Neuropsychopharmacology (2009), 1–11

www.neuropsychopharmacology.org

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

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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.
Neuropsychopharmacology advance online publication, 21 January 2009; doi:10.1038/npp.2008.232

Keywords: α7 nicotinic receptors; cognition; latent inhibition; schizophrenia; positive symptoms; SSR180711

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).

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Received 17 September 2008; revised 11 December 2008; accepted 12 December 2008

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

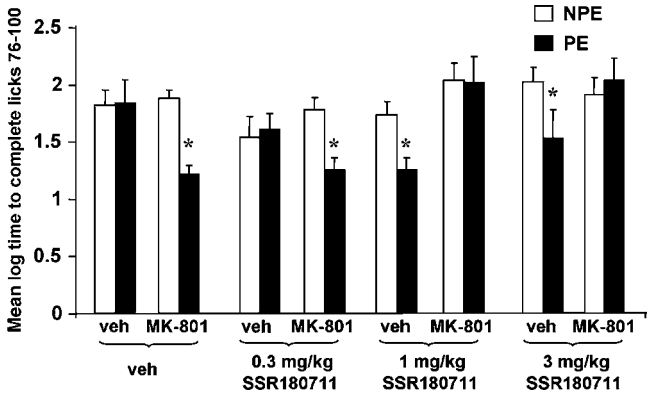

Figure 1 Effects of SSR180711 on MK801-induced persistent LI and LI with strong conditioning. Means and SE of the log times to complete licks 76–100 (after tone onset) of the pre-exposed (PE) and non-pre-exposed (NPE) rats treated with MK801 or vehicle (veh), and pre-treated with SSR180711 at doses of 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.

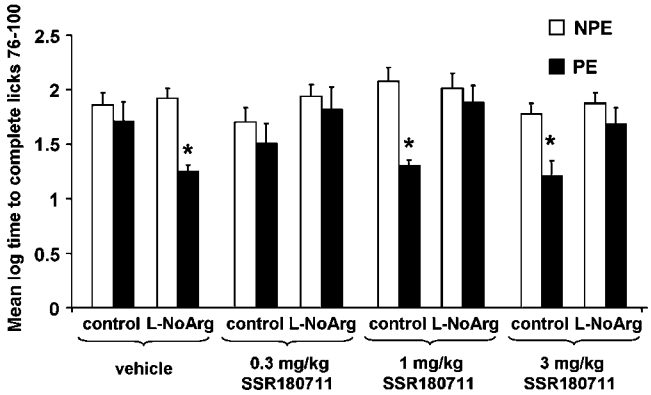

Figure 2 Effects of SSR180711 on neonatal L-NoArg-induced persistent LI and LI with strong conditioning. Means and SE of the log times to complete licks 76–100 (after tone onset) of the pre-exposed (PE) and non-pre-exposed (NPE) rats neonatally treated with L-NoArg or vehicle (control), injected with 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.

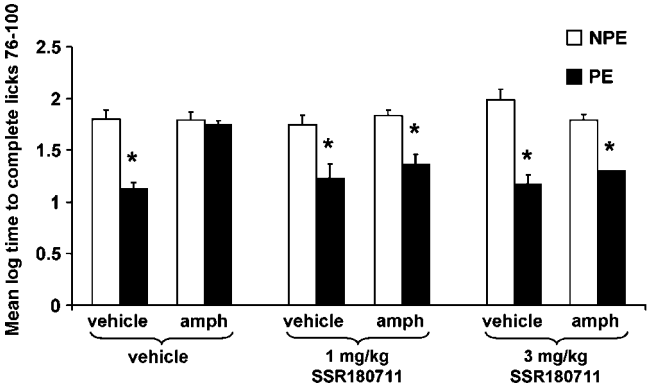

Figure 3 Effects of SSR180711 on amphetamine-induced LI disruption. Means and SE of the log times to complete licks 76–100 (after tone onset) of the pre-exposed (PE) and non-pre-exposed (NPE) rats treated with amphetamine (amph) or vehicle, and pre-treated with SSR180711 at doses of 1 or 3 mg/kg, or 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.

ACKNOWLEDGEMENTS

This research was supported by the Israel Science Foundation (grant no. 1234/07, IW) and by the Josef Sagol Fellowship Program in Brain Studies at Tel-Aviv University (SB).

DISCLOSURE/CONFLICT OF INTEREST

The reported experiments are part of a research collaboration supported by Sanofi-Aventis. The authors have neither conflicts of interest to report, nor any involvement to disclose, financial or otherwise, that may bias the conduct, interpretation, or presentation of this work. Organizations from which the authors have received compensation for professional services: GG and MDB are employees of Sanofi-Aventis.

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