Metabotropic glutamate receptor modulation of dopamine release in the nucleus accumbens shell is unaffected by phencyclidine pretreatment: in vitro assessment using fast-scan cyclic voltammetry rat brain slices

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Abstract

The non-competitive glutamate antagonist, phencyclidine is used in rodents to model behavioural deficits see in schizophrenia. Importantly, these deficits endure long after the cessation of short-term chronic treatment (sub-chronic), indicating that the drug treatment causes long-term changes in the physiology and/or chemistry of the brain. There is evidence that this may occur through glutamatergic modulation of mesolimbic dopamine release, perhaps involving metabotropic glutamate receptors (mGluR). This study sought to investigate the effect of sub-chronic phencyclidine pretreatment on modulation of dopamine neurotransmission by metabotropic glutamate receptors 2 and 5 (mGluR2 and mGluR5) in the nucleus accumbens shell in vitro, with the hypothesis that phencyclidine pretreatment would disrupt the mGluR-mediated modulation of dopamine release. We showed that the orthosteric mGluR2 agonist LY379268 (0.1 μM, 1 μM and 10 μM) and mGluR5 positive allosteric modulator CDPPB (1 μM and 10 μM) both attenuated potassium-evoked dopamine release, underscoring their role in modulating dopamine neurotransmission in the nucleus accumbens. Sub-chronic PCP treatment, which caused cognitive deficits measured by performance in the novel object recognition task, modelling aspects of behavioral deficits seen in schizophrenia, induced neurobiological changes that enhanced dopamine release in the nucleus accumbens, but had no effect on mGluR2 or mGluR5 mediated changes in dopamine release. Therefore it is unlikely that schizophrenia-related behavioural changes seen after sub-chronic phencyclidine pre-treatment are mediated through mGluR modulation of dopamine release.

Keywords

Dopamine; Fast-scan cyclic voltammetry; Glutamate; Metabotropic glutamate receptor; Nucleus accumbens shell; Phencyclidine.

Abbreviations

ACSF	Artificial cerebrospinal fluid
ANOVA	Analysis of variance
CDPPB	3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide
DI	Discrimination index
DMSO	Dimethyl sulfoxide
FCV	Fast-scan cyclic voltammetry
mGluR	Metabotropic glutamate receptor
NAc	Nucleus accumbens
NMDA	N-methyl-D-aspartate
NMDA-R	N-methyl-D-aspartate type glutamate receptors
NOR	Novel object recognition
PCP	Phencyclidine

1. Introduction

Schizophrenia is chronic psychiatric illness that affects 1% of the worldwide population, and is characterised by positive symptoms (psychosis and delusions), negative symptoms (apathy, anhedonia and social withdrawal) and cognitive symptoms (impaired memory and cognition). Current antipsychotic treatment, provides reasonable control of acute positive symptoms, but a high proportion of patients continue to suffer a relapsing course of positive symptoms, and enduring negative and cognitive symptoms, leading to long-term social and cognitive dysfunction and reduced quality of life (reviewed in van Os & Kapur, 2009). Therefore a clearer understanding of the processes underlying the symptoms, leading to better treatment strategies, is a key goal (Neill et al 2010).

Neurochemical theories propose a critical role for both dopamine and glutamate in the dysfunctions seen in schizophrenia (Howes & Kapur, 2009; Javitt, 2007; Jentsch & Roth, 1999). The dopamine theory posits that the disorder is caused by abnormal dopamine neurotransmission in mesolimbic and mesocortical circuits. It derives from observations that dopaminomimetic drugs such as amphetamines induce positive symptoms, and that classical antipsychotic drugs used to treat the condition are antagonists at dopamine D_2 receptors (Seeman, 1987). However, dopamine models do not adequately account for negative of cognitive symptoms, and it therefore is unlikely that excess dopamine is the core pathological change in schizophrenia. Studies have also implicated disturbances in glutamate systems in the pathology of schizophrenia. Non-competitive antagonists at NMDA-type glutamate receptors (NMDA-R) such as phencyclidine (PCP) and ketamine are capable of mimicking schizophrenia symptoms in all three domains in healthy volunteers and exacerbating these symptoms in patients (Adler et al., 1998; Lahti et al., 2001; Malhotra et al., 1997). As a synthesis of both theories, it has been suggested that core deficits in glutamatergic transmission may cause dysregulation of glutamate-dopamine interactions, particularly involving the mesolimbic and mesocortical dopamine pathways (Grace 2000, 2012; Javitt, 2007). In particular, modulation of dopamine systems in nucleus accumbens (NAc) shell are implicated, given the important role of this region in attentional processes, including those disrupted in schizophrenia.

Sub-chronic PCP pretreatment (twice per day for 5 to 7 days (Grayson et al, 2007; Sood et al., 2011)) provides a rodent model of dysfunctions seen in schizophrenia (Neill et al., 2010; Cadinu et al., 2017). In rats, such PCP pretreatment causes impairments in cognition (Barnes et al. 2012; McLean et al. 2008), memory and attention (Barnes et al., 2012, McLean et al., 2009; Sood et al., 2011), sensorimotor gating (Kinney et al., 2003), and social withdrawal (Balla et al., 2001; Barnes et al., 2012). Moreover, these effects of PCP endure for 2 to 6 months after drug treatment: this is believed to be a long-lasting effect of the treatment, rather than a response to the

withdrawal of the drug (Neill et al., 2010), suggesting that PCP evokes long-term conformational changes in brain chemistry and/or physiology. Such sub-chronic treatment with PCP, or other non-competitive NMDA antagonists (MK801, ketamine) enhances dopamine mediated behaviours (Jentsch et al., 1998b) and activate mesolimbic dopamine neurons (Katayama et al., 2013; Uramura et al., 2014), increasing dopamine release in NAc (Balla et al., 2001; Kegeles et al, 2000). This implies that the effect may involve glutamatergic modulation of activity in mesolimbic and/or mesocortical dopamine systems (Javitt, 2007; Jentsch et al., 1998a,b; Jentsch & Roth, 1999). However, little is known about the long-term effects of sub-chronic treatment on dopamine function: therefore the present study aimed to investigate these changes.

Metabotropic glutamate receptors (mGluR) are present in high densities in NAc and show functional interactions with dopaminergic neurons (Testa et al., 1994; Vezina & Kim, 1999). Eight mGluR subtypes (mGluR 1-8) have so far been identified, and are divided into three categories according to their structure and pharmacological properties (Conn & Pinn, 1997). Of these, Group 1 (mGluR 1 and 5) and Group 2 (mGluR2 and 3) have been implicated in processes of schizophrenia, and drugs acting at mGluRs may have therapeutic benefit in the treatment of schizophrenia (Chaki, 2010; Fell et al., 2012; Krivoy et al, 2008; Matosin & Newell, 2013; Vinson & Conn, 2012). In this context, it is relevant that several lines of evidence suggest a role for mGluRs in modulation of accumbal dopamine release, and that changes in this modulation may account for the effects of mGluRs on PCP-evoked behaviours. For example mGluR2 stimulation reduced accumbal dopamine release (Chaki et al, 2006; Greenslade & Mitchell, 2004), and inhibited the expression of conditioned hyperactivity to amphetamine (Kim et al., 2000), while mGluR2 blockade induced hyper-locomotion in cocaine sensitized rats (Yoon et al., 2008). Moreover, mGluR2 activation also attenuated or abolished disruptions in behaviour evoked by PCP (Cartmell et al., 1999; Fell et al., 2012; Moghaddam & Adams, 1998; Woolley et al., 2008). Similarly, activation of mGluR5 decreased accumbal dopamine (Liu et al., 2008), and attenuated or abolished PCP-evoked aberrant behaviours (Chan et al., 2008; Liu et al., 2008; Stefani et al., 2010; Uslaner et al., 2009).

Given the known interactions between mGluRs and dopamine mediated behaviours, which are affected by PCP pretreatment, the present studies aimed to assess whether sub-chronic PCP pretreatment affected K^+-stimulated dopamine release, and whether this effect was mediated through changes in mGluR2 or mGluR5 controlled modulation of dopamine release in NAc.

2. Results

2.1 Novel object recognition (NOR) testing

In order to verify that the PCP pretreatment had been effective, animals were tested behaviorally using NOR. Although there was no difference in overall time spent active (data not shown), two-way analysis of variance (ANOVA) of acquisition trial data, PCP pretreated animals showed reduced total exploration time on the objects (main effect of PCP pretreatment, $F_{1,19}$ = 8.882, P = .008), but no main effect of object position ($F_{1,19}$ = 0.453, P = .509) nor any PCP pretreatment x object position interaction ($F_{1,19}$ = 0.048, P = .829: figure 1a).

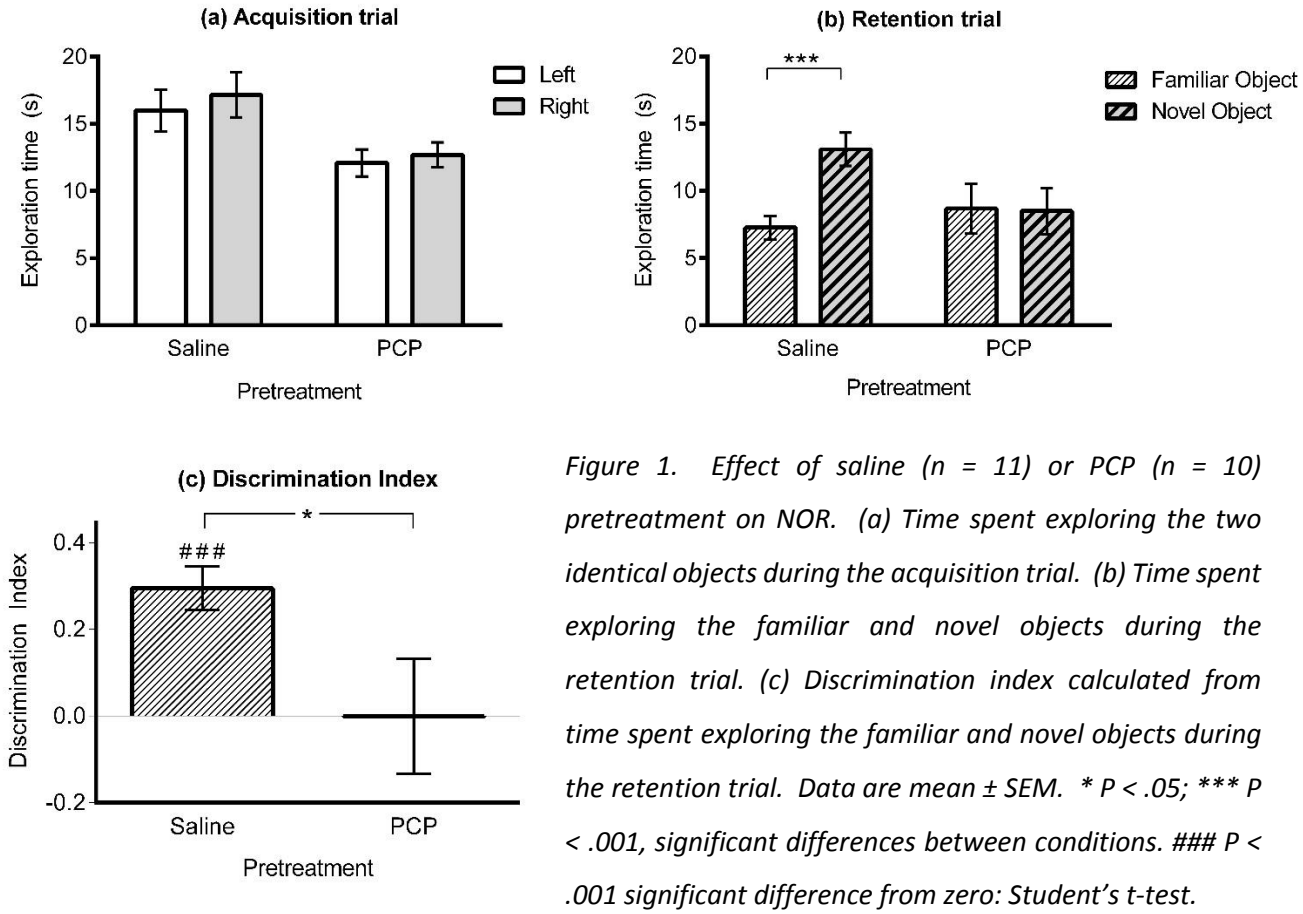

*Figure 1. Effect of saline (n = 11) or PCP (n = 10) pretreatment on NOR. (a) Time spent exploring the two identical objects during the acquisition trial. (b) Time spent exploring the familiar and novel objects during the retention trial. (c) Discrimination index calculated from time spent exploring the familiar and novel objects during the retention trial. Data are mean ± SEM. * P < .05; *** P < .001, significant differences between conditions. ### P < .001 significant difference from zero: Student's t-test.*

In the retention trial, saline pretreated animals showed a preference towards exploration of the novel object which was not observed in the PCP pretreated animals. There was no main effect of PCP pretreatment ($F_{1,19}$ = 0.717, P = .408:), but there was a main effect of object type ($F_{1,19}$ = 13.02, P = .002) and a PCP pretreatment x object type interaction ($F_{1,19}$ = 14.94, P = .001: two-way ANOVA: Figure 1b). Subsequent post hoc t-tests based

on planned comparisons revealed a difference between exploration of the novel and familiar objects in the saline pretreatment group (t_{10} = 4.860, P < 0.001) but not the PCP pretreatment group (t_9 = 0.208, P = 0.840: figure 1b).

There was a significant difference in discrimination index (DI) between saline pretreated and PCP pretreated animals (t_{19} = 2.158, P = .044: figure 1c). Furthermore, saline pretreated animals showed discrimination between the novel and familiar objects (DI score significantly different from zero: t_{10} = 5.837, P < .001), whereas PCP pretreated animals did not (t_9 = .007, P = 0.995: figure 1c).

2.2 Effect of Sub-chronic PCP on Peak dopamine release

Dopamine release was measured by fast-scan cyclic voltammetry (FCV) in brain slices taken from saline or PCP pretreated animals. K^+-evoked dopamine at stimulus S1 (i.e. before bath application of the drug) was significantly potentiated in slices taken from PCP pretreated animals, compared to slices taken from saline pretreated animals (Saline pretreated: 2.763 ± .224 µM; PCP pretreated 4.535 ± .300 µM: t_{102} = 5.52, P < 0.001; Student's t-test)

2.3 Effect of LY379268 and 3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide (CDPPB) in pretreated animals

The effects of bath-applied drugs were assessed by S2:S1 ratios. In slices superfused with artificial cerebrospinal fluid (aCSF) throughout (i.e. no drugs applied), there was no change in the magnitude of the K^+-evoked response across the two stimuli in slices from either saline (S2:S1 ratio = .951 ± .054) or PCP (S2:S1 ratio = .943 ± .098) pretreated rats (Difference from 1.0: Saline pretreated t_{11} = .922; P = .377; PCP pretreated, t_9 = .577; P = .578). However, application of either LY379268 or CDPPB during S2 caused a decrease in the K^+-evoked dopamine release, seen as a reduction in the S2:S1 ratio in both pretreatment groups (figure 2).

Two-way ANOVA revealed a main effect of LY379268 ($F_{3,60}$ = 26.42, P < .001), but no main effect of PCP pretreatment ($F_{1,60}$ = 1.559, P = .217) nor any LY379268 x PCP pretreatment interaction ($F_{3,60}$ = .194, P = .900: figure 2a). Post-hoc analysis with Dunnett's test revealed that LY379268 100nM, 1µM and 10µM all significantly attenuated peak-dopamine release in both saline and PCP pretreated animals (all adjusted p-values < .001).

Two-way ANOVA revealed a main effect of CDPPB ($F_{2,43}$ = 34.64, P < .001), but no main effect of PCP pretreatment (F(1,43) = .056, p = .809) nor any CDPPB x PCP pretreatment interaction ($F_{2,43}$ = 0.042, P = .959:

figure 2b). Post-hoc analysis with Dunnett's test revealed that CDPPB 1µM and 10µM significantly attenuated peak-dopamine release in both saline and PCP pretreated animals (all corrected p-values < .001).

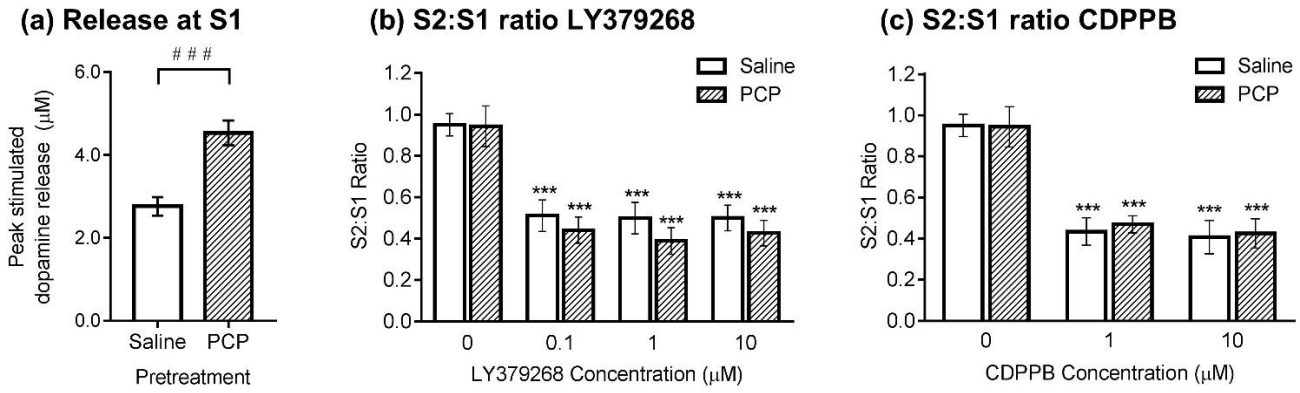

*Figure 2. (a) Effect of PCP on K^+-stimulated release: combined data from S1 (pre-drug) stimulations from all slices (saline, n = 22; PCP, n = 20). (b) Effect of LY379268 and (c) effect of CDPPB on K^+-stimulated release of dopamine in NAcS of brain slices taken from saline (n = 11) or PCP (n = 10) pretreated animals. Data are mean ± SEM S2:S1 ratios, where the drug is present at S2 only. ### p < .001, significant difference between saline and PCP pretreated slices; *** P < .001, significant difference from control (0 µM drug): Dunnett's post hoc test.*

3. Discussion

The present study confirmed that PCP pretreatment led to enhanced K^+-stimulated dopamine release in NAc shell brain slices in vitro. In addition, both mGluR2 and mGluR5 activation caused a reduction in stimulated dopamine release, but neither change was affected by pretreatment with PCP, suggesting that the hypersensitivity of dopamine systems induced by PCP pretreatment is not mediated through these mGluRs.

The suggestion that dysregulated glutamate-dopamine interactions underlying schizophrenia (Javitt, 2007; Jentsch & Roth, 1999) may be regulated by mGluR-mediated mechanisms (Matosin & Newell, 2013;) has led to an upsurge in interest in drugs acting at mGluRs in the treatment of schizophrenia (Chaki, 2010; Conn et al., 2009; Fell et al. 2012; Vinson & Conn, 2012). The data reported here focus on two subtypes of mGluR, mGluR2 and mGluR5, which have both been implicated in these functions.

Drugs affecting mGluR2 impinge on mesolimbic dopamine systems, influencing dopamine-mediated behaviours (Kim et al., 2000; Kim & Vezina, 2002; Yoon et al., 2008), including those which model behavioural dysfunctions in schizophrenia (Cartmell et al., 1999; Pitsikas & Markou, 2014; Schlumberger et al., 2009; Woolley et al., 2008), suggesting that modulation of these receptor types may be beneficial in the treatment of schizophrenia (Chaki 2010; Fell et al., 2012). Consistent with this, mGluR2 activation inhibited dopamine release from NAc in vitro (Chaki et al., 2006), and in vivo (Greenslade & Mitchell, 2004; Hu et al., 1999), and the mixed mGlu2R/mGlu3R agonist, LY354740 reversed PCP-induced cognitive disruptions (Moghaddam & Adams, 1998). The present findings confirm the mGluR2- mediated reduction of stimulated dopamine release from brain slices. Similarly, mGluR5 antagonists have been shown to reduce amphetamine induced hyperlocomotion (Gormley & Rompre, 2011) and L-DOPA induced dyskinesia in rodent models of Parkinson's disease (Chen et al., 2009; Gregoire et al., 2011), possibly through a reversal of the abnormal firing of dopaminergic neurons (Chen et al., 2009). In addition, mGluR5 blockade reduced psychostimulant-induced locomotor activation, a behaviour mediated through accumbal dopamine systems (Martinez-Rivera et al., 2013). On this basis mGluR5 has also been suggested as a therapeutic target for treatment of schizophrenia (Conn et al., 2009; Vinson & Conn, 2012). We found that the CDPPB, a positive allosteric modulator of mGluR5, decreased K^+-stimulated release of dopamine at all doses tested: to our knowledge, our study is the first to report the effect of mGluR5 activation on K^+-stimulated dopamine release in NAc shell. This is consistent with the report that the mGluR5 antagonist, MPEP, enhanced dopamine release in the prefrontal cortex (Homayoun et al., 2010), but contrary to the study of Lecourtier et al (2007) who failed to show any effect of CDPPB on dopamine release in frontal cortex in vivo. However, the authors themselves suggested that their finding was ambiguous, as any drug-induced decrease would have been masked by a simultaneous increase caused by the dimethyl sulfoxide (DMSO) vehicle (Lecourtier et al., 2007). In our experiments, DMSO was only present at concentrations less than 0.01% in the superfusate applied to the tissue, and at these concentrations it had no effect on dopamine release (data not shown). Thus, our findings show that CDPPB does indeed modulate accumbal dopamine release and this would be consistent with the reported behavioural effects of mGluR5 activation (see above).

In terms of the mechanism of the modulation of dopamine function by mGluRs, we can discount long-loop feedback involving projections from NAc to ventral tegmental area, either directly or via ventral pallidum, since our recordings were made in coronal brain slices, which contain only local circuitry. It is unlikely that the reductions in stimulated dopamine release caused by either LY379268 or CDPPB can be accounted for by a direct action on the dopamine neurones, since the available evidence suggests that neither mGluR2 nor mGluR5 are located on dopamine terminals themselves (Testa et al., 1994): rather they are located presynaptically on other neurone types, including glutamatergic and GABAergic neurones (Fagni et al, 2015; Gu et al., 2008), where they

modulate local circuits, intrinsic to NAc. In the case of mGluR2, this is most likely to be through an indirect attenuation in glutamate mediated facilitation of dopamine release, since mGluR2s has been shown to modulate glutamate release locally (Xi et al., 2002). In the case of mGluR5, there are two main possibilities. First, the effect may be through activating inhibitory GABA neurons which in turn modulate dopamine output (Smolders et al., 1995), since mGluR5 activation enhances GABA efflux from accumbal neurons (Diaz-Cabiale et al., 2002). Second, they may be mediated through cholinergic interneurons, where mGluR5s are widely expressed (Tallaksen-Greene et al., 1998), and have been shown to modulate cell excitability (Bonsi et al., 2005). However, further studies using more circumspect methods of stimulation would be required to pinpoint the mechanisms. The recent discovery of glutamate co-release from mesolimbic dopamine neurons (Stuber et al., 2010) raises the possibility that the modulation derives from glutamate co-released with dopamine, implying a self-regulation of mesolimbic neuronal function, although this would need further study. The drugs used were chosen based on published reports of their behavioural actions (Amitai & Markou, 2010; Greenslade & Mitchell, 2004; Woolley et al., 2008) mGluR activation. Although CPDDB is a positive allosteric modulator, while LY379268 is an orthosteric agonist, it is unlikely that the mechanistic differences have a major impact on our interpretation, since both drugs ultimately activate their respective receptors.

On the basis on the link between mGluR function and dopamine-dependent behaviours (see above), and the evidence to suggest that PCP pretreatment affects glutamate/dopamine interactions (Javitt, 2007; Jentsch et al., 1998a,b; Jentsch & Roth, 1999), the second key question addressed in this study was whether the effects of sub-chronic PCP are mediated through changes in mGluR regulation of dopamine release. Previous studies have shown that impairments in NOR performance following PCP pretreatment are reversed by dopamine D1 receptor (McLean et al., 2009) and D4 receptor (Sood et al., 2011) stimulation, while saline pretreated animals show a significant increase in dopamine utilization during the retention trial compared to PCP counterparts (McLean et al., 2017; Neill et al., 2010), albeit that this effect was seen in the prefrontal cortex rather than NAc.

However, in our experiments, we saw no evidence of any changes in the regulation of K^+-stimulated dopamine release mediated by either CDPPB or LY379268, indicating that this was not the case, although we know from preliminary data using dopaminergic drugs (data not shown), that changes following PCP pretreated can be measured using this technique. One possibility is that the PCP pretreatment itself was not effective. However two lines of evidence from our study suggest that this was not the case. First, we saw a significant enhancement of K^+-evoked dopamine release in slices taken from PCP pretreated animals, compared to those from saline pretreated animals. This finding is consistent with previous studies showing increases in dopamine after chronic

PCP treatment (Balla et al., 2001; Kegeles et al, 2000), and confirms that this PCP pretreatment regime does indeed cause an increase in accumbal dopamine function.

Second, we showed a significant behavioural effect of PCP pretreatment, in the disruption of NOR in PCP pretreated rats, thus replicating previously reported behavioural effects (e.g. Grayson et al, 2007, Sood et al., 2011), and providing evidence of an effect of PCP pretreatment in the current experiments. Although NOR is thought to be mediated through frontal cortex systems (Neill et al., 2010), and so only indirectly influenced by accumbal dopamine (Kellendonk et al., 2006), it does nevertheless provide a robust behavioural measure to ascertain that the PCP pretreatment was effective. Previous studies using the sub-chronic PCP model of schizophrenia have used adult female rats (e.g. Grayson et al., 2007; McLean et al., 2009; Sood et al., 2011). In the present study we used adolescent female rats, where the drug pretreatment occurred around the time of puberty (Sengupta, 2013), thus modelling the timing of supposed changes in brain structure underlying the onset of prodromal features predicting the future emergence of schizophrenic symptoms (Keshaven, 2014). Therefore a key finding from this study is that in these adolescent female rats we did see a reduction in NOR in the PCP pretreated animals, similar to that previously described in adult female rats, thus validating the sub-chronic PCP model in this age of rats.

In summary, these data demonstrate that subchronic PCP pretreatment for 5 days followed by a 7-day washout period impairs performance in the NOR task in juvenile female Wistar rats, as previously described in adults. This treatment causes a long-term neurobiological change in the CNS that increases dopamine neurotransmission in the NAc shell, an effect which endures after the cessation of PCP treatment. Consistent with findings from other studies, mGluR stimulation attenuates dopamine neurotransmission in the NAc shell but the effect of these drugs which activate these receptors is not changed in PCP pretreated animals, indicating that the action is not mediated by interactions with mGluR2 or mGluR5.

4. Experimental procedures

4.1 Animals

Twenty-four female juvenile Wistar rats (Central Research Facility, University of Leicester) were used. All animals were housed in groups of three under standard laboratory conditions (45(L) x 36 (W) x 38 (H) cm two level, individually ventilated cage : 12-hour light/dark cycles with lights on at 07:00, 21 ± 2°C, 40-50% humidity) with free access to food and water. All experimental procedures were carried out in accordance with the Animals

Scientific Procedures Act, UK 1986, under appropriate project (PPL 6004390) and personal license authority, and were approved by the University of Leicester Animal Welfare and Ethical Review Body (AWERB). Experimental procedures conformed to ARRIVE guidelines where appropriate.

4.2 Pretreatment

During the week after weaning (23 to 27 days old; 50 to 70 g), animals were randomly allocated to two treatment groups, and pre-treated with PCP (2 mg/kg) or vehicle (0.9% saline) in a volume of 1 ml/kg, i.p. twice daily for 5 days. Following pretreatment, they remained drug-free for the remainder of the experiment.

4.3 Novel Object Recognition (NOR) Testing

NOR testing was performed as described by Grayson et al. (2007), 7 days after the end of drug pretreatment. The testing arena comprised a black plexiglass box, 60 cm x 60 cm, with 60 cm high walls. Two types of object were used: a filled metal cylinder (food can: 12cm high x 10 cm diameter) and a glass jar (9cm high x 10 cm diameter).

On the two days immediately before testing, animals were habituated to the test arena, with no objects present, for 20 min. On the test day, each animal was first placed in the arena for a further 3 minute habituation period, with no objects in the arena, followed by 1 minute in a holding cage (20 x 20 cm). The acquisition trial followed this: two identical objects were placed in the arena in opposite corners, 10 cm from the arena walls, and rats were placed in the arena and allowed to explore for 3 minutes. Following this, animals were placed back in the holding cage for a 1 minute inter-trial interval, while the objects were changed for a third object identical to the ones from acquisition (familiar object) and a novel object, again placed in the same positions in opposite corners of the arena, with the positions of the familiar and novel objects counterbalanced across animals. The animals were then returned to the arena and allowed to explore for a further 3 minute retention trial. In each case the animal was introduced to the arena in one of the two corners not occupied by an object: the same corner was used for each animal, but the corners were counterbalanced across animals.

Acquisition and retention sessions were video recorded (Logitech c525 HD webcam) and analysed off line independently by two experimenters who were blinded to the pretreatment condition. Object exploration was defined as when the animal's head was within 2 cm of the object and it was sniffing or licking the objects, or

touching the objects with forepaws while sniffing; this included when the animal was sitting on the object with its head down (Grayson et al., 2007). However, leaning against, circling around, or standing or sitting on the objects with its head up was not deemed to be exploratory behaviour. The exploration time of each object in the acquisition and retention trials was recorded using a stop watch, and the DI (discrimination index) was calculated as follows: (novel object exploration time - familiar object exploration time)/(novel object exploration time + familiar object exploration time) (Grayson et al., 2007).

4.4 Fast-scan Cyclic Voltammetry (FCV)

Dopamine was measured in real time by FCV at carbon fibre microelectrodes, fabricated as described by Clark et al. (2010). Briefly, a 2 cm length of 8 µm carbon fibre was inserted into a 1 cm length of vitreous silica tubing (OD 90 µm, ID 20 µm; CM Scientific, Cambridge, UK) under ethanol. After drying for at least 12 hours, the carbon fibre working tip was sealed with epoxy (Devcon, 5 minute epoxy, ITW Polymers, Danvers, USA) and a gold plated pin socket (MillMax, 0667; id 0.6mm; Farnell Electronics, Leeds, UK) was secured to the opposite end with silver, conducting epoxy (Circuitworks CW2400, Farnell Electronics, Leeds, UK), ensuring a contact between the carbon fibre and the socket. Finally the carbon fibre working tip was cut to a length of 120 µm (± 20 µm) with iris scissors. Ag/AgCl reference electrodes comprised a 10 mm length of silver wire (Sigma-Aldrich, UK) attached to a gold plated pin socket (as above). The tip (5 mm) was immersed in 2M KCl, and coated electrolytically using an ACL-01 chlorider (NPI electronics, Tamm, Germany).

4.5 Brain Slice Preparation

Three to seven days after behavioural testing, animals (weight range 140 to 160 g) were culled by cervical dislocation, and the brain was removed and placed in ice-cold aCSF. Consecutive 400 µm coronal slices were cut using a Vibrotome tissue slicer (NVSLM1, World Precision Instruments, UK). Slices containing the NAcS were immediately transferred to a slice saver, comprising a wire mesh suspended in 500 ml of aCSF continuously bubbled with 95%O_2/5%CO_2 at room temperature (21 ± 2°C) for at least 1 hour before FCV experimentation.

4.6 Procedure

For FCV recording, a slice was transferred to the tissue chamber (approx. 1 ml) superfused continuously with artificial cerebrospinal fluid (aCSF) at a flow rate of 100 ml/hr, delivered by a syringe pump (P3000, IVAC Medical Systems). The recording electrode was inserted into shell region of NAc (Paxinos & Watson, 1998), under micromanipulator control, until the carbon fibre tip was inserted approximately 75 µm below the tissue surface. The reference electrode was placed remotely in the tissue chamber away from the recording electrode. Voltammetric scans were applied and recordings displayed in real-time on a desktop computer using Demon Voltammetry and Analysis Software (Wake Forest University, USA (Yorgason et al., 2011)). The voltage scan (-0.4 V to +1.3 V to -0.4 V vs Ag/AgCl electrode; 400 V/s) was applied to the working electrode, at a frequency of 1 Hz, and dopamine release was identified as oxidation at +600 mV and reduction at -200 mV. The dopamine signal was quantified by measuring the amplitude of the oxidation peak, following automated subtraction of the background (non-Faradaic) current (Demon Voltammetry software).

High-K^+ aCSF (1 ml) was administered into the superfusate, via a Rheodyne 7125 injection valve, incorporating a 1 ml injection loop, 5 minutes (S1) and 35 minutes (S2) into the recording, and the recording continued for a further 5 min (total recording time, 40 min): evoked dopamine release was plotted as a current vs time plot. Where drugs were applied to the tissue, the superfusion fluid was changed for aCSF containing the appropriate drug concentration 25 min into the recording, and it remained in the superfusate until the end of the second K^+ stimulation. Six experimental conditions (control (no drug), LY379268 (0.1 µM, 1 µM, 10 µM) and CDPPB (1 µM and 10 µM)) were used: where possible one of each condition was obtained from each animal, with the order of testing counterbalanced across animals.

Peak-dopamine concentration (µM) was calculated from maximum current (nA) generated during dopamine release, by calibration against a 5 µM dopamine standard performed on the morning of experiments. Mean peak dopamine concentration at S1 was compared across saline and PCP pretreatment groups to investigate the effect of PCP on accumbal dopamine release, and the effect of drugs applied in the superfusate was assessed by calculating the ratio of peak dopamine release during S2 compared to peak release during S1: that is S2:S1 ratio.

4.7 Drugs and solutions

Artificial cerebrospinal fluid (aCSF), comprising (mM) NaCl (126), KCl (2), KH_2PO_4 (1.4), $MgSO_4$ (2), $NaHCO_3$ (26), $CaCl_2$ (2.4), (+)-glucose (10) (Sigma-Aldrich, UK), bubbled for at least 15 min with 95% O_2 / 5% CO_2, and high-K^+ aCSF (identical except that KCl concentration was increased to 100 mM, with an equivalent decrease in NaCl

concentration to 28 mM) were prepared daily. Phencyclidine hydrochloride (Sigma-Aldrich, UK) for pre-treatment was dissolved in sterile 0.9% saline. The mGluR2 agonist LY379268 (Tocris, UK) was dissolved at 10 mM in distilled water, and frozen in 20 µl aliquots at -80°C. The mGluR5 positive allosteric modulator CDPPB (Tocris, UK) was dissolved at a concentration of 10 mM in 10% DMSO (Sigma-Aldrich, UK), and frozen in 20 µl aliquots at -80°C. On the day of the experiment, one aliquot of each drug was thawed and diluted with aCSF or high-K^+ aCSF to working concentrations of 0.1 µM, 1 µM or 10 µM for LY379268, and 1 µM or 10 µM for CDPPB. Concentrations of LY379268 and CDPPB were derived from previously published work using the two drugs (Greenslade & Mitchell, 2004 and Kinney et al, 2005, respectively)

4.8 Statistical Analysis

All data are expressed as mean ± SEM. For the behavioural experiments, statistical analyses of object exploration times in the acquisition and retention trials were performed using a two-way mixed design ANOVA. Planned follow-up paired t-tests were used to analyze the difference in exploration between the novel and familiar objects within pretreatment groups. Statistical comparison of the DI between pretreatment groups was performed using the student's t-test. Statistical analysis of the DI of each pretreatment group (compared to zero) was performed using a one-sample t-test.

For the FCV experiments, statistical analysis of the effects of PCP pretreatment on stimulated release at S1 was by independent sample t-test. The effects of LY379268 and CDPPB were analysed using two-way ANOVA on the S2:S1 ratio data, with post hoc analysis by Dunnett's test where appropriate. All analysis was performed using GraphPad Prism version 6.

Acknowledgements

We would like to thank Kate Peters for her helpful discussions during the preparation of the manuscript.

Funding

IG was funded by an Association of Clinical Pathologists Student Research Award. Otherwise this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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