PPI (Levin *et al*, 2005).

The activity of SSR180711 in the hypoglutamatergic models is most likely a consequence of its capacity to increase, through activation of presynaptic α7-nAChRs present on glutamatergic neurons, glutamate levels in areas

such as the prefrontal cortex (PFC), the hippocampus the amygdala (Biton *et al*, 2007; Pichat *et al*, 2007). The convergence of glutamatergic inputs from these regions and their modulation by dopamine at the nucleus accumbens (NAC) level are known to play a key role in the ability to switch between behavioral repertoires in response to changing environmental contingencies (Floresco *et al*, 2001; Howland *et al*, 2002; Kelley *et al*, 2003), and abnormally persistent LI was attributed to reduced glutamatergic inputs from these regions to the NAC (Weiner, 2003). Thus, by virtue of increasing prefrontal and limbic glutamate, SSR180711 would be able to restore flexible responding in LI. Another action of SSR180711 that could mediate or contribute to the efficacy of this compound in the MK801 model is enhancement of the extracellular ACh levels in the hippocampus and PFC (Biton *et al*, 2007), because such enhanced levels would activate also M1 receptors, which have been suggested to potentiate NMDA activity (Marino *et al*, 1998; Sur *et al*, 2003).

Although the pharmacological MK801 LI model may mimic the acute neurotransmitter dysfunction at the NMDA receptor believed to play a role in schizophrenia symptoms, neurodevelopmental models of schizophrenia can shed light on long-term, neurodevelopmental changes in the brain and on the capacity of the tested drug to show effectiveness under such changes. Indeed, these models are believed to mimic more closely the widespread disruption of cortico-mesolimbic circuitries implicated in the pathophysiology of schizophrenia (Lipska and Weinberger, 2000). Here, we showed that SSR180711 reversed persistent LI induced by neonatal inhibition of NOS, implying that α7-nAChR agonism is a potentially effective treatment for widespread aspects of schizophrenia pathophysiology. As the neurodevelopmental model requires no psychomimetic challenge, our demonstration that SSR180711 is active in such a model suggests that the α7-nAChR mechanism/s may be effective at the neuronal circuits level underlying LI, rather than merely interfering with the psychomimetic drug activity. One could speculate that the limbic regions responsible for behavioral flexibility were underactive in animals neonatally treated with L-NoArg; and SSR180711 thus was able to raise the developmentally induced hypoglutamatergic state. Previously SSR180711 was shown to reverse selective attention deficit induced by neonatal PCP treatment, as measured in social novelty discrimination task (Pichat *et al*, 2007). Also in this task, neonatal treatment led to attentional perseveration and SSR180711 restored attentional flexibility. Taken together, the capacity of SSR180711 to reverse pharmacologically and neurodevelopmentally induced attentional perseveration provides a solid case for the efficacy of this drug for treating negative/cognitive symptoms of schizophrenia.

Reversal of Disrupted LI: Putative Efficacy for Positive Symptoms

In experiments 1 and 2, in addition to reversing persistent LI, SSR180711 administered on its own potentiated LI under conditions of strong conditioning that disrupted LI in normal rats. This finding is in line with previous demonstrations that nicotine and other nicotinic agonists potentiated LI under conditions that disrupted LI in control

animals (Gould *et al*, 2001; Rochford *et al*, 1996), and suggests that this effect is mediated by α7-nAChR. Given that LI potentiation is the *sine qua non* of antipsychotic activity in the LI model, obtained with a wide variety of typical and atypical APDs differing in their *in vivo* and *in vitro* pharmacology (Moser *et al*, 2000; Weiner, 2003), our finding indicated that SSR180711 may possess antipsychotic properties. This was further supported by our finding that SSR180711 reversed amphetamine-induced LI disruption. Taken together, the efficacy of SSR180711 to alleviate non-pharmacologically and pharmacologically induced LI disruption is thus indicative of its therapeutic capacity for positive symptoms in schizophrenia. This contrasts with findings on SSR180711 in other models predictive of activity against positive symptoms. Thus, we have recently found that spontaneous locomotor hyperactivity in a transgenic mouse line NMDA Nr1$^{neo-/-}$ was reversed by clozapine and the novel Glyt1 inhibitor SSR103800 but not by SSR180711 (Boulay *et al*, 2007). In addition, SSR180711 had no effect on amphetamine- or MK801-induced locomotor hyperactivity in mice, and failed to increase spontaneously low PPI levels DBA/2 mice and to reverse apomorphine-induced PPI disruption in rats (Griebel G, unpublished observations), effects consistently produced by APDs. Other α7 agonists were also found ineffective in enhancing spontaneously low PPI levels in mice (Olivier *et al*, 2001; Schreiber *et al*, 2002). Overall, with the exception of several studies showing that α7-nAChR agonists reverse amphetamine-induced deficit in physiological auditory gating measured by auditory-evoked potentials in the hippocampus of anesthesized rats (Hajos *et al*, 2005; Hurst *et al*, 2005), extant data on α7 agonists in behavioral models predictive of activity against positive symptoms are scarce, and provide no evidence for such activity. The present results imply that additional efforts should be directed at screening α7 agonists in positive symptom models. Alternatively, they raise the possibility that the disrupted LI model is more sensitive than other models to some aspects of α7 agonism relevant to positive symptoms and their treatment.

Disruption of LI by amphetamine as well as by parametric manipulations is mediated by increased DA release in the NAC, and that is where APDs, by virtue of their DA antagonism, act to restore LI in amphetamine-treated rats and potentiate LI in normal rats (Gray *et al*, 1997; Weiner, 2003; Weiner and Feldon, 1997; Young *et al*, 1993). Although little is known on the effects of SSR180711 on mesolimbic DA dynamics (Hansen *et al*, 2007), it seems unlikely that this agent would directly block NAC DA increase, given the well known action of nicotine to increase DA release in the NAC (Wonnacott *et al*, 2005), an effect blocked by α7 antagonists (Schilstrom *et al*, 1998, 2000). The capacity of SSR180711 to increase glutamate neurotransmission in the hippocampus as well as increase dopamine levels in the PFC (Biton *et al*, 2007; Pichat *et al*, 2007) could underlie reversal of amphetamine-induced disruption and potentiation of LI, since both would be expected to reduce mesolimbic DA function and block behavioral effects of amphetamine (Goto and Grace, 2005, 2007; Grace, 1991; Jackson and Moghaddam, 2001). Alternatively, the capacity of SSR180711 to restore disrupted LI may stem from an action that is unrelated to dopaminergic function. One possibility is that SSR180711 restores LI by

increasing frontal ACh levels (Biton et al, 2007), because such an increase is expected to facilitate attentional processing (Hasselmo and McGaughy, 2004; Sarter and Bruno, 2000) through both nicotinic and muscarinic receptors (Hasselmo, 2006; Hasselmo and McGaughy, 2004). In this case, α7 partial agonism would be expected to target positive symptoms directly through modulation of aberrant stimulus salience.

SSR180711-Behavioral and Psychological Profile

Although the precise mechanisms underlying the effects of SSR180711 seen here remain to be investigated, our results demonstrate that this agent possesses in the LI model a behavioral profile of atypical APDs, which consists of LI potentiation when given on their own, reversal of amphetamine-induced disrupted LI and reversal of MK801-induced persistent LI (Gaisler-Salomon et al, 2008; Gaisler-Salomon and Weiner, 2003; Lipina et al, 2005; Shadach et al, 2000; Weiner, 2003). This is unlike the typical APDs, which fail to reverse MK801-induced LI persistence. Although this is to the best of our knowledge the first behavioral–pharmacological characterization of SSR180711 as an atypical APD, SSR180711 was shown to stimulate the expression of the immediate early gene c-fos in the NAC shell and the PFC of the rat but not in the NAC core or dorsal striatum (Hansen et al, 2007), a profile mimicking that of atypical rather than typical APDs (Fink-Jensen and Kristensen, 1994; Robertson and Fibiger, 1992).

It should be noted in this context that although amphetamine- and MK801-induced behavioral abnormalities and their reversal are widely used to model positive and negative/cognitive symptoms and their treatment (Ellenbroek and Cools, 2000; Geyer et al, 2001; Javitt and Zukin, 1991; Krystal et al, 2003; Robinson and Becker, 1986; Weiner, 2003), a unique characteristic of the LI model is that these two psychomimetics produce two poles of behavioral abnormality, namely, disrupted LI under conditions which lead to LI in normal rats, and abnormally persistent LI under conditions which disrupt it in normal rats. This bidirectional abnormality in LI implies that positive-like vs negative/cognitive-like symptoms in the model result from disruption of distinct psychological processes. Thus, amphetamine and MK801 can be seen as producing two poles of dysfunctional attentional control, namely, a failure to inhibit attention to irrelevant stimuli and a failure to re-deploy attention when previously irrelevant stimuli become relevant. The former would likely give rise to aberrantly increased salience perception and cognitive overswitching/distractibility that are associated with increased dopaminergic stimulation and psychotic symptoms (Gray et al, 1991; Ikemoto and Panksepp, 1999; Kapur, 2003; Smith et al, 2006; Swerdlow and Koob, 1987; Weiner, 1990, 2003; Weiner and Joel, 2002), whereas the latter would likely result in cognitive inflexibility and impaired attentional shifting that are associated with decreased glutamatergic transmission and negative/cognitive symptoms (Carlsson and Carlsson, 1990; Krystal et al, 2003; Moghaddam et al, 1997; Weiner, 2003).

This duality offers an important advantage in terms of differentiating between drugs that are active in the two models, because treatments effective in the two models must target distinct cognitive abnormalities presumably relevant to the two symptom clusters. Indeed in operational terms, effective treatments must produce distinct and in fact opposite actions on the LI phenomenon. Thus, drugs effective in the amphetamine model restore disrupted LI, and the same applies to the weak LI model, whereas drugs effective in the MK801 model disrupt LI.

SSR180711 produced both effects: it restored LI that was disrupted by amphetamine or strong conditioning, and disrupted excessive LI in MK801- and neonatal L-NoArg-treated rats. In psychological terms, SSR180711 strengthened/restored the capacity to ignore irrelevant stimuli in normal rats given prolonged conditioning and in amphetamine-treated rats, and enabled flexible re-deployment of attentional resources according to current situational demands in MK801 and neonatal L-NoArg-treated rats. Although the specific processes suggested here are at present highly speculative, the former would be beneficial in the treatment of positive symptoms/psychosis characterized by superfluous significance of stimuli (Kapur, 2003); whereas the latter would be beneficial in the treatment of negative and cognitive symptoms characterized by inattention and inflexibility (Morice, 1990).

α7 agonists have been shown to improve performance in various cognitive tasks in rodents, including one-way active avoidance, 8 or 17-arm radial maze, Morris water maze, object recognition and social recognition (Arendash et al, 1995; Hashimoto et al, 2008; Kem, 2000; Levin et al, 1999; Pichat et al, 2007; Timmermann et al, 2007; Van Kampen et al, 2004; Wishka et al, 2006). The dual effect of SSR180711 exerted on disrupted and persistent LI is particularly remarkable in that in terms of effects on performance, the drug influenced the pre-exposed MK801 and neonatal L-NoArg groups in opposite direction from that of the pre-exposed amphetamine group, namely, improved conditioning in the former and impaired conditioning in the latter. Thus, the action of SSR180711 may be seen as reflecting optimal cognitive enhancement, namely, improvement of the underlying cognitive process irrespective of the overt behavioral manifestation associated with such improvement.

CONCLUSION

To conclude, using the LI paradigm as readout, SSR180711 appears to be effective in models predictive of activity against cognitive symptoms of schizophrenia, including efficacy in a neurodevelopmental model of schizophrenia based on postnatal NOS inhibition, as well as in models predictive of activity against positive symptoms. Importantly, although the former characteristic of this drug is in line with many reports on α7 agonists (Arendash et al, 1995; Levin et al, 1999; Meyer et al, 1998; Olincy and Stevens, 2007; Pichat et al, 2007; Timmermann et al, 2007; Wishka et al, 2006), the latter capacity to the best of our knowledge is demonstrated here for the first time. Thus, this study suggests that α7-nAChR (partial) agonists can be viewed as promising targets not only for cognitive impairments in schizophrenia, but for treating the wide spectrum of symptoms in schizophrenia, including positive symptoms.

REFERENCES

Adams CE, Yonchek JC, Zheng L, Collins AC, Stevens KE (2008). Altered hippocampal circuit function in C3H alpha7 null mutant heterozygous mice. *Brain Res* **1194**: 138–145.

Adler LE, Olincy A, Waldo M, Harris JG, Griffith J, Stevens K et al (1998). Schizophrenia, sensory gating, and nicotinic receptors. *Schizophr Bull* **24**: 189–202.

Anscombe R (1987). The disorder of consciousness in schizophrenia. *Schizophr Bull* **13**: 241–260.

Arendash GW, Sengstock GJ, Sanberg PR, Kem WR (1995). Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. *Brain Res* **674**: 252–259.

Barak S, Weiner I (2008). Towards an animal model of an antipsychotic drug-resistant cognitive impairment in schizophrenia: scopolamine induces abnormally persistent latent inhibition, which can be reversed by cognitive enhancers but not by antipsychotic drugs. *Int J Neuropsychopharmacol*, print copy in press (originally published online 08 August 2008, at http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=2052992).

Bernstein HG, Bogerts B, Keilhoff G (2005). The many faces of nitric oxide in schizophrenia. A review. *Schizophr Res* **78**: 69–86.

Biton B, Bergis OE, Galli F, Nedelec A, Lochead AW, Jegham S et al (2007). SSR180711, a novel selective alpha7 nicotinic receptor partial agonist: (1) binding and functional profile. *Neuropsychopharmacology* **32**: 1–16.

Black MD, Selk DE, Hitchcock JM, Wettstein JG, Sorensen SM (1999). On the effect of neonatal nitric oxide synthase inhibition in rats: a potential neurodevelopmental model of schizophrenia. *Neuropharmacology* **38**: 1299–1306.

Black MD, Simmonds J, Senyah Y, Wettstein JG (2002). Neonatal nitric oxide synthase inhibition: social interaction deficits in adulthood and reversal by antipsychotic drugs. *Neuropharmacology* **42**: 414–420.

Black MD, Varty GB, Arad M, Barak S, De Levie M, Boulay D et al (2008). Procognitive and antipsychotic efficacy of Glycine transport 1 inhibitors (GlyT1) in acute and neurodevelopmental models of schizophrenia. Latent inhibition studies in the rat. *Psychopharmacology (Berl)*, print copy in press (originally published online 16 August 2008, at http://www.springerlink.com/content/k317514v396n7171/fulltext.pdf).

Boulay D, Pichat P, Bergis O, Avenet P, Griebel G (2007). Effects of SSR103800, a novel GlyT1 inhibitor, on the behavior of NMDA Nr1 hypomorphic mice, a model of schizophrenia. *Eur Neuropsychopharmacol* **17**(Supplement 4): S478–S479.

Bouton ME (1993). Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychol Bull* **114**: 80–99.

Buchanan RW, Freedman R, Javitt DC, Abi-Dargham A, Lieberman JA (2007). Recent advances in the development of novel pharmacological agents for the treatment of cognitive impairments in schizophrenia. *Schizophr Bull* **33**: 1120–1130.

Carlsson M, Carlsson A (1990). Interactions between glutamatergic and monoaminergic systems within the basal ganglia—implications for schizophrenia and Parkinson's disease. *Trends Neurosci* **13**: 272–276.

Ellenbroek BA, Cools AR (2000). Animal models for the negative symptoms of schizophrenia. *Behav Pharmacol* **11**: 223–233.

Fink-Jensen A, Kristensen P (1994). Effects of typical and atypical neuroleptics on Fos protein expression in the rat forebrain. *Neurosci Lett* **182**: 115–118.

Floresco SB, Blaha CD, Yang CR, Phillips AG (2001). Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: cellular mechanisms of input selection. *J Neurosci* **21**: 2851–2860.

Freedman R, Hall M, Adler LE, Leonard S (1995). Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. *Biol Psychiatry* **38**: 22–33.

Friedman JI (2004). Cholinergic targets for cognitive enhancement in schizophrenia: focus on cholinesterase inhibitors and muscarinic agonists. *Psychopharmacology (Berlin)* **174**: 45–53.

Furfine ES, Harmon MF, Paith JE, Garvey EP (1993). Selective inhibition of constitutive nitric oxide synthase by L-NG-nitroarginine. *Biochemistry* **32**: 8512–8517.

Gaisler-Salomon I, Diamant L, Rubin C, Weiner I (2008). Abnormally persistent latent inhibition induced by MK801 is reversed by risperidone and by positive modulators of NMDA receptor function: differential efficacy depending on the stage of the task at which they are administered. *Psychopharmacology (Berlin)* **196**: 255–267.

Gaisler-Salomon I, Weiner I (2003). Systemic administration of MK-801 produces an abnormally persistent latent inhibition which is reversed by clozapine but not haloperidol. *Psychopharmacology (Berlin)* **166**: 333–342.

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 (Berlin)* **156**: 117–154.

Goto Y, Grace AA (2005). Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. *Nat Neurosci* **8**: 805–812.

Goto Y, Grace AA (2007). The dopamine system and the pathophysiology of schizophrenia: a basic science perspective. *Int Rev Neurobiol* **78C**: 41–68.

Gould TJ, Collins AC, Wehner JM (2001). Nicotine enhances latent inhibition and ameliorates ethanol-induced deficits in latent inhibition. *Nicotine Tob Res* **3**: 17–24.

Grace AA (1991). Phasic *vs* tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* **41**: 1–24.

Gray JA, Feldon J, Rawlins JNP, Hemsley DR, Smith AD (1991). The neuropsychology of schizophrenia. *Behav Brain Sci* **14**: 1–20.

Gray JA, Moran PM, Grigoryan G, Peters SL, Young AM, Joseph MH (1997). Latent inhibition: the nucleus accumbens connection revisited. *Behav Brain Res* **88**: 27–34.

Green MF, Nuechterlein KH, Gaier DJ (1992). Sustained and selective attention in schizophrenia. *Prog Exp Pers Psychopathol Res* **15**: 290–313.

Guan ZZ, Zhang X, Blennow K, Nordberg A (1999). Decreased protein level of nicotinic receptor alpha7 subunit in the frontal cortex from schizophrenic brain. *Neuroreport* **10**: 1779–1782.

Hajos M (2006). Targeting information-processing deficit in schizophrenia: a novel approach to psychotherapeutic drug discovery. *Trends Pharmacol Sci* 27: 391–398.

Hajos M, Hurst RS, Hoffmann WE, Krause M, Wall TM, Higdon NR et al (2005). The selective alpha7 nicotinic acetylcholine receptor agonist PNU-282987 [N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride] enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. *J Pharmacol Exp Ther* 312: 1213–1222.

Hansen HH, Timmermann DB, Peters D, Walters C, Damaj MI, Mikkelsen JD (2007). Alpha-7 nicotinic acetylcholine receptor agonists selectively activate limbic regions of the rat forebrain: an effect similar to antipsychotics. *J Neurosci Res* 85: 1810–1818.

Harvey PD, Rabinowitz J, Eerdekens M, Davidson M (2005). Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry* 162: 1888–1895.

Hashimoto K, Ishima T, Fujita Y, Matsuo M, Kobashi T, Takahagi M et al (2008). Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the novel selective alpha7 nicotinic receptor agonist SSR180711. *Biol Psychiatry* 63: 92–97.

Hashimoto K, Koike K, Shimizu E, Iyo M (2005). alpha7 Nicotinic receptor agonists as potential therapeutic drugs for schizophrenia. *Curr Med Chem Cent Nerv Syst Agents* 5: 171.

Hasselmo ME (2006). The role of acetylcholine in learning and memory. *Curr Opin Neurobiol* 16: 710–715.

Hasselmo ME, McGaughy J (2004). High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. *Prog Brain Res* 145: 207–231.

Heinrichs RW (2005). The primacy of cognition in schizophrenia. *Am Psychol* 60: 229–242.

Heresco-Levy U, Javitt DC, Ebstein R, Vass A, Lichtenberg P, Bar G et al (2005). D-serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. *Biol Psychiatry* 57: 577–585.

Howland JG, Taepavarapruk P, Phillips AG (2002). Glutamate receptor-dependent modulation of dopamine efflux in the nucleus accumbens by basolateral, but not central, nucleus of the amygdala in rats. *J Neurosci* 22: 1137–1145.

Hoyle E, Genn RF, Fernandes C, Stolerman IP (2006). Impaired performance of alpha7 nicotinic receptor knockout mice in the five-choice serial reaction time task. *Psychopharmacology (Berlin)* 189: 211–223.

Hurst RS, Hajos M, Raggenbass M, Wall TM, Higdon NR, Lawson JA et al (2005). A novel positive allosteric modulator of the alpha7 neuronal nicotinic acetylcholine receptor: *in vitro* and *in vivo* characterization. *J Neurosci* 25: 4396–4405.

Ikemoto S, Panksepp J (1999). The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. *Brain Res Brain Res Rev* 31: 6–41.

Jackson ME, Moghaddam B (2001). Amygdala regulation of nucleus accumbens dopamine output is governed by the prefrontal cortex. *J Neurosci* 21: 676–681.

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

Jentsch JD, Taylor JR (2001). Impaired inhibition of conditioned responses produced by subchronic administration of phencyclidine to rats. *Neuropsychopharmacology* 24: 66–74.

Kapur S (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 160: 13–23.

Kelley AE, Andrzejewski ME, Baldwin AE, Hernandez PJ, Pratt WE (2003). Glutamate-mediated plasticity in corticostriatal networks: role in adaptive motor learning. *Ann NY Acad Sci* 1003: 159–168.

Kem WR (2000). The brain alpha7 nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease: studies with DMXBA (GTS-21). *Behav Brain Res* 113: 169–181.

Kilts CD (2001). The changing roles and targets for animal models of schizophrenia. *Biol Psychiatry* 50: 845–855.

Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R (2003). NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. *Psychopharmacology (Berlin)* 169: 215–233.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD et al (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51: 199–214.

Levin ED, Bettegowda C, Blosser J, Gordon J (1999). AR-R17779, and alpha7 nicotinic agonist, improves learning and memory in rats. *Behav Pharmacol* 10: 675–680.

Levin ED, Petro A, Caldwell DP (2005). Nicotine and clozapine actions on pre-pulse inhibition deficits caused by N-methyl-d-aspartate (NMDA) glutamatergic receptor blockade. *Prog Neuro-Psychopharmacol Biol Psychiatry* 29: 581–586.

Lipina T, Labrie V, Weiner I, Roder J (2005). Modulators of the glycine site on NMDA receptors, D: -serine and ALX 5407, display similar beneficial effects to clozapine in mouse models of schizophrenia. *Psychopharmacology (Berlin)* 179: 54–67.

Lipska BK (2004). Using animal models to test a neurodevelopmental hypothesis of schizophrenia. *J Psychiatry Neurosci* 29: 282–286.

Lipska BK, Weinberger DR (2000). To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* 23: 223–239.

Lubow RE (2005). Construct validity of the animal latent inhibition model of selective attention deficits in schizophrenia. *Schizophr Bull* 31: 139–153.

Luck SJ, Gold JM (2008). The construct of attention in schizophrenia. *Biol Psychiatry* 64: 34–39.

Marino MJ, Rouse ST, Levey AI, Potter LT, Conn PJ (1998). Activation of the genetically defined m1 muscarinic receptor potentiates N-methyl-D-aspartate (NMDA) receptor currents in hippocampal pyramidal cells. *Proc Natl Acad Sci USA* 95: 11465–11470.

Martin LF, Kem WR, Freedman R (2004). Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berlin)* 174: 54–64.

Mastropaolo J, Rosse RB, Deutsch SI (2004). Anabasine, a selective nicotinic acetylcholine receptor agonist, antagonizes MK-801-elicited mouse popping behavior, an animal model of schizophrenia. *Behav Brain Res* 153: 419–422.

McCartan D, Bell R, Green JF, Campbell C, Trimble K, Pickering A et al (2001). The differential effects of chlorpromazine and haloperidol on latent inhibition in healthy volunteers. *J Psychopharmacol* 15: 96–104.

Meyer EM, Tay ET, Zoltewicz JA, Meyers C, King MA, Papke RL et al (1998). Neuroprotective and memory-related actions of novel alpha-7 nicotinic agents with different mixed agonist/antagonist properties. *J Pharmacol Exp Ther* 284: 1026–1032.

Miyamoto S, Duncan GE, Marx CE, Lieberman JA (2005). Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry* 10: 79–104.

Moghaddam B, Adams B, Verma A, Daly D (1997). Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic

and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* **17**: 2921–2927.

Moghaddam B, Jackson ME (2003). Glutamatergic animal models of schizophrenia. *Ann NY Acad Sci* **1003**: 131–137.

Morice R (1990). Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania. *Br J Psychiatry* **157**: 50–54.

Moser PC, Hitchcock JM, Lister S, Moran PM (2000). The pharmacology of latent inhibition as an animal model of schizophrenia. *Brain Res Brain Res Rev* **33**: 275–307.

Olincy A, Harris JG, Johnson LL, Pender V, Kongs S, Allensworth D *et al* (2006). Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry* **63**: 630–638.

Olincy A, Stevens KE (2007). Treating schizophrenia symptoms with an alpha7 nicotinic agonist, from mice to men. *Biochem Pharmacol* **74**: 1192–1201.

Olivier B, Leahy C, Mullen T, Paylor R, Groppi VE, Sarnyai Z *et al* (2001). The DBA/2J strain and prepulse inhibition of startle: a model system to test antipsychotics? *Psychopharmacology (Berlin)* **156**: 284–290.

Pichat P, Bergis OE, Terranova JP, Urani A, Duarte C, Santucci V *et al* (2007). SSR180711, a novel selective alpha7 nicotinic receptor partial agonist: (II) efficacy in experimental models predictive of activity against cognitive symptoms of schizophrenia. *Neuropsychopharmacology* **32**: 17–34.

Powell CM, Miyakawa T (2006). Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? *Biol Psychiatry* **59**: 1198–1207.

Raedler TJ, Bymaster FP, Tandon R, Copolov D, Dean B (2007). Towards a muscarinic hypothesis of schizophrenia. *Mol Psychiatry* **12**: 232–246.

Rascle C, Mazas O, Vaiva G, Tournant M, Raybois O, Goudemand M *et al* (2001). Clinical features of latent inhibition in schizophrenia. *Schizophr Res* **51**: 149–161.

Rescorla RA (2002). Savings tests: separating differences in rate of learning from differences in initial levels. *J Exp Psychol Anim Behav Process* **28**: 369–377.

Rezvani AH, Levin ED (2003). Nicotinic-glutamatergic interactions and attentional performance on an operant visual signal detection task in female rats. *Eur J Pharmacol* **465**: 83–90.

Robertson GS, Fibiger HC (1992). Neuroleptics increase c-fos expression in the forebrain: contrasting effects of haloperidol and clozapine. *Neuroscience* **46**: 315–328.

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.

Rochford J, Sen AP, Quirion R (1996). Effect of nicotine and nicotinic receptor agonists on latent inhibition in the rat. *J Pharmacol Exp Ther* **277**: 1267–1275.

Sarter M, Bruno JP (2000). Cortical cholinergic inputs mediating arousal, attentional processing and dreaming: differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents. *Neuroscience* **95**: 933–952.

Sarter M, Nelson CL, Bruno JP (2005). Cortical cholinergic transmission and cortical information processing in schizophrenia. *Schizophr Bull* **31**: 117–138.

Schilstrom B, Fagerquist MV, Zhang X, Hertel P, Panagis G, Nomikos GG *et al* (2000). Putative role of presynaptic alpha7* nicotinic receptors in nicotine stimulated increases of extracellular levels of glutamate and aspartate in the ventral tegmental area. *Synapse* **38**: 375–383.

Schilstrom B, Svensson HM, Svensson TH, Nomikos GG (1998). Nicotine and food induced dopamine release in the nucleus accumbens of the rat: putative role of alpha7 nicotinic receptors in the ventral tegmental area. *Neuroscience* **85**: 1005–1009.

Schreiber R, Dalmus M, De Vry J (2002). Effects of alpha 4/beta 2- and alpha 7-nicotine acetylcholine receptor agonists on prepulse

inhibition of the acoustic startle response in rats and mice. *Psychopharmacology (Berlin)* **159**: 248–257.

Shadach E, Gaisler I, Schiller D, Weiner I (2000). The latent inhibition model dissociates between clozapine, haloperidol, and ritanserin. *Neuropsychopharmacology* **23**: 151–161.

Smith A, Li M, Becker S, Kapur S (2006). Dopamine, prediction error and associative learning: a model-based account. *Network* **17**: 61–84.

Smith AJ, Li M, Becker S, Kapur S (2007). Linking animal models of psychosis to computational models of dopamine function. *Neuropsychopharmacology* **32**: 54–66.

Suemaru K, Yasuda K, Umeda K, Araki H, Shibata K, Choshi T *et al* (2004). Nicotine blocks apomorphine-induced disruption of prepulse inhibition of the acoustic startle in rats: possible involvement of central nicotinic alpha7 receptors. *Br J Pharmacol* **142**: 843–850.

Sur C, Mallorga PJ, Wittmann M, Jacobson MA, Pascarella D, Williams JB *et al* (2003). N-desmethylclozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. *Proc Natl Acad Sci USA* **100**: 13674–13679.

Svensson TH (2000). Dysfunctional brain dopamine systems induced by psychotomimetic NMDA-receptor antagonists and the effects of antipsychotic drugs. *Brain Res Brain Res Rev* **31**: 320–329.

Swerdlow NR, Koob GF (1987). Lesions of the dorsomedial nucleus of the thalamus, medial prefrontal cortex and pedunculopontine nucleus: effects on locomotor activity mediated by nucleus accumbens-ventral pallidal circuitry. *Brain Res* **412**: 233–243.

Thornton JC, Dawe S, Lee C, Capstick C, Corr PJ, Cotter P *et al* (1996). Effects of nicotine and amphetamine on latent inhibition in human subjects. *Psychopharmacology (Berlin)* **127**: 164–173.

Timmermann DB, Gronlien JH, Kohlhaas KL, Nielsen EO, Dam E, Jorgensen TD *et al* (2007). An allosteric modulator of the alpha7 nicotinic acetylcholine receptor possessing cognition-enhancing properties *in vivo*. *J Pharmacol Exp Ther* **323**: 294–307.

Tizabi Y, Mastropaolo J, Park CH, Riggs RL, Powell D, Rosse RB *et al* (1998). Both nicotine and mecamylamine block dizocilpine-induced explosive jumping behavior in mice: psychiatric implications. *Psychopharmacology (Berlin)* **140**: 202–205.

van der Meulen JA, Bilbija L, Joosten RN, de Bruin JP, Feenstra MG (2003). The NMDA-receptor antagonist MK-801 selectively disrupts reversal learning in rats. *Neuroreport* **14**: 2225–2228.

Van Kampen M, Selbach K, Schneider R, Schiegel E, Boess F, Schreiber R (2004). AR-R 17779 improves social recognition in rats by activation of nicotinic alpha7 receptors. *Psychopharmacology (Berlin)* **172**: 375–383.

Weiner I (1990). Neural substrates of latent inhibition: the switching model. *Psychol Bull* **108**: 442–461.

Weiner I (2003). The "two-headed" latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. *Psychopharmacology (Berlin)* **169**: 257–297.

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

Weiner I, Joel D (2002). Dopamine in schizophrenia: dysfunctional information processing in basal ganglia-thalamocortical split circuits. In: Di Chiara G (ed). *Handbook of Experimental Pharmacology*, Vol 54/II, Dopamine in the CNS II. Springer: Berlin. pp 418–472.

Weiner I, Lubow RE, Feldon J (1984). Abolition of the expression but not the acquisition of latent inhibition by chronic amphetamine in rats. *Psychopharmacology (Berlin)* **83**: 194–199.

Weiner I, Lubow RE, Feldon J (1988). Disruption of latent inhibition by acute administration of low doses of amphetamine. *Pharmacol Biochem Behav* **30**: 871–878.

Wiedl KH, Schottke H, Green MF, Nuechterlein KH (2004). Dynamic testing in schizophrenia: does training change the construct validity of a test? *Schizophr Bull* **30**: 703–711.

Williams JH, Wellman NA, Geaney DP, Feldon J, Cowen PJ, Rawlins JN (1997). Haloperidol enhances latent inhibition in visual tasks in healthy people. *Psychopharmacology (Berlin)* **133**: 262–268.

Wishka DG, Walker DP, Yates KM, Reitz SC, Jia S, Myers JK et al (2006). Discovery of N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-furo[2,3-c]pyridine-5-carboxamide, an agonist of the alpha7 nicotinic acetylcholine receptor, for the potential treatment of cognitive deficits in schizophrenia: synthesis and structure-—activity relationship. *J Med Chem* **49**: 4425–4436.

Wonnacott S, Sidhpura N, Balfour DJ (2005). Nicotine: from molecular mechanisms to behaviour. *Curr Opin Pharmacol* **5**: 53–59.

Young AM, Joseph MH, Gray JA (1993). Latent inhibition of conditioned dopamine release in rat nucleus accumbens. *Neuroscience* **54**: 5–9.

Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C et al (2007). Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. *Eur Neuropsychopharmacol* **17**: 145–155.

Young JW, Finlayson K, Spratt C, Marston HM, Crawford N, Kelly JS et al (2004). Nicotine improves sustained attention in mice: evidence for involvement of the alpha7 nicotinic acetylcholine receptor. *Neuropsychopharmacology* **29**: 891–900.