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ORIGINAL INVESTIGATION

Enhancement of social novelty discrimination by positive allosteric modulators at metabotropic glutamate 5 receptors: adolescent administration prevents adult-onset deficits induced by neonatal treatment with phencyclidine

Nicholas E. Clifton · Nadège Morisot · Sylvie Girardon · Mark J. Millan · Florence Loiseau

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Abstract Metabotropic glutamate-5 receptors (mGluR5), which physically and functionally interact with *N*-methyl-D-Aspartate (NMDA) receptors, likewise control cognitive processes and have been proposed as targets for novel classes of antipsychotic agent. Since social cognition is impaired in schizophrenia and disrupted by NMDA receptor antagonists like dizocilpine, we evaluated its potential modulation by mGluR5. Acute administration (0.63–40 mg/kg) of the mGluR5 positive allosteric modulators (PAMs), 3-cyano-*N*-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) and ADX47273, reversed a delay-induced impairment in social novelty discrimination (SND) in adult rats. The action of CDPPB was blocked by the mGluR5 antagonist, 2-methyl-6-(phenylethynyl)-pyridine (2.5–10 mg/kg), and was also expressed upon microinjection into frontal cortex (0.63–10 μg/side), but not striatum. Supporting an interrelationship between mGluR5 and NMDA receptors, enhancement of SND by CDPPB was blocked by dizocilpine (0.08 mg/kg) while, reciprocally, dizocilpine-induced impairment in SND was attenuated by CDPPB (10 mg/kg). The SND deficit elicited by post-natal administration of phencyclidine (10 mg/kg, days 7–11) was reversed by CDPPB or ADX47273 in adults at week 8. This phencyclidine-induced impairment in cognition emerged in adult rats from week 7 on, and chronic, *pre-symptomatic* treatment of adolescent rats with CDPPB over weeks 5–6 (10 mg/kg per day) *prevented* the appearance of SND deficits in adults until at least week 13. In conclusion, as evaluated by a SND procedure, mGluR5 PAMs promote social cognition via actions expressed in interaction with NMDA receptors and exerted in frontal cortex. MGluR5 PAMs not only reverse but also (when given during adolescence) prevent the emergence of cognitive impairment associated with a developmental model of schizophrenia.

Keywords Metabotropic glutamate mGlu5 receptor · NMDA receptor · Social novelty discrimination · Adolescence · Development

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Introduction

Glutamate, the major excitatory neurotransmitter in the central nervous system, influences a broad range of functional domains, including cognition, mood and motor behaviour, via two families of receptor: ionotropic, comprised of NMDA, kainate and AMPA ligand-gated ion channels, and metabotropic G-protein-coupled receptors (mGluR). Eight classes of mGluR have been cloned to date, which are separated into three clusters based on sequence, ligand recognition and coupling characteristics: group I (mGlu1 and 5) receptors are positively coupled to inositol phosphate, whereas groups II (mGlu2 and 3) and III (mGlu4, 6, 7 and 8) receptors are negatively coupled to adenylate cyclase (Nicoletti et al. 2010; Niswender and Conn 2010).

Together with Group II mGluR2/3, group I mGlu5 receptors have attracted particular interest as targets for the treatment of psychiatric and neurological disorders (Cleva and Olive 2011; Lea and Faden 2003). Moreover, both possess well-defined allosteric sites amplifying chemical scope for

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the discovery of small molecules permitting their selective modulation. The potential role of mGlu5 receptors in the control of cognition has received particular interest in view of their concentration in frontal cortex (FCX), striatum and hippocampus (Manahan-Vaughan and Braunewell 2005; Simonyi et al. 2010). Accordingly, agonists and/or or positive allosteric modulators (PAMs) at mGlu5 receptors are active in a broad range of cognitive procedures encompassing measures of visual, spatial, working and/or declarative memory, as well as cognitive flexibility and inhibitory avoidance (Ayala et al. 2009; Balschun et al. 2006; Darrah et al. 2008; Stefani and Moghaddam 2010; Uslaner et al. 2009). Conversely, mGlu5 receptor antagonists like 2-methyl-6-(phenylethynyl)-pyridine (MPEP) impair working and spatial memory (Christoffersen et al. 2008; Homayoun et al. 2004), while mGluR5 knockout mice were reported to show deficits in sensorimotor gating and in a paradigm of hippocampus-dependent learning, the Morris Water Maze task (Brody et al. 2004; Lu et al. 1997).

Interestingly, there is evidence that the mGluR5 are both physically (via intracellular scaffolding proteins) and functionally (via protein kinase C mediated phosphorylation) linked with NMDA receptors, which are likewise involved in cognitive processes (Alagarsamy et al. 2005; Bertaso et al. 2010; Niswender and Conn 2010). Accordingly, activation of mGluR5 potentiates NMDA receptor evoked currents (Awad et al. 2000; Chen et al. 2011), and their recruitment is an attractive strategy for countering the hypoactivity of FCX-localised NMDA receptors implicated in schizophrenia (Javitt 2010). In line with this possibility, agonists and PAMs at mGluR5 have been reported to block the cognitive impairment induced by NMDA receptor antagonists in the novel object recognition test and certain other cognitive procedures (Fowler et al. 2010; Stefani and Moghaddam 2010; Uslaner et al. 2009; Millan et al. 2012). Indicative of the more general significance of such interactions to schizophrenia, mGlu5 receptor stimulation blunts the hyperlocomotion, stereotypy, impaired conditioned avoidance responses and decreased sucrose preference induced by MK-801 (Chan et al. 2008; Kinney et al. 2003, 2005; Liu et al. 2008; Rosenbrock et al. 2010; Schlumberger et al. 2010; Vardigan et al. 2010).

Despite these encouraging observations, no study has as yet investigated the effects of mGlu5 receptor recruitment on cognitive deficits associated with developmental models of schizophrenia. In this regard, social cognition is of particular relevance since (1) it represents a core cognitive domain impacted in schizophrenia as recognised by the MATRICS initiative; (2) impaired social cognition is related to social withdrawal, a cardinal feature of negative symptoms, as well as delusions (false attributions) an archetypal component of positive symptoms (Derntl and Habel 2011; Lincoln et al. 2011); and (3), the influence of mGlu5 receptor ligands in models of social cognition in rodents has not yet been documented. Amongst several interrelated and well-validated procedures (Ferguson et al. 2002), social cognition can be explored in rodents by use of the social novelty discrimination test (SND), which measures the ability of rats to discriminate novel versus familiar conspecifics. Notably, deficits in SND can be induced not only by parametric manipulation (delay) but also by acute blockade of NMDA receptors and by disruption of NMDA neurotransmission in neonatal rodents, a developmental model of schizophrenia (Harich et al. 2007; Pichat et al. 2007; Terranova et al. 2005).

Thus, post-natal administration to rats of phencyclidine (PCP), a non-competitive antagonist (channel blocker) at NMDA receptors, during the first two post-natal weeks disrupts neuronal development and synaptogenesis by, for example, triggering apoptotic neurodegeneration of frontocortical neurones (Fredriksson et al. 2004; Monti and Contestabile 2000). This is associated with the delayed appearance in adults of a spectrum of behavioural schizophrenia-like impairments such as hyperactivity, reduced sensory gating and cognitive deficits, including a robust perturbation of SND (Harich et al. 2007; Mouri et al. 2007; Pichat et al. 2007; Terranova et al. 2005). The relevance of this developmental model of schizophrenia is underpinned by the fact that this neonatal period in rats corresponds to the second trimester of pregnancy in humans during which exposure to environmental insults increases the probability of schizophrenia later in life (Clancy et al. 2001).

In light of the above observations, the present study evaluated the potential influence of PAMs at mGlu5 receptors upon the following: *first*, delay-induced deficits in SND in adult rats; *second*, the potential role of the FCX in the expression of their actions; *third*, the interrelationship of mGluR5 to NMDA receptors in the control of SND; *fourth*, the deficit in SND seen in adult rats induced by neonatal exposure to PCP; and, *finally*, the potential preventive effect of chronic treatment by a mGluR5 PAM during adolescence upon the subsequent development of impaired SND in adult animals.

Methods

Subjects

Animals were male Wistar rats from Janvier (Le Genest-Saint-Isle, France). Upon arrival, adults were 240–260 g, juveniles were 21 days old and pups were 3 days old and with their mother. All rats were housed in sawdust-lined cages with food (chow) and water access ad libitum, with a 12-h light (70 lx)/12 h dark cycle and constant room temperature (21±1 °C) and humidity (60±5 %). Experiments were assessed during the light phase of the cycle. Animals were left to acclimatise for at least 4 days following arrival, and adults were isolated in individual cages 2 days before testing. The procedures to be described conform to European (86/609-EEC) and French (87/848) decrees for

the care and use of laboratory animals and have received approval from the internal ethics committees of Servier.

Social novelty discrimination procedure

SND experiments compared the social investigation times of an adult rat with a familiar and a novel juvenile rat. The procedure is replicated from previous studies (Engelmann et al. 1995; Harich et al. 2007; Pichat et al. 2007; Terranova et al. 2005). Testing consisted of two consecutive juvenile presentation periods to an adult subject: period 1 (P1) and period 2 (P2). At the beginning of P1, one juvenile was placed into the adult home cage and the time spent by the adult investigating the juvenile (anogenital sniffing, licking, close pursuing and pawing; Engelmann et al. 1995) was recorded manually for 5 min. During P2, the same juvenile and a second, novel juvenile from a different litter were placed in the cage together with the adult, and the times spent by the adult investigating each juvenile were measured independently for 5 min. A different pair of juvenile rats was presented to each adult tested. Manual scoring was conducted by an experimenter blinded to the subject treatment and to which juvenile rat was familiar versus novel. The procedure was split into two distinct protocols, defined by the nature of the cognitive deficit induced: a *parametric deficit* protocol, in which SND was weakened by a time delay, and a *pharmacological deficit* protocol, in which SND was impaired by pharmacological intervention (Terranova et al. 2005). In the *parametric deficit* protocol, P1 was 5 min in length and there was a 30 min delay between P1 and P2, for which time the adult was alone. 3-Cyano-*N*-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB; 0.16–40 mg/kg, IP), ADX47273 (0.16–10 mg/kg, IP) or vehicle was injected 30 min before P1. In interaction experiments of this protocol, MK801 (0.08 mg/kg, SC), MPEP (2.5 or 10 mg/kg, IP) or vehicle was injected 45 min before P1. In the *pharmacological deficit* protocol, P1 was 30 min, and there was no delay between P1 and P2. In these conditions, SND is expected to be high in control (vehicle-injected) rats, and to be disrupted by MK801 (0.08 mg/kg, SC) administered 30 min before P1. CDPPB (10 mg/kg) or vehicle was injected 15 min before MK801 or vehicle.

Neonatal PCP treatment model

Rats of the neonatal PCP model were received at 3 days of age, grouped as 10 male pups per adult mother. PCP (10 mg/kg, SC) or vehicle administration was on post-natal days (PND) 7, 9 and 11, separated by strict 48-h intervals. Half of the pups were injected with PCP and half with vehicle. All pups of the same litter received the same treatment. The rats were weaned from their mother at PND 21, at which time they were marked, separated at random and housed in mixed-litter groups of four. At PND 28, all animals received subcutaneously implanted electronic chips (Biolog-ID, Bernay, France) whilst under isoflurane anaesthesia. Social novelty discrimination tests followed the *pharmacological deficit* protocol: P1 was 30 min, and there was no delay between P1 and P2. Investigation times were measured manually for the first 5 min of each presentation period. During these tests, the experimenter was blind to the neonatal treatment of each rat. In an acute social novelty discrimination study, adult rats of 8–10 weeks, treated neonatally with PCP or vehicle, were administered with CDPPB (0.63–10 mg/kg, IP), ADX47273 (0.16–2.5 mg/kg, IP) or vehicle 30 min before P1. In a longitudinal study, no drugs were administered other than neonatal PCP or vehicle. Rats were then tested for social novelty discrimination at ages 4, 5, 6, 7 and 8 weeks to examine the age-dependent effects of neonatal PCP. All subjects were tested with a new juvenile pair on each week. A further neonatal PCP study featured chronic treatment with CDPPB (10 mg/kg per day) or vehicle on each of 12 days over either weeks5 and 6 [PND 35–46=adolescence (Piontkewitz et al. 2009); exp 1] or weeks10 and 11 (PND 70–81; exp 2; Fig. 1). All animals were tested at 8 and 13 weeks of age.

Microinjection studies

Cannulae were fitted 1 week before social novelty discrimination tests to allow for microinfusion into the frontal cortex (FCX) or the striatum (Fig. 2). The procedure was

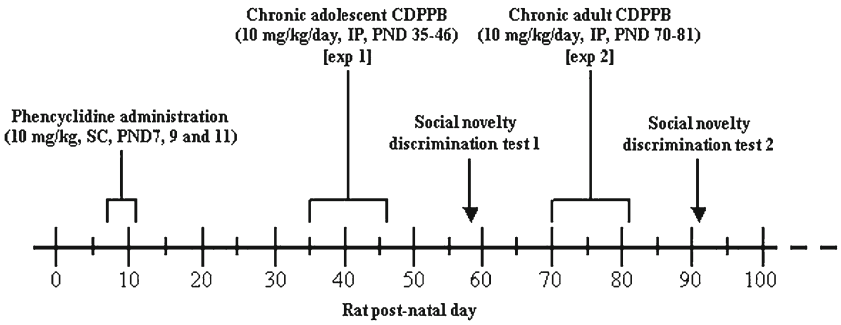

Fig. 1 Treatment and test procedure for longitudinal tests of the neonatal PCP model. Chronic treatment was either over adolescence (*exp 1*) or adulthood (*exp 2*)

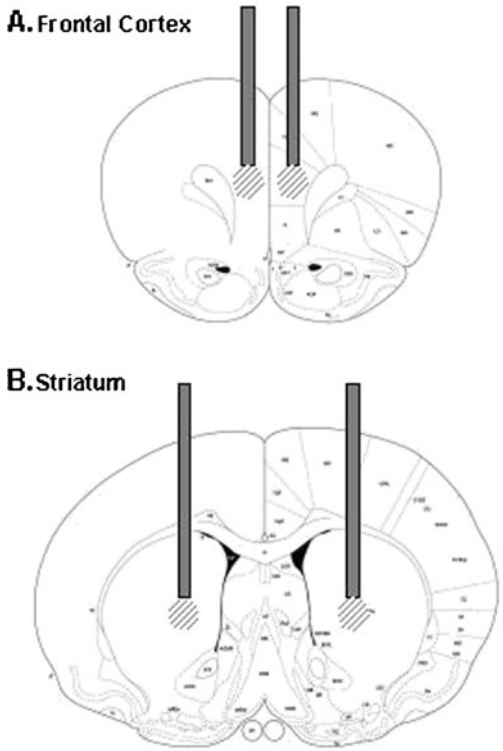

Fig. 2 Schematic illustration of the sites of bilateral microinjection into the frontal cortex and striatum. The *crosshatched area* represents the theoretical site of microinjection at the coordinates indicated in "Methods"

adapted from Chudasama and Robbins (2004). Rats were anaesthetised with chloral hydrate (400 mg/kg, IP, in a volume of 10 ml/kg) and positioned in a stereotaxic frame (David Kopf Instruments, Phymep, Paris) for surgery. The skull was exposed and craniotomies were made above the target region of the brain. A bilateral stainless steel guide cannula, consisting of two 22-gauge metal tubes [inner diameter, 0.39 mm; length, 3 mm (FCX) or 5 mm (striatum); distance apart, 1.5 mm (FCX) or 5 mm (striatum); Plastics One, USA], was lowered through the craniotomies at the following coordinates from bregma: FCX: AP of +3.0, L of ±0.7, DV of −2.3; striatum: AP of +0.5, L of ±2.5, DV of −4.0 (Paxinos and Watson 1997). It was fixed with dental cement and stainless steel screws, and dummy stylets (Plastics One, Phymep, Paris, France) were fitted inside the guide cannula to prevent occlusion. On the day of the test, dummy stylets were replaced with 28-gauge (inner diameter, 0.18 mm; Plastics One, Phymep, Paris, France) stainless steel injectors, which extended 1.0 mm beyond the guide cannula. These were connected, via tubing (inner diameter, 0.12 mm; Plastics One, USA), to two 10-μl precision syringes (Hamilton, Phymep, Paris, France) positioned in an infusion pump (Harvard Apparatus, Holliston, MA, USA). Solutions were infused bilaterally at 0.5 μl/min for 2 min, 10 min before P1. A further 2-min delay was respected before removing the injectors to allow for diffusion. Following the completion of behavioural testing, brains were removed, frozen and sectioned for verification of microinfusion cannulae placement.

Statistics

The P2 novel and familiar juvenile investigation times were used to provide a discrimination ratio (time spent investigating novel juvenile/time spent investigating familiar juvenile). For experiments involving only one variable, i.e. non-interaction tests, and with only two groups, the discrimination ratios were analysed by a Mann–Whitney test. Experiments with one variable and more than two groups were analysed by a Kruskal–Wallis test, and significant results were further analysed by a Holm-corrected Mann–Whitney multiple comparison test. For experiments with two or more variables, the results were analysed by two-way rank interaction analysis, followed by post hoc Dunnett's test. Total investigation times during P1 and during P2 were compared using a one-way analysis of variance, followed by Dunnett's test.

Drugs

All stock solutions were made up on the day of use and injected at volumes of 1 ml/kg, with the exception of PCP administration to rat pups, which was injected at volumes of 10 ml/kg. CDPPB (Lindsley et al. 2004) and MPEP were bought from Tocris (Cookson, Bristol, UK) and (*S*)-(4-fluorophenyl)-3-[3-(4-fluoro-phenyl)-[1,2,4]-oxidiazol-5-yl] piperidon-1-yl)methanone (ADX47273; Liu et al. 2008) was bought from Orphachem (Saint-Beauzire, France). CDPPB, MPEP and ADX47273 were each suspended in distilled water plus Tween 80 and injected IP. For microinjection studies, CDPPB was completely dissolved in a vehicle consisting of Ringer's solution [NaCl (147.2 mM), KCl (4 mM) and CaCl2 (2.3 mM) buffered with phosphate at pH7.3] plus 10 % dimethyl sulfoxyde (Riedel-de Haën, Germany). Dizocilpine maleate (MK801) was bought from Sigma Chemie, France, dissolved in a saline solution and injected SC. On PND 7, 9 and 11, pups of the neonatal PCP model were injected SC with 10 mg/kg PCP, from Sigma, dissolved in saline.

Results

Effect of mGlu5 receptor PAMs on social novelty discrimination in the parametric deficit protocol

Following a 30 min delay from P1, subjects administered with vehicle spent an equal time investigating the familiar and novel juvenile during P2, giving a novel/familiar discrimination ratio of close to 1.0, which represents a failure to socially discriminate (Fig. 3 and Table 1). CDPPB and ADX47273 modified the discrimination ratio ($P<0.001$ and $P<0.05$, respectively) with

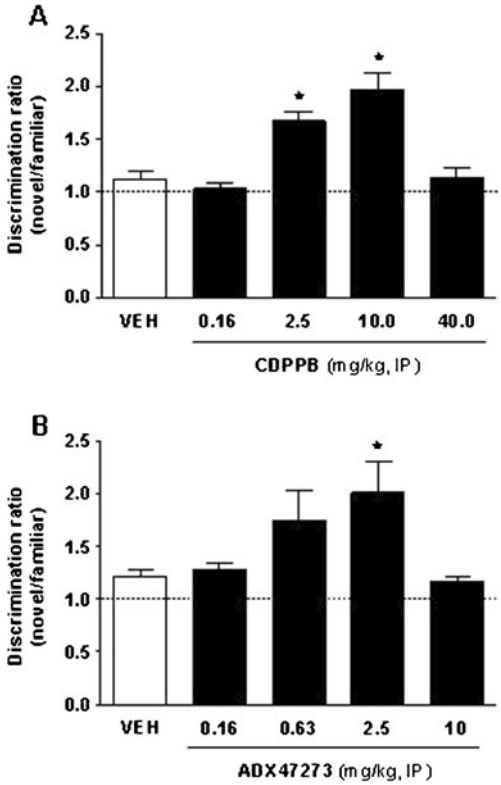

Fig. 3 MGluR5 PAMs, CDPPB, and ADX47273, enhance social novelty discrimination in a *parametric deficit* (30 min delay) protocol. Bars represent mean±SEM of discrimination ratio (P2 time spent investigating novel juvenile/time spent investigating familiar juvenile). N=5–13. CDPPB (**a** 0.16–40 mg/kg), ADX47273 (**b** 0.16–10 mg/kg) or vehicle was administered IP, 30 min before P1. *Stars* represent significance of drug effect vs. vehicle (*VEH*) in post hoc test, following Kruskal–Wallis test (P<0.05)

an inverted U dose–response relationship. Drugs demonstrated a significant increase from vehicle at 2.5 and 10 mg/kg (P<0.05 and P<0.001, respectively) for CDPPB or 2.5 mg/kg (P<0.05) for ADX47273. Except CDPPB at 0.16 mg/kg, which caused a significant decrease in total P2 investigation time (P<0.05), there were no other significant differences in total investigation times during P1 and P2.

Brain region-specific effects of CDPPB on social novelty discrimination

Similarly to that shown by IP administration, microinfusion of CDPPB into the frontal cortex dose dependently modified the discrimination ratio (P<0.01), with a significant change from control at 2.5 μg/side (P<0.01) (Fig. 4 and Table 1). The same dose of CDPPB administered to the striatum did not significantly modify the discrimination ratio. No dose of CDPPB to either brain region induced a significant change in total investigation times during P1 or P2.

Effects of antagonists MPEP and MK801 on social novelty discrimination enhancement

Two-way rank interaction analysis showed a significant interaction between CDPPB and MPEP (P<0.05). As previously shown, CDPPB significantly enhanced the discrimination ratio (P<0.001) (Figs. 5 and 6 and Table 1). This enhancement was dose dependently reversed by MPEP (2.5 mg/kg, P<0.05 and 10 mg/kg, P<0.001). Similarly, a significant interaction was found between CDPPB and the NMDA antagonist MK801 (P<0.001), and CDPPB treatment significantly enhanced the discrimination ratio (P< 0.001). MK801 (0.08 mg/kg) completely reversed the improvement of social discrimination (P<0.001). There was no significant change in total investigation times during P1 and P2, which demonstrates an absence of influence by nonspecific effects upon the changes found.

Effect of CDPPB on social novelty discrimination impairment by MK801 in the pharmacological deficit protocol

Following an extended P1 period of 30 min and no delay between P1 and P2, subjects administered with vehicle spent significantly more time investigating the novel juvenile than the familiar juvenile (P<0.001), giving a high novel/familiar discrimination ratio (>4), which represents a relatively good ability to socially discriminate (Fig. 7 and Table 2a). MK801 administration dose dependently decreased the discrimination ratio (P<0.05), with a significant change from vehicle at 0.08 mg/kg (P<0.05), as shown by post hoc test. In a following experiment, the same effect was found of MK801. Co-administration with CDPPB, 15 min before, showed a significant two-way interaction (P<0.01). The reduction of the discrimination ratio by MK801 (P<0.001) was significantly reversed by CDPPB (10 mg/kg; P<0.05). Total P2 investigation time of the vehicle/MK801 interaction group differed significantly from that of the vehicle/vehicle group (P<0.05). There were no other significant differences in total investigation times during the first 5 min of P1 and P2 for either experiment.

Effect of acute mGlu5 receptor PAMs on social novelty discrimination in the neonatal PCP model of schizophrenia

Rats administered with 10 mg/kg PCP on PND 7, 9 and 11 showed reduced novel/familiar discrimination ratios, compared to those of rats administered with vehicle at the same age. Two-way rank interaction analysis of CDPPB vs. PCP and ADX47273 vs. PCP revealed a significant interaction between each pair of treatments (P<0.01, CDPPB; P<0.05, ADX47273) (Fig. 8 and Table 2b). Neonatal PCP treatment significantly reduced the discrimination ratio from control in the two experiments (P<0.001 and P<0.01, respectively),

Table 1 Effects of drugs on interaction time (s) during P1 (5 min) and P2 (5 min) in the social novelty discrimination test

Drugs/dose (mg/kg)		*N*	Total interaction time	
			P1 (s)	P2 (s)
Effects of mGluR5 PAMs, CDPPB and ADX47273 on social novelty discrimination in the parametric deficit (30 min delay) protocol[a]				
CDPPB	0	13	113.1±6.4	106.9±10.4
	0.16	5	99.9±4.2	56.6±6.8 *
	2.5	9	118.5±9.3	90.0±11.7
	10	13	119.8±5.9	103.6±11.8
	40	5	126.3±21.7	143.7±25.7
ADX47273	0	10	130.4±4.1	132.9±9.4
	0.16	7	128.5±7.0	143.3±12.6
	0.63	7	118.8±6.8	129.5±14.8
	2.5	8	121.3±7.1	138.5±4.4
	10	5	131.6±9.1	168.9±13.1
	40	5	129.9±12.1	149.1±5.5
Effects of CDPPB on novelty discrimination following microinjection into the frontal cortex or striatum in the parametric deficit protocol[b]				
CDPPB	0	5	142.8±14.6	135.6±6.0
Frontal cortex	0.63	5	123.6±13.6	105.1±19.7
	2.5	5	132.4±16.1	131.8±16.1
	10	5	120.6±9.3	128.8±19.9
CDPPB	0	7	135.5±11.4	124.8±10.3
Striatum	2.5	7	129.9±9.3	116.2±10.8
Effects of mGluR5 antagonist, MPEP and NMDA receptor antagonist, MK801, on novelty discrimination enhancement by CDPPB, in the parametric deficit protocol[c]				
CDPPB	MPEP			
0	0	9	130.8±6.1	146.7±9.5
0	2.5	6	130.6±16.7	160.9±6.7
0	10	3	127.1±16.3	144.5±6.4
10	0	9	133.5±3.5	138.2±4.6
10	2.5	6	122.8±13.7	135.1±7.3
10	10	3	123.6±4.6	111.0±12.7
CDPPB	MK801			
0	0	6	124.1±3.7	146.9±8.1
0	0.08	6	105.8±8.8	127.9±21.5
10	0	6	128.3±8.7	157.4±7.0
10	0.08	6	127.1±12.3	140.0±14.0

Data expressed as mean±SEM

*$P<0.05$ vs. vehicle group in Dunnett's test following one-way ANOVA

[a] See legend to Fig. 3.

[b] See legend to Fig. 4

[c] See legends to Figs. 5 and 6

representing an impairment of social discrimination. Both CDPPB and ADX47273 dose dependently reversed this impairment ($P<0.05$), with a significant change in discrimination ratio at 10 mg/kg (CDPPB; $P<0.01$) or 2.5 mg/kg (ADX47273; $P<0.01$), in post hoc tests. There was no significant independent effect of either drug. For all treatment groups, no significant change from control in total investigation times during P1 and P2 was observed.

Effect of age on the presence of a neonatal PCP-induced social novelty discrimination deficit

Following neonatal PCP administration, rats of 4, 5 and 6 weeks of age showed discrimination ratios analogous to those of control when P1 was 30 min, and there was no delay between P1 and P2 (Table 3). At 7 and 8 weeks of age, the same neonatal PCP-treated rats revealed decreased

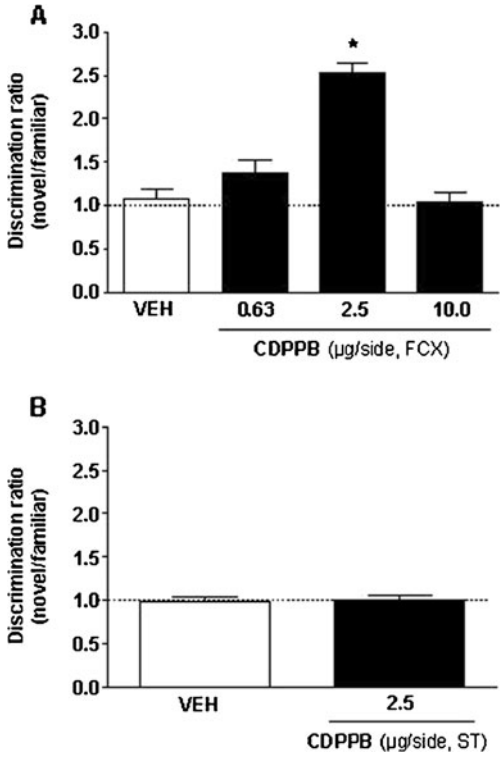

Fig. 4 Differential effects of CDPPB on novelty discrimination following microinjection into the frontal cortex or striatum, in the *parametric deficit* protocol. Bars represent mean±SEM of discrimination ratio (P2 time spent investigating novel juvenile/time spent investigating familiar juvenile). *N*=5 or 7 per group. CDPPB (**a** 0.63–10 µg/side, frontal cortex or **b** 2.5 µg/side, striatum) or vehicle was infused bilaterally at 0.5 µl/min for 2 min, 10 min before P1. *Black star* represents significance of drug effect vs. vehicle (*VEH*) in post hoc test, following Kruskal–Wallis test ($P<0.01$)

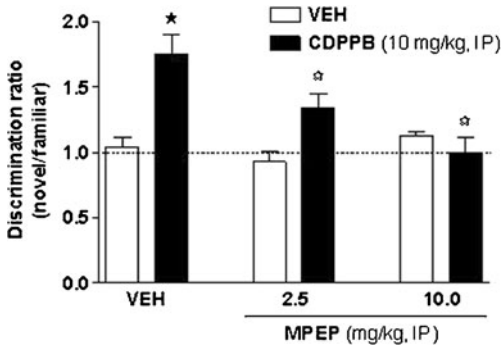

Fig. 5 MGlu5 receptor antagonist, MPEP, blocks novelty discrimination enhancement by CDPPB, in the *parametric deficit* protocol. Bars represent mean±SEM of discrimination ratio (P2 time spent investigating novel juvenile/time spent investigating familiar juvenile). *N*=5–9. MPEP (2.5 or 10 mg/kg) or vehicle was administered IP, 45 min before P1. CDPPB (10 mg/kg) or vehicle was administered IP, 30 min before P1. *Black star* represents significance of vehicle (*VEH*)/CDPPB vs. vehicle/vehicle, whereas *white stars* show significance of MPEP/CDPPB vs. vehicle/CDPPB, in post hoc test following two-way rank interaction analysis ($P<0.05$)

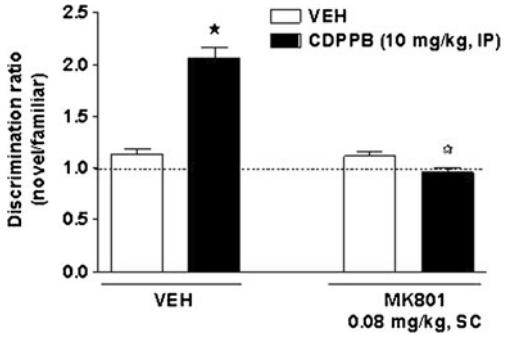

Fig. 6 NMDA receptor antagonist, MK801, blocks novelty discrimination enhancement by CDPPB, in the *parametric deficit* protocol. Bars represent mean±SEM of discrimination ratio (P2 time spent investigating novel juvenile/time spent investigating familiar juvenile). *N*=6 per group. MK801 (0.08 mg/kg) or vehicle was administered subcutaneously (SC), 45 min before P1. CDPPB (10 mg/kg) or vehicle was administered IP, 30 min before P1. *Black star* represents significance of vehicle (VEH)/CDPPB vs. vehicle/vehicle, whereas the *white star* shows significance of MK801/CDPPB vs. vehicle/CDPPB, in post hoc test following two-way rank interaction analysis ($P<0.001$)

discrimination ratio vs. control ($P<0.05$ and $P<0.01$, respectively). For all weeks, no significant change in total P1 and P2 investigation times was found.

Effect of chronic CDPPB treatment on the neonatal PCP-induced social novelty discrimination deficit

Two-way rank interaction analysis revealed a significant interaction between neonatal PCP administration and chronic adolescent 10 mg/kg CDPPB treatment for each of 12 days following 5 weeks of age, when testing was at 8 weeks ($P<0.001$) (Fig. 9 and Table 4). Neonatal PCP rats treated with chronic vehicle displayed significantly reduced discrimination ratios at 8 weeks of age when compared to rats treated with neonatal vehicle and chronic vehicle, similarly before ($P<0.001$). This deficit was significantly blocked by chronic adolescent CDPPB ($P<0.01$). When the same rats were tested again 5 weeks later (week 13), the significant interaction between neonatal and chronic treatment remained ($P<0.01$), and post hoc tests again showed a significant reduction of discrimination ratio by neonatal PCP treatment ($P<0.01$) and prevention by chronic adolescent CDPPB ($P<0.05$). When chronic treatment started at 10 weeks of age, testing at 8 weeks old found a significant decrease in the discrimination ratio of neonatal PCP-treated rats, compared to neonatal vehicle-treated rats ($P<0.001$), as before. Chronic treatment groups were chosen based upon week 8 discrimination ratio scores to achieve equivalent means and SEM for each neonatal PCP and neonatal vehicle groups. At 13 weeks, following chronic administration of vehicle or CDPPB, neonatal PCP significantly reduced the discrimination ratio in chronic control

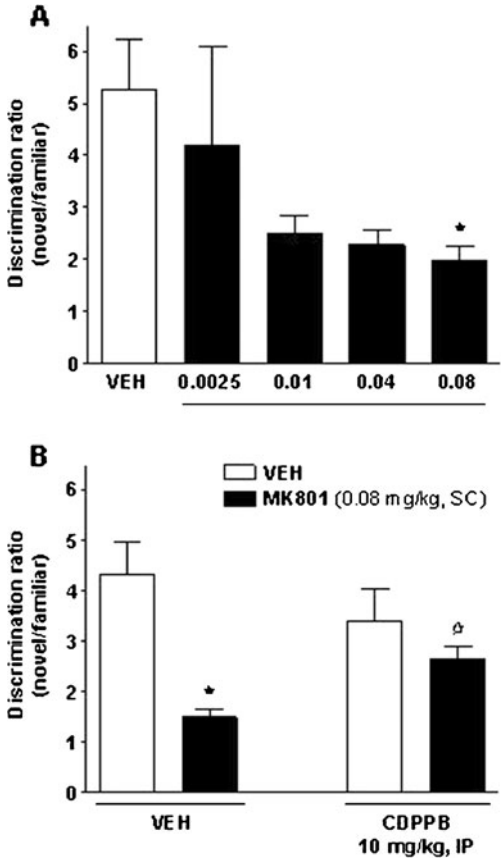

Fig. 7 MK801 induces a deficit in social novelty discrimination (**a**), which is reversed by CDPPB (**b**) in the *pharmacological deficit* (no delay) protocol. *Bars* represent mean±SEM of discrimination ratio (P2 time spent investigating novel juvenile/time spent investigating familiar juvenile). **a** MK801 (0.0025–0.08 mg/kg) or vehicle was administered SC, 30 min before P1. N=3–7. *Black star* represents significance of MK801 drug effect vs. vehicle (*VEH*) in Dunn's multiple comparison test, following Kruskal–Wallis test (P<0.05). **b** CDPPB (10 mg/kg) or vehicle was administered intraperitoneally (IP), 45 min before P1. MK801 (0.08 mg/kg) or vehicle was administered SC, 30 min before P1. N=9 per group. *Black star* represents significance of vehicle (*VEH*)/MK801 vs. vehicle/vehicle, and the *white star* represents significance of CDPPB/MK801 vs. vehicle/MK801 in post hoc tests following two-way rank interaction analysis (P<0.01)

rats, as before (P<0.001). Two-way rank interaction analysis found no significant interaction between neonatal and chronic treatments, showing a lack of effect by CDPPB. For chronic experiments, no significant changes in total P1 or P2 investigation times were found.

Discussion

MGluR5 PAM enhancement of social novelty discrimination: pharmacological and regional specificity

The present study shows that the mGluR5 PAMs, CDPPB and ADX47273 counter a delay-induced impairment in SND. These observations suggest a positive influence of mGluR5 activation upon social cognition, paralleling data, indicating that they similarly enhance other cognitive domains impacted in schizophrenia, like working memory and executive function (see "Introduction").

Furthermore, the doses of CDPPB and ADX47273 that promoted SND herein are comparable to those employed in other studies of cognitive function, and they induced no significant change in total investigation times during P1 or P2 indicating, in line with previous work, that their actions reflect a specific impact on cognitive processing (Darrah et al. 2008; Liu et al. 2008; Stefani and Moghaddam 2010). Inasmuch as CDPPB reversed the delay-induced impairment in SND when administered 1 min *after* P1 (Morisot et al. 2010), its effect is unlikely to reflect an improvement in acquisition during P1. Although it might then be contended that mGluR5 PAMs improve "memory" (consolidation, retention, recall) of the familiar juvenile, this is not necessarily the case since the delay (30 min) utilised does not appear sufficient to induce "forgetting". Accordingly, when the familiar juvenile was presented *alone* during P2, the adult rat spent less time in investigation than if the novel juvenile was presented alone (unpublished observations). In addition, the adult rat can successfully discriminate the novel from the familiar juvenile if their movement is restricted by placement in mesh cages on opposite sides of the arena (Terranova et al. 2005). Thus, it is likely that facilitation of SND under these conditions reflects a reinforcement of sustained and selective attention as well as working memory (Engelmann et al. 1995; Terranova et al. 2005). These processes are integrated and controlled by frontocortico-striatal circuits and both the FCX and striatum contain dense populations of glutamatergic neurons and mGlur5 receptors (Gupta et al. 2005; Packard et al. 2001).

As regards their respective roles, CDPPB increased SND performance upon microinjection into the FCX but not to the striatum, suggesting that prefrontal populations of mGluR5 favour social cognition. This observation is in line with increasing evidence for top–down prefrontal "cognitive control" of diverse cognitive processes and domains (Heatherton and Wagner 2011) and also with reports that the FCX plays an important role in the modulation of social cognition by other drug classes, including dopamine D_3 receptor antagonists that likewise enhance SND (Loiseau et al. 2009; Watson et al. 2012). The activity of CDPPB upon introduction into the FCX renders unlikely the possibility that SND is improved through increased olfactory processing, despite the presence of mGlu5 receptors in the olfactory bulb (Shigemoto et al. 1993). Nonetheless, a role for other mGlu5 receptors in other structures specifically implicated in processing social cognition, like the septum and amygdala (Adolphs 2010), should not be discounted and warrants further investigation.

Table 2 Effects of drugs on interaction time (s) during P1 (5 min) and P2 (5 min) in the social novelty discrimination test

Drugs/dose (mg/kg)		*N*	Total interaction time	
			P1 (s)	P2 (s)
Effect of MK801 alone and of interaction between MK801 and CDPPB in the pharmacological deficit (no delay) protocol[a]				
MK801	0	7	125.0±9.5	123.2±7.3
	0.0025	3	114.1±15.2	87.6±18.8
	0.01	6	110.3±12.8	120.6±9.5
	0.04	6	127.2±11.9	93.7±12.8
	0.08	7	109.3±4.9	108.6±10.2
MK801	CDPPB			
0	0	9	138.6±6.2	135.0±14.5
0	10	9	120.7±6.0	118.4±11.8
0.08	0	9	138.6±6.2	92.5±7.2*
0.08	10	9	124.4±9.7	95.9±7.4
Effects of CDPPB and ADX47273 on a social novelty discrimination deficit induced by the neonatal administration of PCP, using the pharmacological deficit test protocol				
NEONAT	CDPPB			
Saline	0	12	149.7±9.8	154.3±7.4
	0.63	6	154.2±7.8	116.3±13.5
	2.5	6	142.8±13.1	161.4±10.9
	10	6	151.4±6.9	153.6±1.8
PCP	0	12	143.6±6.5	137.0±9.3
	0.63	6	135.6±9.5	118.1±9.6
	2.5	6	154.3±5.8	136.1±9.8
	10	6	141.2±16.5	127.2±10.1
NEONAT	ADX			
Saline	0	9	133.1±5.3	140.6±11.7
	0.16	9	140.8±7.6	141.4±9.7
	0.63	9	142.0±4.5	146.4±9.0
	2.5	9	139.5±5.0	140.9±8.8
PCP	0	9	139.6±5.4	131.6±7.9
	0.16	9	151.4±6.6	129.2±8.2
	0.63	9	131.9±5.9	143.4±5.7
	2.5	9	132.9±6.9	128.8±9.2

Data expressed as mean±SEM

*$P<0.05$ vs. vehicle/vehicle group in Dunnett's test following one-way ANOVA

[a] See legend to Fig. 7

[b] See legend to Fig. 8

As discussed elsewhere (Calabrese 2008; Millan et al. 2012), a remarkably broad and mechanistically diverse range of "pro-cognitive" agents reveal "inverted U" dose–response curves in behavioural and cellular procedures, implying a "set-point" for optimal performance: that is, both under *and* overactivation of the drug target impair cognition. This is not surprising since both deficient *and* excessive LTP and LTD, dendritic spine and neurogenesis, for example, can disrupt cognition. These processes are modulated by glutamatergic mechanisms like mGluR5 receptors, and, while schizophrenia may be characterised by low mGluR5 receptor activity, Fragile X represents the opposite extreme of excessive activation due to loss of Fragile X mental retardation protein, which normally moderates mGluR5 receptor dependent messenger RNA (mRNA) translation (Dölen et al. 2010; Zoghbi and Bear 2012; Bhakar et al. 2012; Millan et al. 2012)

In view of the above comments, it was not surprising that CDPPB and ADX47273 displayed inverted U dose–response curves for enhancing SND, and this despite the lack of any non-specific perturbation in behaviour or suppression of total investigation time. Indeed, though surprisingly few

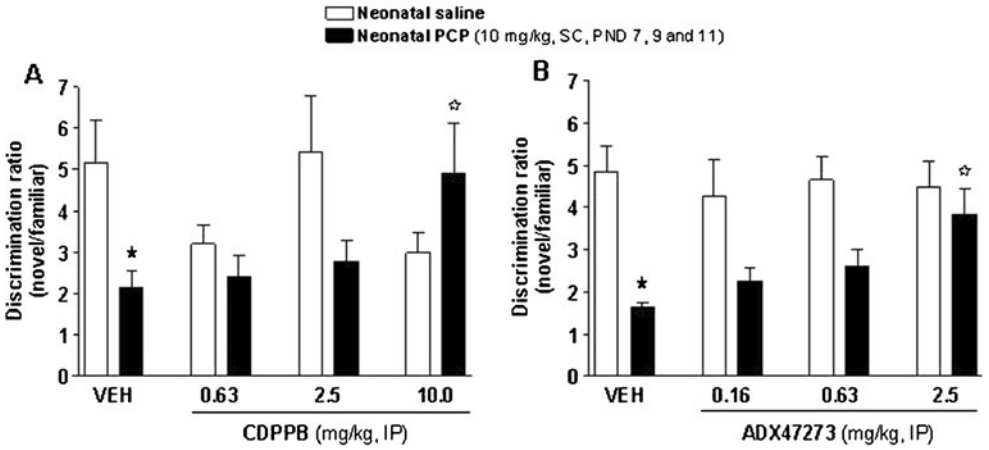

Fig. 8 CDPPB and ADX47273 reverse a social novelty discrimination deficit induced by the neonatal administration of PCP, in the *pharmacological deficit* protocol. Bars represent mean±SEM of discrimination ratio (P2 time spent investigating novel juvenile/time spent investigating familiar juvenile). Neonates were treated with PCP (10 mg/kg) or saline SC, on post-natal days (PND) 7, 9, and 11. (N=6–12). CDPPB (**a** 0.63–10 mg/kg), ADX47273 (**b** 0.16–2.5 mg/kg) or vehicle was administered IP, 30 min before P1. *Black stars* represent significance of neonatal PCP/acute vehicle (VEH) vs. neonatal saline/acute vehicle, whereas *white stars* represent significance of neonatal PCP/acute drug vs. neonatal PCP/acute vehicle, in post hoc tests following two-way rank interaction analysis (**a** P<0.01; **b** P<0.05)

studies have looked at extensive dose response ranges of mGluR5 agonists, Uslaner et al. (2009) reported a bell-shaped dose–response for the influence of CDPPB on novel object recognition: Lower doses of CDPPB countered the interference of recognition provoked by delay and MK801, whereas a higher dose was ineffective. Furthermore, CDPPB displayed an inverted shaped dose–effect for increasing hippocampal and frontocortical levels of phosphorylated protein markers of NMDA receptor signalling. As indicated above, these and the present data may be related to the need for a balance between the modulation of LTP and LTD by mGluR5 receptors (Neyman and Manahan-Vaughan 2008; Ayala et al. 2009; Dölen et al. 2010; Millan et al. 2012). From a pathological perspective, and consistent with the present data, modest doses of mGluR5 agonists would promote cognition by normalising deficits in mGluR5 (and NMDA) receptor signalling seen in (the frontal cortex) in schizophrenia, whereas antagonists would be required to counter the over-stimulation of mGluR5 receptors (in hippocampus and amygdala) seen in Fragile X (Palmer et al. 1997; Ronesi and Huber 2008; Dölen et al. 2010; Stefani and Moghaddam 2010; Horio et al. 2012; Won et al. 2012; Millan et al. 2012; Zoghbi and Bear 2012). Finally, in this light, it should be noted that CDPPB and ADX47273 are highly selective ligands (Kinney et al. 2005; Liu et al. 2008) and the specificity of the enhancement of SND by mGluR5 PAMs

Table 3 Effect of age on the presence of a neonatal PCP-induced social novelty discrimination deficit

Age (weeks)	Neonatal treatment (mg/kg; PND7, 9, 11)		Acute treatment	Ratio	Total interaction time	
	Drug	Dose (mg/kg)			P1 (s)	P2 (s)
4	Saline	0	Saline	1.8±0.2	89.2±4.7	115.9±10.8
	PCP	10	Saline	1.1±0.1	86.0±6.7	103.6±13.2
5	Saline	0	Saline	4.1±1.4	114.1±5.7	120.4±5.5
	PCP	10	Saline	4.5±1.3	113.3±11.1	117.1±8.5
6	Saline	0	Saline	3.7±0.6	140.4±7.3	125.8±5.6
	PCP	10	Saline	5.2±2.3	147.2±5.8	121.2±9.9
7	Saline	0	Saline	4.8±0.5	136.9±7.2	122.3±6.1
	PCP	10	Saline	2.3±0.7	146.6±4.9	139.2±4.5
8	Saline	0	Saline	7.2±1.8	145.0±3.1	134.7±8.0
	PCP	10	Saline	2.6±0.4	148.8±8.5	124.4±8.2

Data expressed as mean±SEM. PCP (10 mg/kg) or saline vehicle was administered SC on each of PND 7, 9 and 11. Saline was administered IP, 30 min before P1. N=7 per group

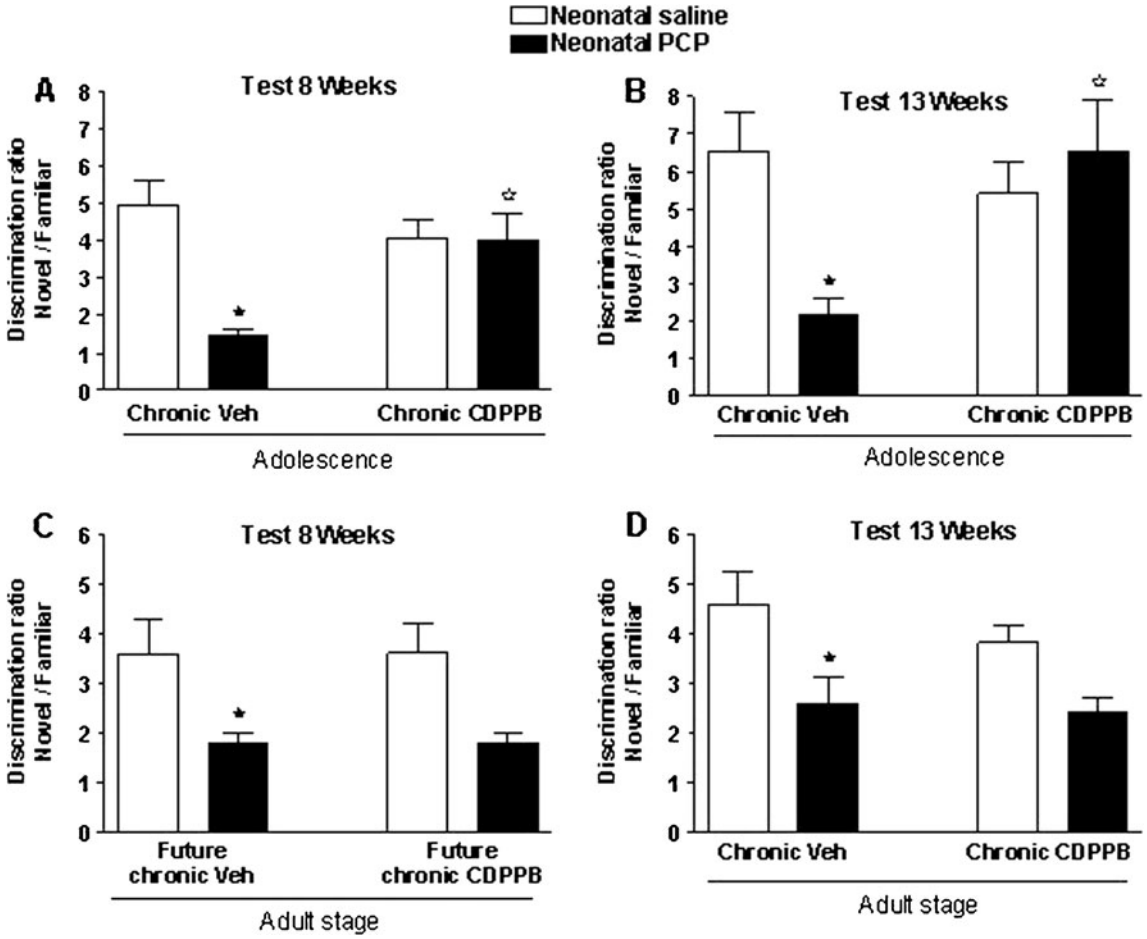

Fig. 9 Chronic adolescent, but not adult, CDPPB prevents a neonatal PCP-induced deficit in social novelty discrimination from emerging in adults. *Bars* represent mean±SEM of P2 discrimination ratio (time investigating novel juvenile/time investigating familiar juvenile) immediately following a P1 of 30 min. N=9 or 10. PCP (10 mg/kg) or saline vehicle was administered SC on each of PND 7, 9, and 11. CDPPB (10 mg/kg, IP) was administered chronically for each of 12 days, starting at 5 weeks of age. Tests were at 8 weeks (**a**, **c**) and 13 weeks (**b**, **d**) of age. Saline was administered IP, 30 min before P1. CDPPB (10 mg/kg, IP) was administered chronically for each of 12 days, starting at 5 weeks of age (**a**, **b**) or 10 weeks of age (**c**, **d**). Data in **c** represent testing before chronic treatment at adulthood. *Black stars* represent significance of neonatal PCP/chronic vehicle vs. neonatal saline/chronic vehicle, whereas *white stars* represent significance of neonatal PCP/chronic CDPPB vs., neonatal PCP/chronic vehicle, in post hoc Dunnett's tests following two-way rank interaction analyses (P<0.01)

herein was underpinned by the blockade of the actions of CDPPB with the selective mGluR5 receptor antagonist, MPEP.

Interrelationship of mGlu5 and NMDA receptors in the modulation of SND

MGluR5 are located predominantly post-synaptically where they functionally and physically interact with NMDA receptors that likewise play an important role in cognitive processes, notably in the FCX (Alagarsamy et al. 2005; Bertaso et al. 2010; Niswender and Conn 2010; Page et al. 2006). MGluR5 activation by agonists and PAMs increases NMDA receptor-1 subunit phosphorylation, thereby potentiating NMDA receptor-evoked currents and enhancing electrophysiological responses in frontocortical and other circuits (Awad et al. 2000; Chen et al. 2007; Choe et al. 2006; Lecourtier et al. 2007). Consistent with these reports, the NMDA receptor antagonist (open channel blocker), MK801 blocked the increase of SND elicited by CDPPB demonstrating dependency upon functionally intact NMDA receptors. Mimicking the actions of a further NMDA receptor antagonist, phencyclidine (Terranova et al. 2005), MK801 itself impaired SND and pre-administration of CDPPB blunted this deficit underscoring the reciprocal interrelationship amongst mGluR5 and NMDA receptors in cognitive processing. In line with this observation, mGluR5 PAMs reversed MK801-induced deficits previously in procedures cognitive flexibility, executive function, episodic memory and aversive

Table 4 Effect of chronic CDPPB on the neonatal PCP-induced deficit in social novelty discrimination

Neonatal treatment (mg/kg; PND7, 9, 11)		Chronic treatment (mg/kg/day)			Acute treatment		N	Total interaction time	
Drug	Dose	Drug	Dose	Age (weeks)	Drug	Test age		P1 (s)	P2 (s)
PCP	0	CDPPB	0	5–6	Saline	8	10	90.5±4.0	103.7±7.2
	10		0				9	97.8±4.6	73.6±6.7
	0		10				10	91.9±4.9	120.0±8.5
	10		10				9	101.0±4.9	107.2±10.5
	0		0			13	10	101.6±6.7	119.3±4.3
	10		0				9	115.6±3.6	106.3±4.8
	0		10				10	121.4±8.9	127.2±8.6
	10		10				9	108.9±8.1	114.7±12.7
PCP	0	CDPPB	0	10–11	Saline	8	10	115.2±6.0	131.1±8.2
	10		0				10	123.4±7.3	122.0±9.3
	0		10				9	110.2±8.5	117.2±5.9
	10		10				10	110.9±9.1	102.1±10.6
	0		0			13	10	117.3±4.7	123.8±7.1
	10		0				10	106.1±6.5	110.2±3.6
	0		10				9	110.6±8.5	116.2±7.4
	10		10				10	106.6±6.4	112.3±7.9

Data expressed as mean±SEM. PCP (10 mg/kg) or saline vehicle was administered SC on each of PND 7, 9 and 11. CDPPB (10 mg/kg, IP) was administered chronically for each of 12 days over age shown. Tests were at 8 and 13 weeks of age. Saline was administered IP, 30 min before P1

learning (Darrah et al. 2008; Fowler et al. 2010; Stefani and Moghaddam 2010; Uslaner et al. 2009; Vales et al. 2010). Conversely, an mGluR5 antagonist (MPEP) enhanced the detrimental effect of MK801 and PCP on learning, spatial and working memory (Campbell et al. 2004; Homayoun et al. 2004). Finally, in a five-choice serial reaction time task of sustained attention impairment has been documented both with NMDA receptor antagonists and with MPEP (Amitai and Markou 2010; Quarta et al. 2007). The present work then extends to a model of social cognition, the close interrelationship of mGluR5 and NMDA receptors in the control of cognitive processing.

Influence of mGluR5 PAMs upon adult deficits in SND induced by neonatal exposure to PCP

The present work extends studies of adult deficits in other cognitive domains like spatial learning, spatial memory, working memory, reversal learning and cognitive flexibility upon neonatal administration of PCP (Andersen and Pouzet 2004; Nakatani-Pawlak et al. 2009; Secher et al. 2009; Sircar 2003; Stefani and Moghaddam 2005; Wang et al. 2001) to a procedure probing social cognition. Moreover, we show herein that acute administration of CDPPB and ADX47273 to adult rats reverses the neonatal PCP-induced deficit in SND. Although mGluR5 ligands have not, to our knowledge, been studied in such a developmental model of schizophrenia, the mGlu2/3 receptor agonist, LY354740, likewise alleviated the deficit in SND shown by neonatal PCP-treated rats (Harich et al. 2007). Thus, mGluR5 clearly fulfilled a particularly important role in this respect, and, in view of the above discussion, it is interesting that stimulation of mGlu2/3 receptors was recently reported to enhance NMDA receptor activity via Akt/GSK-3b signalling (Xi et al. 2011). Furthermore, compounds that directly increase NMDA transmission, such as GlyT1 inhibitors and the co-agonist D-serine, also counter cognitive deficits in this developmental model (Andersen and Pouzet 2004; Boulay et al. 2008; Depoortère et al. 2005; Millan 2005). These observations are also in line with reports that NMDA receptor neurotransmission is impaired in adults rats neonataly exposed to PCP (Baier et al. 2009; du Bois et al. 2009; Sircar et al. 1996, 2003).

Prevention by chronic treatment with mGluR5 PAM of adult deficits in SND induced by neonatal PCP

In the present work, we show, to our knowledge for the first time, the post-adolescent, adult onset of a cognitive deficit (in SND) triggered by neonatal exposure to PCP. This result concurs with other studies that reported the peri- or post-pubertal emergence of schizophrenia-related behavioural deficits in a variety of developemental models. For example, Uehara et al. (2010) reported that rats neonatally treated with MK801 displayed deficits of prepulse inhibition and methamphetamine-induced hyperlocomotion at the adult stage (PND 64–66) but not in adolescence (PND36–38). Similarly, following neonatal

ventral hippocampal lesions, the deficit in sensory gating and an increased locomotor response to amphetamine emerged only after puberty (Lipska et al. 1993, 1995). Finally, immune activation during pregnancy by administration of the viral mimic, polyriboinosinic–polyribocytidylic acid (Polyl:C), was accompanied by post-pubertal onset of disrupted latent inhibition and hyper-sensitivity to amphetamine (Ozawa et al. 2006; Zuckerman et al. 2003). Although the processes accounting for the delayed appearance of cognitive (and other) impairments in rodent models remain to be elucidated, these observations clearly parallel clinical schizophrenia in which psychotic symptoms are very rarely manifested prior to young adulthood (Gorwood et al. 1995).

Importantly, chronic administration of mGluR5 PAMs during adolescence, but *not* in adulthood, suppressed the disruption of SND induced by neonatal PCP, and this preventive effect persisted well into adulthood. What might be the underlying mechanisms? A number of reports indicate that recruitment of mGluR5 is neuroprotective, while mGluR5 PAMs display anti-apoptotic properties in neuronal cultures (Allen et al. 2000; Movsesyan et al. 2004), so they may protect the FCX from excessive apoptosis-related neuronal pruning in adolescence. Furthermore, mGluR5 stimulation during adolescence may, perhaps via NMDA receptor recruitment, enhance BDNF-related neuroprotective mechanisms. In support of this contention, activation of group I mGluRs by DHPG induced BDNF mRNA and protein expression via mGluR5 subtype in glials cells, whereas the mGluR5 antagonist, MPEP, decreases cortical BDNF expression (Legutko et al. 2006; Viwatpinyo and Chongthammakun 2009). In addition, stimulation of mGluR5 on oligodendrocytes reduced their excitotoxic death in culture, suggesting that their activation may protect white matter fibres from degeneration during adolescence in PCP pretreated rats (Deng et al. 2004; Luyt et al. 2006). Finally, mGluR5 PAMs possess anti-inflammatory properties in microglial cultures (Byrnes et al. 2009), and they may counter anomalous immuno-inflammatory processes occurring during adolescence in animals neonataly exposed to PCP.

Inasmuch as CDPPB prevented the adult appearance of cognitive deficits in neonatal PCP-treated rats, apart from exploring underlying mechanisms, it would be interesting to extend such studies to other cognitive domains and to additional behavioural abnormalities related to clinical symptoms of schizophrenia. Thus, rats exposed to NMDA non-competitive antagonists (PCP or MK801) at the neonatal stage display impaired cognitive flexibility (set-shifting) (Stefani and Moghaddam 2005) enhanced locomotor activity (Harris et al. 2003; Wang et al. 2001) and disrupted prepulse inhibition (Rasmussen et al. 2007; Takahashi et al. 2006; Uehara et al. 2010).

It would also be interesting to see whether other drug classes mimic the influence of mGluR5 PAMs on SND deficits in neonatal PCP-treated rats, since adolescent administration of clozapine prevented the postpubertal emergence of brain structural pathology and behavioural anomalies like impaired prepulse inhibition, deficient latent inhibition and hyper-sensitivity to psychostimulants in rats prenatally exposed to Polyl:C (Meyer et al. 2010; Piontkewitz et al. 2009, 2010). Furthermore, risperidone prevented the appearance of elevated locomotor activity following neonatal lesions of ventral hippocampus (Richtand et al. 2006). There is even some evidence that early treatment with low doses of antipsychotics like risperidone hinders first-episode psychosis (McGorry et al. 2002). Since add-on therapy with minocycline, a second generation tetracycline (Levkovitz et al. 2010) and with long-chain omega-3 polyunsaturated fatty acids in early phase schizophrenia reduced the risk of progression to psychotic disorders, their actions would also be interesting to explore (Amminger et al. 2010).

Conclusions

The present data show that mGluR5 PAMs block deficits of SND induced by either a time delay, administration of an NMDA antagonist and, most interestingly, a developmental model of schizophrenia, neonatal PCP administration. These observations indicate a role for mGluR5 in the control of social cognition, at least partly expressed in the FCX and in interaction with NMDA receptors, though further exploration of underlying mechanisms is warranted. These observations support the relevance of mGluR5 receptors as targets for alleviating the cognitive deficits of schizophrenia, and possibly other CNS disorders in which deficits in social cognition and other cognitive domains are prominent (Millan et al. 2012). Moreover, the ability of mGluR5 PAMs to interfere with the onset of adult deficits in SND when given during adolescence to neonatal PCP-treated rats raises the intriguing possibility that precocious pre-symptomatic recruitment of mGluR5 sites may interrupt aberrant neurodevelopmental processes that ultimately lead to schizophrenia. This possibility clearly justifies further evaluation employing both the procedures employed herein and other behavioural measures in both developmental and genetic models of schizophrenia.

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