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ORIGINAL INVESTIGATION

Procognitive and antipsychotic efficacy of glycine transport 1 inhibitors (GlyT1) in acute and neurodevelopmental models of schizophrenia: latent inhibition studies in the rat

Mark D. Black · Geoffrey B. Varty · Michal Arad · Segev Barak · Amaya De Levie · Denis Boulay · Philippe Pichat · Guy Griebel · Ina Weiner

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Abstract
Rationale SSR103800 and SSR504734 are novel glycine transport 1 (GlyT1) inhibitors with therapeutic potential for the treatment of schizophrenia.
Objective The present studies investigated the effects of GlyT1 inhibitors in acute pharmacological and neurodevelopmental models of schizophrenia using latent inhibition in the rat; these latent inhibition (LI) models are believed to be predictive for treatments of positive, negative, and cognitive aspects of schizophrenia.
Materials and methods LI, the poorer conditioning to a previously irrelevant stimulus, was measured in a conditioned emotional response procedure in male rats. The effects of SSR103800 or SSR504734 (both at 1, 3, and 10 mg/kg, i.p.) were determined on amphetamine-induced disrupted LI, MK-801-induced abnormally persistent LI, and neurodevelopmentally induced abnormally persistent LI in adult animals that had been neonatally treated with a nitric oxide synthase inhibitor.
Results SSR103800 (1 and 3 mg/kg) and SSR504734 (1 and 10 mg/kg) potentiated LI under conditions where LI was not present in nontreated controls and SSR103800 (1 mg/kg) reversed amphetamine-induced disrupted LI while not affecting LI on its own. Additionally, SSR103800 (1 and 3 mg/kg) and SSR504734 (3 and 10 mg/kg) reversed abnormally persistent LI induced by MK-801. In the neurodevelopmental model, SSR504734 (3 and 10 mg/kg) reverted the LI back to control (normal) levels.
Conclusions These preclinical data, from acute and neurodevelopmental models, suggest that GlyT1 inhibition may exhibit activity in the positive, negative, and cognitive symptom domains of schizophrenia.

Keywords Schizophrenia · Cognition · Glycine transport 1 inhibitors · Latent inhibition · Rat · SSR504734 · SSR103800

M. D. Black (✉) · G. B. Varty
CNS Department, Sanofi-Aventis,
1041 Route 202/206,
Bridgewater, NJ 08807, USA
e-mail: mark.black@sanofi-aventis.com

D. Boulay · P. Pichat · G. Griebel
CNS Department, Sanofi-Aventis,
31 Avenue Paul Vaillant Couturier,
Bagneux, France

M. Arad · S. Barak · A. De Levie · I. Weiner
Department of Psychology, Tel Aviv University,
Tel Aviv, Israel

Introduction

Significant evidence exists for neurochemical disturbances in the brains of schizophrenic patients, and alterations in both dopaminergic and glutamatergic transmissions are strongly implicated in schizophrenia (see Coyle 2006; Stone et al. 2007 for reviews). Therefore, not surprisingly, preclinical research into schizophrenia frequently employs agents that manipulate the dopaminergic (e.g., amphetamine—a dopamine reuptake inhibitor) and glutamatergic (e.g., MK-801—NMDA receptor antagonist) systems.

The use of NMDA antagonists to model or mimic schizophrenia in animal systems is commonplace in preclinical studies (Mouri et al. 2007; Enomoto et al. 2007; Javitt and Zukin 1991; Jentsch and Roth 1999; Moghaddam and Jackson 2003), but supportive evidence, for hypoglutametergic transmission, also exists in clinical studies (Allen and Young 1978; Lahti et al. 1995;

Tamminga et al. 1995). When one forms a hypothesis that a particular disease such as schizophrenia has NMDA hypotransmission (Carlsson et al. 2000, 2004; Gluck et al. 2002) as a core feature, it thus follows that potential new therapies for such a disorder could be aimed at reversing or stimulating that system (e.g., increase NMDA transmission). Indeed, compounds that potentiate NMDA transmission (Johnson and Ascher 1987) through an allosteric site within the receptor complex (e.g., D-cycloserine, glycine, and D-serine) improve some aspects of negative symptomatology and cognitive dysfunction without interfering with the beneficial effects of antipsychotics on positive symptoms (Goff et al. 1995, 1996, 1999; Tsai et al. 1998; Heresco-Levy 2003; Heresco-Levy and Javitt 2004, Heresco-Levy et al. 2005; Javitt et al. 2001; Javitt 2008; Evins et al. 2002). Therefore, the strength of the glutamatergic neurotransmission can be influenced by the synaptic concentration of glycine within the vicinity of NMDA receptors. Levels of synaptic glycine are tightly controlled by two types of specific transporters, GlyT1 and GlyT2. GlyT1 is localized on glial cells, as well as neurons, and is present in high levels in the forebrain (Cubelos et al. 2005). GlyT2 is colocalized with inhibitory (i.e., strychnine sensitive) glycine receptors (for review, see Gomeza et al. 2003) and is present in high levels in the spinal cord. Importantly, GlyT1 is closely associated with the NMDA receptor. Therefore, by increasing the synaptic concentration of glycine, inhibitors of GlyT1 will potentiate glutamatergic transmission, and as such potentially ameliorate the hypoglutamatergia. Indeed, several GlyT1 inhibitors [ALX 5407 (also known as NFPS), ORG 24461, ORG 24598, CP 802,079, SSR504734] have been reported to possess preclinical profiles of putative antipsychotics in several animal models (Bergeron et al. 1998; Atkinson et al. 2001; Brown et al. 2001; Harsing et al. 2003, Kinney et al. 2003, Le Pen et al. 2003, Martina et al. 2004; Depoortere et al. 2005).

In the present studies, we examined the antipsychotic potential of GlyT1 inhibitors further by testing the novel GlyT1 inhibitors, SSR103800, and SSR504734 in acute pharmacological and neurodevelopmental models of latent inhibition (LI).

LI is a cross-species selective attention phenomenon manifested as the proactive interference of a nonreinforced stimulus preexposure with the capacity of that stimulus to acquire behavioral control when it is subsequently paired with reinforcement. LI is commonly considered to index the ability to ignore stimuli that were irrelevant in the past (Lubow 1989; Lubow et al. 1981); as such, LI abnormalities in rodents are used to model the widely documented attentional impairments in schizophrenia.

LI is disrupted in rodents and normal humans treated with amphetamine and in the acute stages of schizophrenia (Weiner and Feldon 1986; Weiner et al. 1984, 1996; Gray et al. 1992; Thornton et al. 1996; Rascle et al. 2001). Both typical and atypical antipsychotics restore LI in amphetamine-treated rodents and potentiate LI in naïve animals under conditions that normally do not yield robust LI. The latter effect is obtained also in humans and is the most widely used index—and the sine qua non—of antipsychotic activity in the LI model (for reviews, see Weiner 1990, 2003; Weiner and Feldon 1997; Moser et al. 2000). Amphetamine-induced disruption of LI and its reversal by APDs is a well-established model of positive symptoms of schizophrenia (for reviews, see Gray et al. 1991; Moser et al. 2000; Weiner 1990, 2003; Weiner and Feldon 1997).

Unlike amphetamine, acute administration of low-dose NMDA antagonists spares LI under conditions yielding LI in nontreated controls (Weiner and Feldon 1992; Aguado et al. 1994; Klamer et al. 2004; Palsson et al. 2005; Robinson et al. 1993; Turgeon et al. 1998, 2000) and in fact, produce an *opposite* behavioral effect on LI from that of amphetamine, namely, an abnormally persistent LI, that becomes manifested under conditions that prevent the expression of LI in no-drug controls (Gaisler-Salomon and Weiner 2003; Gaisler-Salomon et al. 2008; Lipina et al. 2005). This MK-801-induced attentional perseveration is reversed by atypical (clozapine and risperidone) but not typical (haloperidol) antipsychotic drugs (Gaisler-Salomon and Weiner 2003; Gaisler-Salomon et al. 2008). Reversal of NMDA antagonist-induced abnormally persistent LI is believed to reflect potential therapeutic activity in negative symptoms of schizophrenia (Gaisler-Solomon and Weiner 2003; Gaisler-Solomon et al. 2008). MK-801-induced persistent LI is also reversed by glycinergic compounds, including agonists like glycine, D-cycloserine, and D-serine and the GlyT1 inhibitor ALX5407; thus, this model may also be predictive for procognitive agents (Gaisler-Salomon et al. 2008; Lipina et al. 2005). In addition, glycinergic compounds were found to potentiate LI in naïve mice (Lipina et al. 2005) but not rats (Gaisler-Solomon and Weiner 2003; Gaisler-Solomon et al. 2008), suggesting that they may posses activity against positive symptoms in the LI model. To date, it is not known whether these compounds can reverse amphetamine-induced LI disruption.

While the predominant approaches towards new therapeutics for schizophrenia involve manipulations of dopamine and glutamate based pharmacological models, another important aspect of schizophrenia is the neurodevelopmental nature of the disease. The neurodevelopmental hypothesis of schizophrenia proposes that a proportion of schizophrenia is the result of an early brain insult, either pre- or perinatal, which affects brain development leading to abnormalities, which are expressed in the mature brain (Weinberger 1987; Bloom 1993; Bogarts 1993; Weinberger and Lipska 1995). Although the neurodevelopmental

hypothesis has spawned an abundance of animal neurodevelopmental models, the use of these models for drug development has been relatively scarce. We have recently shown that SSR504734 was effective in reversing long-term behavioral deficits resulting from neonatal NMDA blockade (Depoortere et al. 2005). Here, we tested the efficacy of SSR504734 in a related model, that of neonatal nitric oxide synthase (NOS) inhibition.

As stated earlier, the predominant approaches towards new therapeutics for schizophrenia involve manipulations of dopamine and glutamate, and for glutamate, the focus has been on the involvement of the NMDA receptor. The relationship between the NMDA receptor and NOS is well reported (Garthwaite et al. 1988; Brenman and Bredt 1997; Kiss and Vizi 2001; Lipton 2007), although evidence exists for positive and negative influence of NOS inhibition on NMDA receptor-mediated transmission (Lipton et al. 2002; Hopper and Garthwaite 2006; Wass et al. 2006; Fejgin et al. 2008; Lipton 2007). Evidence also exists that NOS can influence brain development (Roskams et al. 1994; Wu et al. 2003; Sánchez-Islas and León-Olea 2004). NADPH-d is a NOS capable of generating nitric oxide (NO) (Hope et al. 1991; Dawson et al. 1991), and the migration of NADPH-d neurons is impaired in the prefrontal cortex, hippocampal formation, and lateral temporal lobe of schizophrenic patients (Akbarian et al. 1993, 1996; Bloom 1993), brain areas intimately linked to the disease. Nitric oxide (NO) itself is known to play a role in brain development and neuronal connectivity during the pre- and perinatal period. We previously showed that interfering with NO production during the very early postnatal period reproduced some of the aspects of schizophrenia in adult animals (Black et al. 1999, 2002). Neonatal rats treated with the NOS inhibitor, L-NoArg, exhibited amphetamine and PCP hypersensitivity, impaired social interaction, and prepulse inhibition (PPI) disruption (Black et al. 1999). Recently, we have found that neonatal NOS inhibition leads to abnormally persistent LI at adulthood, which was reversed by atypical APDs and glycine, but not typical APDs (De Levie et al. unpublished observations). Based on these findings, the present studies aimed to test whether GlyT1 inhibitors were efficacious in reversing persistent LI in the L-NoArg neurodevelopmental model.

In summary, as it is important to characterize potential novel drugs for treatment of schizophrenia in both pharmacological and neurodevelopmental models, in the present studies, we examined the effects of the novel GlyT1 inhibitors, SSR103800 or SSR504734, in acute psychostimulant and neurodevelopmental models of LI. Specifically, we tested for the ability of these compounds to improve pharmacologically induced abnormalities in LI using amphetamine or MK-801, as well as neurodevelopmentally induced abnormality in LI.

Materials and methods

Subjects

Male Wistar rats weighing 350–450 g were used. Rats were housed four per cage under reversed cycle lighting (lights on: 07:00–19:00), with ad lib access to food and water except for the duration of the LI experiments (see below). 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).

Neonatal treatment

Wistar rats (Tel Aviv University Medical School) were mated at an age of 3 months. At birth, litters were culled to ten, composed of five males and five females 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) or vehicle. L-NoArg was dissolved in 1 N 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 by sex, litter, and neonatal treatment and maintained undisturbed till 3 months of age, with the exception of basic husbandry. In each cage, there were four L-NoArg- or saline-treated pups. At adulthood, each cage was assigned to preexposed or non-preexposed condition (see below), and each of the four rats in a cage was assigned to a different drug condition (0, 1, 3, and 10 mg/kg SSR504734), with the provision that in each experimental group there was no more than one rat from the same litter.

Apparatus and procedure

Rats were tested in rodent test chambers (Campden Instruments, Loughborough, UK) containing a retractable bottle. When the bottle was not present, the hole was covered by a metal lid. Licks were detected by a lickometer. The preexposed to-be-conditioned stimulus was a 10-s, 80-dB, 2.8-kHz tone produced by a Sonalert module. Shock was supplied through the floor by a shock generator and shock scrambler set at 0.5-mA amplitude and 1-s duration. Equipment programming and data recording were computer-controlled.

LI was measured in a thirst-motivated conditioned emotional response procedure by comparing the suppression of drinking to a tone previously paired with a foot shock in rats that received nonreinforced exposure to the tone prior to conditioning (preexposed) and in rats for whom the tone was novel (non-preexposed).

Prior to the beginning of each LI experiment, rats were handled for about 2 min daily for 5 days. A 23-h water restriction schedule was initiated simultaneously with handling and continued throughout the experiment. On the next 5 days, rats were trained to drink in the experimental chamber for 20 min/day. 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 the following stages: *Preexposure.* With the bottle removed, the preexposed (PE) rats received 40 tone presentations with an inter-stimulus interval of 50 s. The non-preexposed (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 or five tone-shock pairings given 5 min apart. Shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the session. After the last pairing, rats were left in the experimental chamber for an additional 5 min. The amphetamine experiment used two conditioning trials that normally produce LI and thus allow the demonstration of disruption of LI. For experiments involving MK-801 or neonatal NOS, five conditioning trials that counteract LI in no-drug controls were used because persistent LI can be manifested only under such conditions. *Rebaseline.* Rats were given a 15-min drinking session as in 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 logarithmically transformed to allow parametric analysis of variance. Longer log times indicate stronger suppression of drinking. LI is defined as significantly shorter log times to complete licks 76–100 of the preexposed as compared to non-preexposed rats.

Drugs

All drugs were administered intraperitoneally. MK-801 (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, at a volume of 1 ml/kg 30 min prior to preexposure and conditioning. SSR504734 (Depoortere et al. 2005) and SSR103800 (Boulay et al. 2008) were synthesized by the CNS Medicinal Chemistry Department of Sanofi-Aventis. SSR504734 and SSR103800 (Sanofi-Aventis, France) were dissolved in 2% Tween 80 solution (polyoxyethylene sorbitan monooleate; Sigma, Israel), diluted in saline, and administered in a volume of 3 ml/kg at doses of 1, 3, or 10 mg/kg 30 min prior to preexposure and conditioning stages. Haloperidol and glycine were used as positive controls in the amphetamine and MK-801 experiments, respectively. Haloperidol was prepared from an ampoule containing 5 mg haloperidol in 1 ml solvent containing 6 mg lactic acid (Abic Ltd, Israel), diluted with saline, and administered at a dose of 0.1 mg/kg 60 min prior to the behavioral sessions. Glycine (Sigma, Israel) was diluted with saline and administered at a dose of 0.8 g/kg in volume of 3 ml/kg 30 min prior to preexposure and conditioning. The 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 preexposure and drug conditions. In cases of significant interactions involving the factor of preexposure, LSD post hoc comparisons were used to assess the difference between the PE and NPE groups within each treatment condition.

Results

The effects of SSR103800 on amphetamine-induced disrupted LI

The experiment included 189 rats (run in four replications) divided to 20 groups (n=8–10 per group) in a 2×2×5 design, with main factors of preexposure (PE, NPE), treatment (vehicle, amphetamine), and pretreatment (vehicle, 1, 3, and 10 mg/kg SSR103800, haloperidol).

The 20 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=7.77 s). As expected with two conditioning trials, vehicle-injected rats showed LI, but LI was absent in amphetamine-treated rats (Fig. 1). LI was restored in amphetamine-treated rats by haloperidol, as well as by 1 mg/kg SSR103800, but not by 3 or 10 mg/kg SSR103800.

Three-way ANOVA with main factors of preexposure, treatment, and pretreatment yielded significant main effects of preexposure [$F(1,169)=138.09$, $p<0.0001$], treatment [$F(1,169)=33.87$, $p<0.0001$], and pretreatment [$F(4,169)=3.52$, $p<0.01$], as well as significant interactions of preexposure×treatment [$F(1,169)=49.34$, $p<0.0001$] and preexposure×treatment×pretreatment [$F(4,169)=6.91$, $p<0.0001$]. Post hoc comparisons revealed a significant difference between the preexposed and non-preexposed groups in the vehicle–vehicle ($p<0.01$), vehicle–1 mg/kg

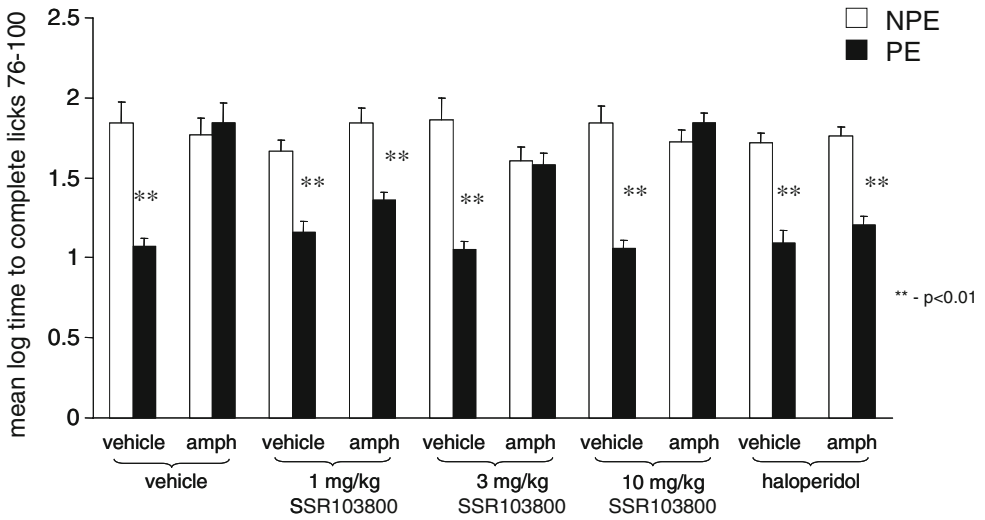

Fig. 1 The effects of SSR103800 on amphetamine-induced disrupted LI. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (*PE*) and non-preexposed (*NPE*) rats treated with amphetamine (*amph*) or vehicle and pretreated with SSR103800 at doses of 1, 3, or 10 mg/kg, 0.1 mg/kg haloperidol, or vehicle (all drugs administered i.p.). Forty preexposures and two conditioning trials were used. SSR103800, haloperidol, and amphetamine were administered prior to the preexposure and conditioning stages. *Asterisks* indicate a significant difference between the PE and NPE groups, namely, presence of LI

($p<0.01$), vehicle–3 mg/kg ($p<0.01$), vehicle–10 mg/kg ($p<0.01$), vehicle–haloperidol ($p<0.01$), amphetamine–1 mg/kg ($p<0.01$), and amphetamine–haloperidol ($p<0.01$) conditions, but not in all the other conditions ($p>0.05$).

The effects of SSR103800 on MK-801-induced abnormally persistent LI

The experiment included 186 rats (run in four replications) divided into 20 groups (n=8–11 per group) in a 2×2×5 design, with main factors of preexposure (PE, NPE), treatment (vehicle, MK-801), and pretreatment (vehicle, 1, 3, and 10 mg/kg SSR103800, glycine).

The 20 experimental groups did not differ in their times to complete licks 51–75 before tone onset (all p's>0.5; overall mean A period=7.67 s). As expected with five conditioning trials, vehicle-injected rats did not show LI, whereas MK-801-treated rats showed LI in spite of extended conditioning (Fig. 2). MK-801-induced abnormally persistent LI was reversed by 1 and 3 mg/kg

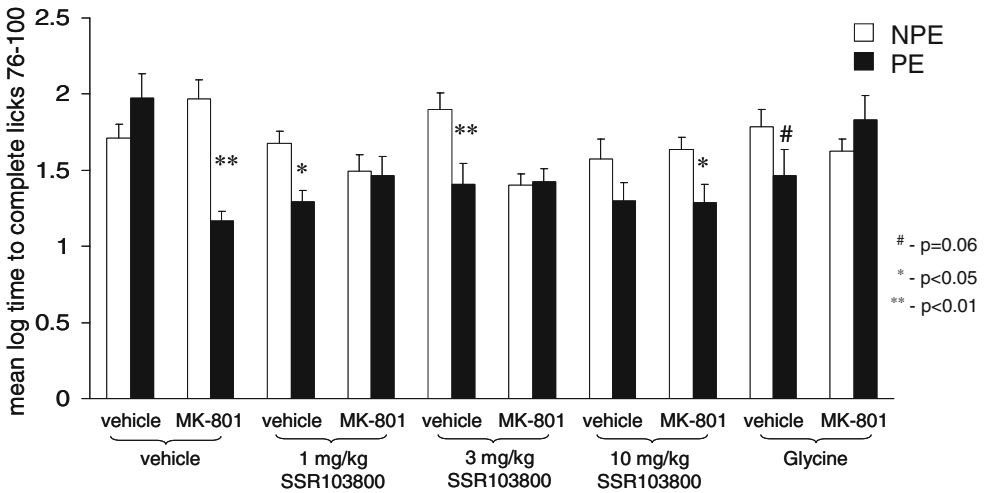

Fig. 2 The effects of SSR103800 on MK-801-induced abnormally persistent LI. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (*PE*) and non-preexposed (*NPE*) rats treated with MK-801 or vehicle and pretreated with SSR103800 in doses of 1, 3, or 10 mg/kg, 0.8 g/kg glycine, or vehicle (all drugs administered i.p.). Forty preexposures and five conditioning trials were used. SSR103800 and glycine were administered prior to the preexposure and conditioning stages; MK-801 was administered prior to the conditioning stage. *Asterisks* indicate a significant difference between the PE and NPE groups, namely, presence of LI

SSR103800 and glycine, but not by 10 mg/kg SSR103800. In addition, 1 and 3 mg/kg SSR103800 and glycine, but not 10 mg/kg SSR103800, potentiated LI when administered to vehicle-treated rats. Three-way ANOVA with main factors of preexposure treatment and pretreatment yielded significant main effects of preexposure [$F(1,166)=17.61$, $p<0.0001$] and pretreatment [$F(4,166)=4.05$, $p<0.01$], as well as a significant interaction of preexposure×treatment×pretreatment [$F(4,166)=8.21$, $p<0.0001$]. Post hoc comparisons revealed a significant difference between the preexposed and non-preexposed groups in the MK-801–vehicle ($p<0.0001$), the vehicle–3 mg/kg ($p<0.01$), the vehicle–1 mg/kg, and the MK-801–10 mg/kg conditions ($p<0.05$) and a near significant effect in the vehicle–glycine condition ($p=0.06$), but not in all the other conditions ($p>0.05$).

The effects of SSR504734 on MK-801-induced abnormally persistent LI

The experiment included 186 rats (run in four replications) in 20 groups ($n=8$–11 per group) in a 2×2×5 design, with main factors of preexposure (PE, NPE), treatment (vehicle, MK-801), and pretreatment (vehicle, 1, 3, and 10 mg/kg SSR504734, glycine).

The 20 experimental groups did not differ in their times to complete licks 51–75 before tone onset (all p's>0.5; overall mean A period=7.56 s). Vehicle-injected rats did not show LI, whereas MK-801-treated rats showed LI in spite of extended conditioning (Fig. 3). MK-801-induced abnormally persistent LI was reversed by 3 and 10 mg/kg SSR504734 and glycine, but not by 1 mg/kg SSR504734. In addition, 1 and 10 mg/kg SSR504734, but not 3 mg/kg SSR504734 and glycine, potentiated LI in vehicle-treated rats.

Three-way ANOVA with main factors of preexposure, treatment, and pretreatment yielded significant main effects of preexposure [$F(1,165)=13.42$, $p<0.0001$] and treatment [$F(1,165)=18.31$, $p<0.0005$] and a significant interaction of preexposure×pretreatment [$F(4,165)=2.48$, $p<0.05$]. Post hoc comparisons revealed a significant difference between the preexposed and non-preexposed groups in the MK-801–vehicle ($p<0.01$), the MK-801–1 mg/kg SSR 504734 ($p<0.01$), the vehicle–1 mg/kg SSR504734 ($p<0.05$), and the vehicle–10 mg/kg SSR504734 ($p<0.05$) conditions, but not in all the other conditions ($p>0.05$).

The effects of SSR504734 on neonatal L-NoArg-induced abnormally persistent LI

The experiment included 143 rats divided into 16 groups ($n=6$–9 per group) in a 2×2×4 design, with main factors of preexposure (0, 40), neonatal treatment (vehicle, L-NoArg), and adult treatment (vehicle, 1, 3, and 10 mg/kg SSR504734). 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=7.38 s). LI was absent in rats neonatally treated with vehicle, but rats neonatally treated with L-NoArg showed LI. Neonatal L-NoArg-induced abnormally persistent LI was reversed by all doses of SSR504734 (Fig. 4). In addition, 3 and 10 mg/kg of SSR504734 potentiated LI in neonatally vehicle-treated rats. Three-way ANOVA with main factors of preexposure, neonatal treatment, and adult treatment yielded a significant

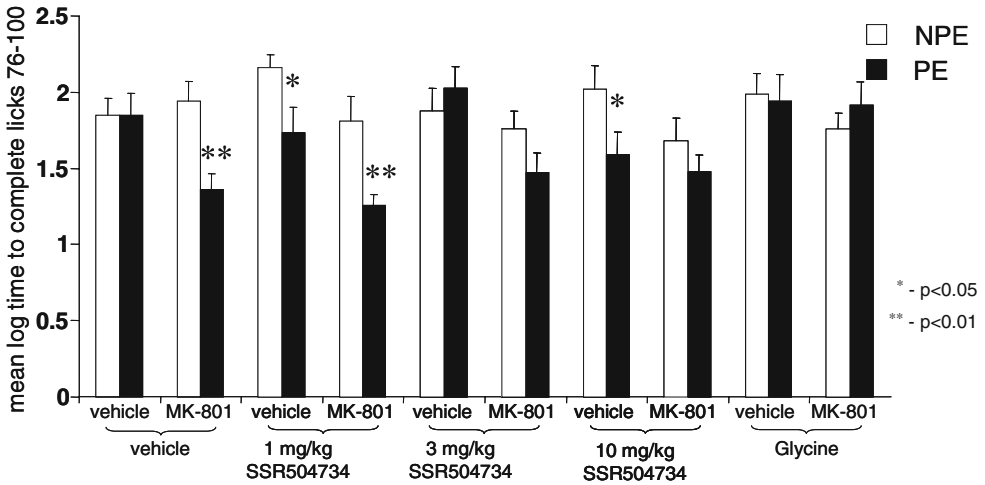

Fig. 3 The effects of SSR504734 on MK-801-induced abnormally persistent LI. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (*PE*) and non-preexposed (*NPE*) rats treated with MK-801 or vehicle and pretreated with SSR504734 in doses of either 1, 3, or 10 mg/kg, or with 0.8 g/kg glycine, or vehicle (all drugs administered i.p.). Forty preexposures and five conditioning trials were used. SSR504734 and glycine were administered prior to the preexposure and conditioning stages; MK-801 was administered prior to the conditioning stage. *Asterisks* indicate a significant difference between the PE and NPE groups, namely, presence of LI

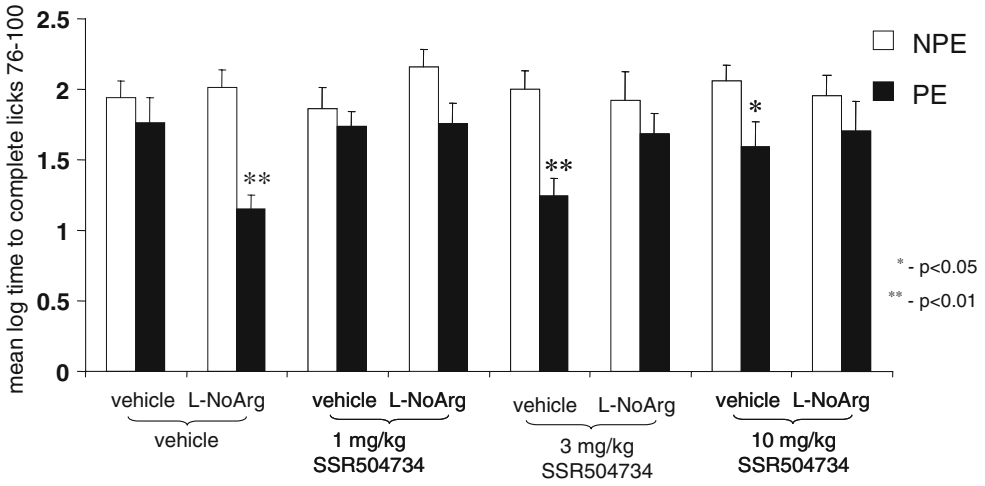

Fig. 4 The effects of SSR504734 on L-NoArg-induced abnormally persistent LI. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (*PE*) and non-preexposed (*NPE*) rats neonatally treated with L-NoArg or vehicle, injected with SSR504734 in doses of either 1, 3, or 10 mg/kg or vehicle (all drugs administered i.p.). Forty preexposures and five conditioning trials were used. SSR504734 was administered in the preexposure and conditioning stages. *Asterisks* indicate a significant difference between the PE and NPE groups, namely, presence of LI

main effect of preexposure [$F(1,106)=30.20$, $p<0.0001$] and a significant preexposure×neonatal treatment×adult treatment interaction [$F(3,106)=3.14$, $p=0.028$]. Post hoc comparisons revealed a significant difference between the preexposed and non-preexposed groups in neonatal L-NoArg rats injected with vehicle ($p<0.001$) and in neonatal vehicle rats injected with 3 mg/kg ($p<0.0006$) and 10 mg/kg ($p<0.03$) SSR504734, but not in the other conditions ($p>0.05$).

Discussion

The main aim of these studies was to profile the novel GlyT1 inhibitors, SSR103800 and SSR504734, in acute psychostimulant and neurodevelopmental models of LI. The approach taken was to test the compounds in the LI model for efficacious effects alone (LI potentiation) and following three manipulations. Two of the manipulations were pharmacological-based. The first manipulation used the indirect dopamine agonist, amphetamine, to disrupt LI, an effect reversed by both typical and atypical antipsychotic drugs (positive symptom model), and the second manipulation used the noncompetitive NMDA receptor antagonist, MK-801, to induce abnormally persistent LI, an effect reversed by atypical but not typical antipsychotics and glycinergic agents (cognitive/negative symptom model). The final manipulation was neurodevelopmental in nature in that the NOS inhibitor, L-NoArg, was administered postnatally to rat pups, resulting in abnormally persistent LI during adulthood, an effect sensitive to atypical but not typical antipsychotics and procognitive agents (Weiner et al., unpublished observations)—a neurodevelopmental cognitive/negative symptom model.

In these studies, SSR103800 reversed amphetamine-induced LI disruption, a model thought to reflect increased salience and distractibility that is associated with psychotic symptoms (Weiner 1990, 2003; Weiner and Feldon 1997; Moser et al. 2000). These data are concordant with previously published reports on GlyT1 inhibition and tests predictive of activity in positive symptoms. For example, PCP- and amphetamine-induced hyperactivity are reversed by the GlyT1 inhibitors NFPS and ORG 24461 (Harsing et al. 2003). Also, Depoortere et al. (2005) noted that SSR504734 was able to reverse spontaneous PPI deficits, amphetamine-induced locomotor activity, and ketamine-induced 2-deoxy-glucose changes. Additionally, these studies demonstrated that GlyT1 inhibitors potentiated LI under conditions where LI was not present in no-drug controls, another behavioral effect in the LI model that is considered predictive for positive symptoms of schizophrenia (Weiner 1990, 2003; Gray et al. 1991; Moser et al. 2000). Overall, GlyT1 inhibitors produce antipsychotic-like effects in LI models associated to the positive symptoms of schizophrenia, although given that only one dose was active in the amphetamine model, this effect should be further investigated.

Abnormally persistent LI, induced by MK-801, was reversed by both SSR103800 and SSR504734. This model is thought to reflect impaired set shifting that is associated with cognitive inflexibility and negative symptoms (Weiner 2003). These findings are in agreement with Gaisler-Solomon et al. (2008), who showed that MK-801-induced persistent LI in rats was reversed by glycine and D-

cycloserine and the GlyT1 inhibitor GDA, and Lipina et al. (2005) who demonstrated that D-serine and ALX 5407 reversed MK-801-induced abnormally persistent LI in the mouse. It should also been noted that SSR504734 attenuates PCP-induced deficits in social novelty discrimination and selective attention (Depoortere et al. 2005; Harich et al. 2007). Such models are regarded as predictive of activity in the cognitive domains of schizophrenia, and, as such, GlyT1 inhibitors may have the potential to improve cognition deficits associated with schizophrenia. Again, these data are concordant with the previously published reports on SSR103800 and SSR504734 to have potential activity versus cognitive and negative aspects of schizophrenia (Depoortere et al. 2005; Boulay et al. 2008).

It is worth noting in this context that while reversal of amphetamine- and NMDA antagonist-induced behavioral abnormalities is widely accepted as indexing efficacy against positive and negative/cognitive symptoms, respectively, the LI model offers an important advantage in terms of differentiating between drugs that are active in the two models. Since the DA agonist and the NMDA antagonist LI models are differentiated not only by the class of the propsychotic agent used to produce the behavioral abnormalities but also by their behavioral manifestation (disrupted vs. persistent LI), treatments effective in the two models must produce different and in fact opposite actions on the LI phenomenon. Thus, drugs effective in the amphetamine model, like in the potentiation model, *restore* disrupted LI, and the same applies to the weak LI model, whereas drugs effective in the MK-801 model *disrupt* LI. This implies that efficacy in both models requires the targeting of distinct cognitive and neurochemical/neural mechanisms.

In terms of psychological processes underlying LI, it is believed that during preexposure, the acquisition of an association between the preexposed stimulus and the absence of a significant consequence downgrades the salience, or the significance of the stimulus, which impairs the acquisition of the stimulus–reinforcement association in conditioning (Lubow et al. 1981; Mackintosh 1975) or on more recent accounts, inhibits the expression of the conditioned response resulting from stimulus–reinforcement association acquired during conditioning (Bouton 1993; Gray et al. 1995; Lubow 2005; Weiner 1990, 2003). Thus, LI is the result of animals remaining, during conditioning, under the behavioral control of the information acquired in preexposure (stimulus–no event relationship). Since enhanced dopaminergic stimulation increases stimulus salience and promotes behavioral and cognitive switching (Ikemoto and Panksepp 1999; Kapur et al. 2006; Swerdlow and Koob 1987; Weiner and Joel 2002), amphetamine is believed to abolish LI by favoring switching to respond according to the stimulus–reinforcement contingency and processing the irrelevant stimulus as if it were novel. In contrast to amphetamine, NMDA receptor blockade is known to induce behavioral and cognitive inflexibility, and specifically, impair the capacity to switch between behaviors 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). Therefore, NMDA antagonists are believed to produce abnormally persistent LI by impairing the switching to respond according to the stimulus–reinforcement contingency and perseverating in ignoring the preexposed stimulus under conditions (e.g., strong conditioning) that normally override the inhibitory influence of preexposure (Weiner 1990, 2003).

Thus, amphetamine and MK-801 produce opposite poles of impairment in attentional selectivity: Amphetamine impairs the capacity to in-attend to irrelevant stimuli, whereas MK801 impairs the capacity to re-attend to irrelevant stimuli when they become relevant through pairings with reinforcement, akin to Emil Kraepelin's (1919) distinction between two poles of attentional impairment in schizophrenia patients—inability to fix attention on the one hand and rigidity of attention on the other hand. GlyT1 inhibitors tested here normalized both impairments: They 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. While the specific processes suggested here are at present highly speculative, the former would be beneficial in normalizing superfluous significance of stimuli associated with positive symptoms/psychosis, whereas the latter would be beneficial in the treatment of negative symptoms, which are characterized by inattention and inflexibility (Crider 1997; Morice 1990).

However, in the domain of schizophrenia drug discovery, there are fears that simple reversal of an acute psychomimetic challenge may not be infallible, and, additionally, the most frequent reason for attrition in clinical trials is lack of efficacy (Kola and Landis 2004). These acute models of schizophrenia (amphetamine- or PCP-induced disrupted locomotor activity, PPI, LI, etc.) are focused on phenomena linked to dopamine and/or glutamate as both neurotransmitters are strongly implicated in this disorder. It has become clear, however, that such models, while still having high value in the drug discovery chain, need to be supplemented by new strategies. One such strategy is to deploy neurodevelopmental models of schizophrenia because these models are believed to more closely mimic the widespread disruption of cortico–limbic–mesolimbic circuitries implicated in the pathophysiology of schizophrenia.

Using one such model based on postnatal manipulation of the NO system, we showed that GlyT1 inhibition

reverses neurodevelopmentally induced abnormally persistent LI. Such activity therefore strengthens the case for GlyT1 inhibition as a potentially effective treatment for many aspects of schizophrenia. The neurodevelopmental model requires no psychomimetic challenge; therefore, demonstrating activity in a neurodevelopmental model suggests that the GlyT1 mechanism may be effective at the neuronal level rather than just interfering with psychomimetic activity. SSR504734 had been shown to reverse amphetamine-induced hyperactivity (Depoortere et al. 2005) and impairment of social novelty discrimination (SND) in rats neonatally treated with PCP (Depoortere et al. 2005; Harich et al. 2007). Additionally, glycine and the GlyT1 inhibitor, ORG24461, were found to reverse PPI deficits and amphetamine-induced hyperactivity in rats that had undergone neonatal ventral hippocampal lesions (Kato et al 2001; Le Pen et al. 2003). While most of these models are considered of positive symptoms, it is interesting that impaired social novelty discrimination bears similarity to persistent LI. In the SND, normal rats exposed to familiar and then novel juvenile ignore the familiar and switch to investigate the novel juvenile, but neonatal PCP-treated rats perseverate in exploring the familiar (preexposed) rat. Also, in this task, SSR504734 restored attentional flexibility in the sense that neonatal PCP rats switched to investigate the novel juvenile. Reversal of neurodevelopmentally induced loss of social novelty and persistent LI can be thus both seen as demonstrations of SSR504734 efficacy against negative/cognitive symptoms in neurodevelopmental models.

There are a number of "neurodevelopmental models of schizophrenia" described in the literature, ranging from neonatal brain lesions to gestational immune activation. We do not purport that the NOS inhibition model used here, or any other neurodevelopmental model, are better than another, including the pharmacological models. However, when one combines data from acute tests predictive for antipsychotic activity with a neurodevelopmental model that may capture certain attributes of schizophrenia, the case for such a mechanism becomes stronger.

In concordance with previous published reports on GlyT1 inhibitors, we show that SSR103800 and SSR504734 were able to attenuate hypoglutamatergic states (MK-801) and hyperdopaminergic (amphetamine) states. Hypoactivity in the prefrontal cortex has long been established as a pivotal dysfunction underlying the expression of cognitive and negative aspects of schizophrenia (Goldman-Rakic and Selemon 1997). The activity of SSR103800 and SSR504734 in the hypoglutamatergic models is most likely a consequence of its capacity to increase glutamatergic tone in areas such as the prefrontal cortex and thus directly attenuate the effects of an NMDA antagonist. One could speculate that the prefrontal cortex of those animals in the neurodevelopmental model here described was underactive, and the drugs thus were able to raise the developmentally induced hypoglutamatergic state. An increase of glutamate neurotransmission in the PFC could also underlie reversal of amphetamine-induced disruption and potentiation of LI since such increase inhibits DA release in the NAC (Jackson and Moghaddam 2001). The capacity of SSR103800 and SSR504734 to increase dopamine levels in the prefrontal cortex (Depoortere et al. 2005; Boulay et al. 2008) may also explain their activity in the hyperdopaminergic models. Impaired dopamine transmission in the prefrontal cortex may lead to hyperfunctioning in subcortical areas and potentially lead to the expression of positive symptoms of schizophrenia (Grace 1991). It is speculated that increased levels of dopamine in the prefrontal cortex elicited by GlyT1 inhibitors helps attenuate the amphetamine-mediated increase is subcortical dopamine tone and thus reverse the behavioral effects of amphetamine (Depoortere et al. 2005). Another mechanism of SSR504734 underlying activity in hyperdopaminergic models may stem from its capacity to enhance striatal NMDA-mediated function (Depoortere et al. 2005) since such potentiation would be expected (via NMDA-stimulated GABA release) to lead to inhibition of striatal DA release, an effect that would be expected to counteract amphetamine effects (and be therapeutically beneficial in schizophrenia; Javitt 2004; Javitt et al. 2005).

In summary, using the latent inhibition paradigm as readout, GlyT1 inhibitors appear to be effective in models of positive, negative, and cognitive symptoms of schizophrenia. In addition to activity in acute pharmacological LI models, GlyT1 inhibitors were also efficacious in a neurodevelopmental model of schizophrenia based on postnatal NOS inhibition. While it is true that the only definitive test of drug (or mechanism) efficacy is in a clinical trial, the combined preclinical evidence for the GlyT1 mechanism strongly suggests that this could be an effective antipsychotic therapy.

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