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Nitric oxide synthase inhibition attenuates phencyclidine-induced disruption of cognitive flexibility

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Abstract

Schizophrenia encompasses, amongst other symptoms, a heavy load of cognitive dysfunctionality. Using the psychotomimetic agent, phencyclidine (PCP), we have previously found that PCP-induced disruptions of cognitive function in translational rodent models of schizophrenia are dependent on nitric oxide (NO) production. In the present study, male Sprague–Dawley rats were subjected to a Morris water maze task designed to assess cognitive flexibility (*i.e.* the ability to cope with an increasingly demanding cognitive task) by means of a "constant reversal learning paradigm". Experiments were conducted to evaluate the effects of the NO synthase inhibitor, L-NAME (10 mg/kg), on PCP-induced (2 mg/kg) impairments. Control animals significantly improved their learning over the first 3 consecutive days, whereas PCP-treated animals failed to show any significant learning. Pretreatment with L-NAME normalized the PCP-induced disruption of learning to control levels. These findings suggest that PCP-induced disruptions of cognitive flexibility (*i.e.* ability to modify behaviour according to an increasingly demanding cognitive task) are dependent upon NO production. These observations, together with accumulated clinical findings, suggest that the NO system is a potential treatment target for cognitive dysfunctions in schizophrenia.

Keywords: Phencyclidine; Nitric oxide; Schizophrenia; Morris water maze; L-NAME; Cognitive flexibility; Rats

1. Introduction

Dementia praecox was first described by Kraepelin as a disorder with a heavy cognitive dysfunctional burden and later termed schizophrenia by Bleuler in 1911, signifying a "split-mind" (Adityanjee et al., 1999). The cognitive impairments prevalent in schizophrenia are predictive of disease outcome (Green, 1996; Green et al., 2004; Helldin et al., 2006) and treatment response and thus constitute important targets for the development of new treatment strategies. Cognitive functions such as planning, executive functioning and working memory depend to a large extent upon the prefrontal cortex (PFC) and malfunctions within these domains are included in the abnormalities observed in schizophrenic patients (Mahurin et al., 1998; Harvey et al., 2005). Some of these cognitive dysfunctions are also observed in the first degree relatives of patients with schizophrenia (Toulopoulou et al., 2003). Therefore, these cognitive dysfunctions are not only part of the clinical syndrome but also suggested to be endophenotypic markers of the disease. The above-mentioned aspects of cognition may reflect cognitive flexibility, and malfunction in these domains may be manifested as the cognitive stereotypy (*i.e.* perseveration) observed in schizophrenia.

Several translational animal studies using the phencyclidine (PCP) model of schizophrenia have shown PCP to induce disruptions of cognitive functions that corresponds to dysfunctions observed in the human condition (Jentsch and RH, 1999; Palsson et al., 2005). Some of these PCP-induced disruptions can be reduced by atypical antipsychotics (Didriksen et al., 2007; Fejgin et al., 2007; Jentsch et al., 1997). However, available antipsychotics do not have a satisfactory effect on cognitive dysfunctions in patients with schizophrenia, hence the

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need for novel cognitive enhancing treatments. A putative novel treatment approach is targeting the nitric oxide (NO) signalling pathway. Several experimental studies along with clinical findings indicate that the NO system of the brain is involved in the pathophysiology of schizophrenia (Bernstein et al., 2005). In previous animal studies, our research group has shown that PCP-induced disruption of functions such as pre-attentive information processing, non-associative learning, selective attention, working and long-term memory, can be reduced by pretreatment with a NO synthase (NOS) inhibitor (Johansson et al., 1997; Klamer et al., 2001, 2004a,b,c, 2005a,b,c; Wass et al., 2006a,b). Thus, the NO system may be a suitable treatment target for alleviating cognitive dysfunctions in patients with schizophrenia (Palsson, 2006).

NO is formed in a two-step oxidation reaction catalyzed by NOS between the amino acid, L-arginine, and molecular oxygen. In the brain NO is proposed to be a key link between *N*-methyl-D-aspartate (NMDA) receptor mediated increases in cytoplasmic Ca^{2+} and activity-dependent long-term changes such as neuronal differentiation and synaptic plasticity (Karatinos et al., 1995; Snyder and Ferris, 2000). Moreover, NO seems to be involved in several aspects of cognition, amongst which learning and memory are implicated, as NO may act as a retrograde messenger during long-term potentiation (O'dell et al., 1991; Zhuo et al., 1994; Lu et al., 1999). Interestingly, the psychotomimetic effect of PCP has been attributed to, *e.g.* its action at the glutamatergic NMDA receptor. PCP acts as a non-competitive antagonist of this receptor via a binding site inside the channel complex (Javitt and Zukin, 1991; Lodge and Anis, 1982). Somewhat paradoxically, PCP has been shown to increase glutamate release in regions such as the PFC (Adams and Moghaddam, 1998). This glutamatergic hyperactivity may explain some of the behavioural effects of PCP as well as indications of an increased NO production (Fejgin et al., in press). Thus, the PCP-induced behavioural changes could be caused by a loss of inhibitory control via a blockade of NMDA receptors on GABAergic interneurons. This in turn could result in disinhibition of primary corticolimbic neurons leading to a complex neurofunctional imbalance including several neurotransmission systems (Farber, 2003; Olney et al., 1999; Thornberg and Saklad, 1996). By these complex effects, PCP may mimic unique properties of schizophrenia rendering the PCP-model heuristic potential for identifying new treatment rationales (Lipska and Weinberger, 2000) possibly including cognitive dysfunctions. Furthermore, it has been suggested that NO is involved in several aspects of cognition, *e.g.* learning and memory (Bernstein et al., 2005; Zhuo et al., 1994). Behavioural studies show that inhibitors of NOS disrupt spatial learning (Chapman et al., 1992; Zou et al., 1998) and furthermore that NOS is expressed in *e.g.* pyramidal neurons of the hippocampus *cornu ammonis* 1 (CA1), (Pepicelli et al., 2004).

A behavioural paradigm for testing declarative memory in rodents by utilising these animals' well-developed spatial navigation ability was established decades ago (see, *e.g.*, Morris, 1984). The Morris water maze (MWM) model has since been used widely to assess learning and memory function. Acute treatment with PCP has been shown to induce deficits in both spatial learning, working memory, and long-term memory (Wass et al., 2006a,b). Furthermore, (Hanlon et al., 2006) demonstrated that patients with schizophrenia display deficits in learning and memory function using a computerized, virtual version of the MWM. Thus, the MWM has translational value as a cognitive test, with at least face validity, in both preclinical and clinical schizophrenia research. Recent studies by the present authors (Wass et al., 2006a,b) have shown that NOS inhibition reduces PCP-induced disruption of spatial working and long-term memory using different versions of the MWM model. The present study was designed to further investigate the ability of NOS inhibition to counteract the effects of PCP on cognitive function. To this end, the capacity of the NOS inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), to reduce the effect of PCP in rats was studied using a model in which increasing complexity of the learning task was applied with each testing day ("constant reversal learning" *i.e.* learning a new platform position each training day). In this model, control rats showed an increase in performance over the first three days of training sessions followed by a decline in performance over the last day. One advantage with this model is that it estimates the limit of the rats' cognitive ability.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats with a body weight of 250 g were purchased from B&K Universal AB, Sollentuna, Sweden. Upon arrival to the animal facility the animals were housed three to four per cage in a colony room for two weeks in order to get used to the new environment and human handling before testing started. Food (B&K Feeds) and water were available *ad libitum*, and room temperature (20±1 °C) and humidity (55%) were kept constant. The daylight cycle was maintained artificially, lights off between 18:00 and 07:00 h, and all experiments were performed during the light phase. The study was approved by the Ethics Committee for Animal Experiments, Göteborg, Sweden.

2.2. Drugs

Phencyclidine (1-(1-phenylcyclohexyl)piperidine HCL) (RBI, Natick, USA) and L-NAME (N^G-nitro-L-arginine methyl ester) (RBI) were used. The drugs were dissolved in saline (0.9% NaCl dissolved in distilled water, SAL) and injected in a volume of 2 ml/kg subcutaneously (sc).

2.3. Apparatus

A circular pool with a diameter of 1.4 m and a circular Plexiglas escape platform (HVS Image, UK) with a diameter of 10 cm were used. The pool was filled with water of a temperature of 24±1 °C and the water surface was kept 2 cm above the platform. White paint soluble in water (Allmogefarg, Panduro, Göteborg, Sweden) was used to make the water opaque. The pool was placed in a room with external cues, and these cues were kept in a constant position throughout the whole experimental period.

Data recordings and swimming pattern analysis were made by means of a 2020 Plus Tracking System (HVS Image, UK).

2.4. Experimental design

The design was set up in order to study the ability of rats to deal with an increasingly demanding cognitive task (*i.e.* show cognitive flexibility) in a water maze model modified after (Morris, 1984) and (Baldi et al., 2005). The recorded mean time to find the platform on each of the acquisition days was used to assess learning. Rats were first given an acclimatization training trial in the water maze for 30 s (s) during which the platform was removed. Two days later the acquisition training began. Each swimming session consisted of a total of 11 swimmings, the last swimming being a probe trial (platform removed), and this procedure was repeated for four consecutive days. Each swimming lasted for a maximum of 60 s followed by a 20 s platform rest (except on probe trails) and then a 20 s rest in a plastic cage, followed by the subsequent swimming. Water odour traces were removed during the rest in the plastic cage and then the platform was removed prior to the probe trial. The platform position was held constant *within* each of the acquisition days but varied *between* acquisition days, such that each animal was to find the platform in a novel position on the first swimming of each day. The platform was positioned in a new quadrant randomly on each of the four acquisition days. The starting positions were randomized on each swimming such that the rat was placed in the pool from one of eight positions (North (N), East (E), South (S), West (W), SE, SW, NW, NE), facing the wall of the pool. After each swimming trial the rat was washed and then allowed to dry under a fan heater before put back in the home cage (Fig. 1).

2.5. Drug treatment

On each of the acquisition days, before the session started, the rats ($n=32$) were pretreated with saline or L-NAME (10 mg/kg) 25 min before the first swimming and 10 min prior to a second saline or a PCP (2 mg/kg) injection. The number of rats per treatment group was eight. The doses were selected based on previous findings within the research group (Palsson et al., 2005; Klamer et al., 2005a,b,c). Mean time to find the platform (s) and swimming speed (m/s) was recorded on each of the four acquisition days. Swimming pattern analysis was carried out on Day 2 by adding together all 10 swimmings from one representative animal of each treatment group (Fig. 3).

2.6. Statistics

Data are presented as means ± SEM in the figures. Time to find the platform and swimming speed over the 10 swimming trials on each of the four acquisition days were analysed using a repeated measures three-way ANOVA with pretreatment (saline or L-NAME) and treatment (saline or PCP) as between-subjects factors and acquisition session as within-subjects factor. Post hoc analysis was performed by Bonferroni's Multiple Comparison Test when appropriate. Two-tailed levels of significance were used and $p<0.05$ was considered statistically significant.

3. Results

The acquisition sessions were analysed using a repeated measures three-way ANOVA with pretreatment (saline or L-NAME) and treatment (saline or PCP) as independent factors and acquisition session as dependent factor with four different levels (Days 1–4) (Fig. 2).

3.1. Learning improved on days 2 and 3

Statistical analysis of time to find the platform with treatment collapsed over treatment groups showed a significant main effect of acquisition sessions ($F(3,84)=6.92$, $p<0.001$). Further post hoc analysis showed that time to find the platform was shorter at Days 2 and 3 compared to Day 1 ($p<0.01$, Bonferroni's test),

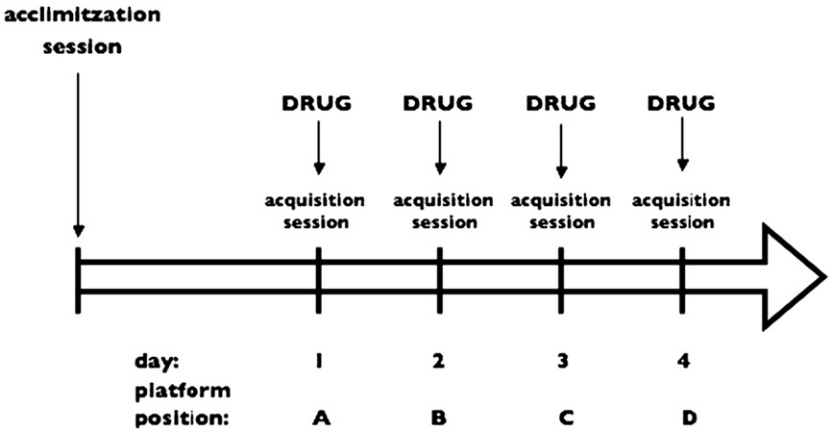

Fig. 1. Experimental design. Acclimatization session consisted of a 30 s swimming trial without platform, two days prior to the first acquisition day. Each acquisition session included 10 consecutive swimmings (maximum 60 s), each followed by a 20 s platform rest and the 10th swimming was followed by one probe trial (i.e. a 60 s swimming without platform). Thus, each daily swimming session consisted of a total of 11 swimmings. Drugs were administered acutely prior to the first swimming of each swimming session, on each of the four acquisition days. Platform positions were randomly varied between acquisition days (positions A, B, C, and D).

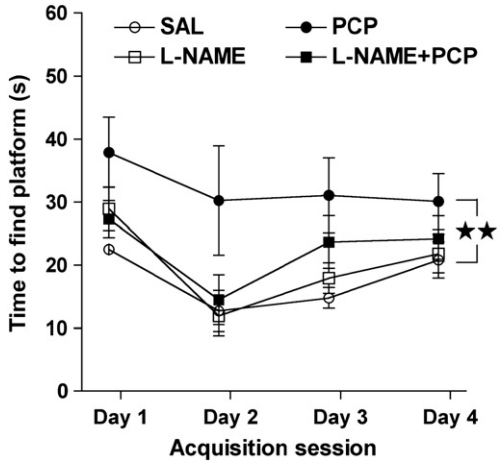

Fig. 2. The effect of saline+saline (SAL, $n=8$), L-NAME (10 mg/kg)+saline ($n=8$), saline+PCP (2 mg/kg, $n=8$), or L-NAME (10 mg/kg) + PCP (2 mg/kg) ($n=8$), on acquisition during a spatial reversal task using the Morris water maze. The results are represented by the mean values±S.E.M. of eight rats in each group. Three-way ANOVA showed significant effects of both treatment ($p<0.01$) and acquisition session ($p<0.001$) indicating disruption of reversal learning in saline+PCP-treated rats. Further, there was also a significant interaction between pretreatment and treatment ($p<0.05$). $^{**}p<0.01$, saline+saline-treated rats compared to saline+PCP-treated rats, acquisition sessions collapsed over training days (Bonferroni's multiple comparison test).

whereas time to find the platform at Day 4 was not significantly different from any of the other acquisition sessions. Based on these findings it was concluded that the rats showed improved performance in the maze over the first 3 acquisition sessions but failed to do so on the last session. Therefore this session was excluded from further statistical analysis.

3.2. PCP treatment impaired acquisition

Statistical analysis of time to find the platform, with acquisition sessions collapsed over days, showed a significant main effect of treatment ($F(1,28)=12.00$, $p<0.01$). Furthermore, a significant pretreatment by treatment interaction effect ($F(1,28)=6.96$, $p<0.05$) was found. Post hoc analysis showed that time to find the platform was significantly prolonged in PCP-treated rats compared to all other treatment groups ($p<0.01$ vs. saline, $p<0.01$ vs. L-NAME, and $p<0.05$ vs. L-NAME+PCP, Bonferroni's test). Based on these findings further statistical analysis was conducted with PCP-treated rats excluded.

3.3. L-NAME treatment restored PCP-impairment to control levels

Analysis (excluding the PCP-treated group) showed no significant differences in performance between saline-, L-NAME-, or L-NAME+PCP-treated rats either with regard to treatment group or acquisition session. This indicated that the effect of PCP was attenuated to control levels by pretreatment with L-NAME. Thus, these analyses indicate that rats from all treatment groups, except PCP-treated rats, could develop successful strategies to deal with the cognitive demands of the task

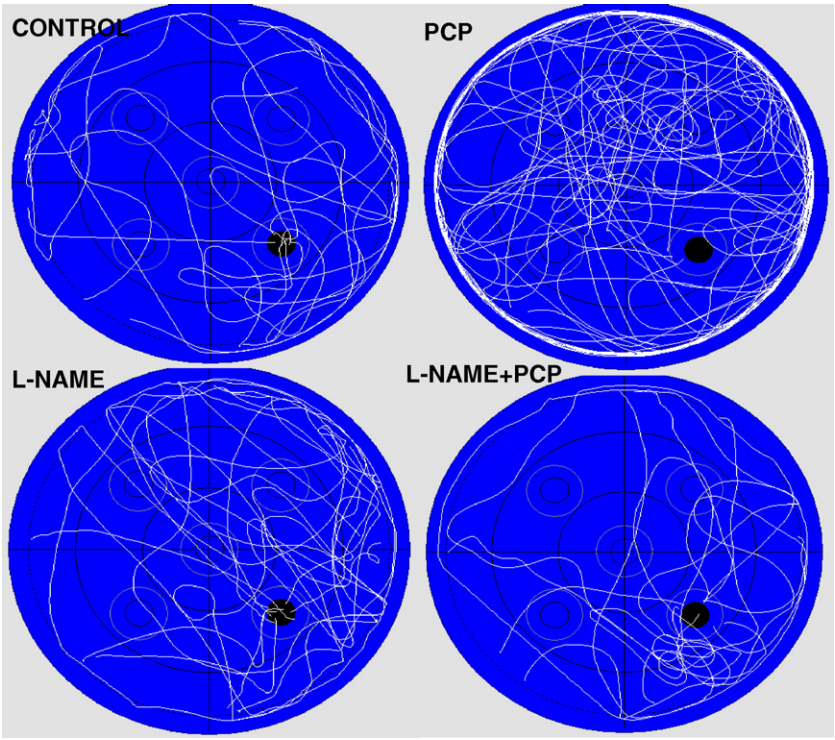

Fig. 3. The effect of saline (SAL, $n=1$), L-NAME (10 mg/kg, $n=1$), PCP (2 mg/kg, $n=1$), or L-NAME + PCP ($n=1$) on swimming behaviour during a spatial reversal task using the Morris water maze. The results are represented by the accumulated swimming path of 10 consecutive swimmings of one representative rat from each treatment group on Day 2. The platform position is marked by the black circle and the swimming paths are drawn in white.

on the first 3 days of training. After the third day complexity reached a level at which the rats could no longer cope with the demands.

3.4. There were no effects of treatment on swimming speed or probe behaviour

Swimming speed was not significantly affected by treatment. Neither was treatment found to significantly affect the rats' performance during probe trials as measured by the averaged swimming distance to the previous platform position.

3.5. PCP affects swimming pattern and induces stereotypic behaviour: reversal by L-NAME pretreatment

Gross observation of the rats' swimming patterns indicated significant differences related to drug treatment mainly explained by a clear-cut thigmotaxis in PCP-treated rats. Fig. 3 shows swimming patterns after saline, L-NAME, PCP or L-NAME+PCP treatment of one representative animal per treatment group over 10 swimming trials on Day 2.

4. Discussion

A Morris water maze model designed to assess cognitive flexibility by increasing the cognitive load was used in the present study. The results indicate that rats treated with saline, L-NAME, or L-NAME+PCP, significantly increased their performance in the maze as measured by time to find the platform between Day 1 and Day 2, and Day 1 and Day 3. When the platform was moved to a new position a fourth time (Day 4) there was a decline in performance. Thus, these rats signalled a certain learned ability how to use the external cues to guide them through the swim maze on Days 2 and 3. However, as the cognitive load increased over the remaining test day with a fourth switching of platform position, they signalled deterioration in their ability to solve the task. PCP-treated rats on the other hand, failed to demonstrate any significant improvement in performance over the acquisition sessions. This indicates a sustained inability to solve the learning task and is in line with previous studies (Wass et al., 2006a,b). Notably, pretreatment with L-NAME attenuated the PCP-induced disruption of learning, as L-NAME+PCP-treated rats performed at the same level as saline-treated rats during the whole testing period.

The present MWM paradigm is a novel approach to investigate how PCP interacts with cognitive flexibility. A similar delayed matching-to-place paradigm was used in order to assess the role of NMDA receptors in encoding and retrieval (Steele and Morris, 1999). In this experiment the platform positions were varied between days, however inter-trial intervals were varied and the training session differed from the present study. In previous studies, PCP has been shown to disrupt learning using other maze paradigms (Abdul-Monim et al., 2003; Handelmann et al., 1987; Idris et al., 2005). Furthermore, NOS inhibition attenuated PCP-induced disruption of learning in the present study whereas L-NAME alone did not affect learning. The latter result is in conflict with previous findings in which L-NAME was found to disrupt learning and memory in the MWM (Majlessi et al., 2003). A possible explanation for the lack of effects of NOS inhibition *per se* on learning and memory, in the present and previous studies, may be that a lower dose of L-NAME has been used (Wass et al., 2006a,b). The same explanation may be applied regarding the comparison of the present findings to the findings by Yamada et al. (1996) which demonstrated that the NMDA receptor antagonist, dizocilpine, as well as the NOS inhibitors, L-NAME and 7-nitro indazole, were found to impair spatial working memory in mice. In addition, these impairments were suggested to be due to a decrease in cGMP production as the memory impairment was reversed by increasing cGMP levels and, since treatment with dizocilpine and NOS inhibitors decreased cGMP levels in the mouse brain ex vivo. These findings suggest that NMDA receptor antagonism impairs spatial learning by reducing NO/cGMP production in the brain (Yamada et al., 1996). On the contrary, we have demonstrated that systemic PCP administration increases cGMP levels, while L-NAME treatment had no effect on basal cGMP production, in the medial PFC of the mouse brain *in vivo* (Fejgin et al., in press).

Gross observations of PCP-treated rats compared to the other treatment groups indicated distinct qualitative differences in swimming patterns (see Fig. 3). Animals receiving PCP treatment showed a marked thigmotaxis (circulating swimming pattern along the walls of the pool) suggesting an aimless searching behaviour. Animals from the other treatment groups showed a more goal-directed searching behaviour as their swimming trails were considerably closer to the platform area. Notably, rats having received pretreatment with L-NAME seemed to respond to PCP treatment to a much smaller extent as their swimming pattern rather resembled saline-treated than PCP-treated rats. Hence, the effects of PCP on water maze behaviour do not seem to be only quantitatively different from that of control animals. It may be speculated that the PCP-induced disruptions of normal searching behaviour resemble the disrupted cognitive flexibility displayed by schizophrenic patients as thigmotaxis is considered a stereotypic behaviour. PCP increases locomotion in rodents when tested in an open arena (Johansson et al., 1997). In the present study, no significant effect of PCP on swimming speed was detected. We have previously shown that PCP increased swimming speed in a water maze paradigm similar to the one used in the present experiment (Wass et al., 2006a). The same study further indicated that the PCP-induced increase in swimming speed could be blocked by NOS inhibition. Systemic administration of L-NAME most likely affects both the motor deficits and the cognitive impairments induced by PCP. We previously demonstrated that L-NAME block PCP-induced hyperlocomotion as well as behaviours ranging from pre-attentive information processing to working memory (Johansson et al., 1998, 1997; Klamer et al., 2001, 2005a; Wass et al., 2006a). Interestingly our most recent publication demonstrates behavioural specificity when blocking NO-dependent cGMP production locally in the medial PFC. This blockade protects against PCP-induced deficits in pre-attentive information processing (using the pre-pulse inhibition model), but had no effect on PCP-induced hyperlocomotion (Fejgin et al., in press). Thus, the ability of L-NAME pretreatment to block the PCP-induced abnormal swimming

pattern suggests that NOS inhibition is effective in ameliorating disturbances of complex cognitive functioning.

Several of the cognitive difficulties connected to high-complexity tasks in patients with schizophrenia are coupled to an impaired integrity of PFC functioning (Weinberger et al., 1986; Ingvar and Franzen, 1974). Deficits of working memory and executive functioning are examples of such higher order cognitive dysfunctions that can be behaviourally assessed in rodents. Although the present study does not explore the specific role of the PFC in cognitive functioning, recent findings from our research group have investigated the role of the PFC in sensory information processing (measured by the pre-pulse inhibition response). Deficits of pre-pulse inhibition have been hypothesized to give rise to higher order cognitive dysfunctions (Braff, 1993) and a normal pre-pulse inhibition response is modulated by the PFC (Bakshi and Geyer, 1998). We have recently found that the NO system of the PFC in mice is important for the effects of PCP on pre-pulse inhibition (Fejgin et al., in press).

As NO production is coupled to activation of the NMDA receptor, it is counterintuitive that PCP as an NMDA receptor antagonist should increase NO levels. However, accumulating data indicate that PCP-induced behavioural and neurochemical changes can be ameliorated by NOS inhibition (Wiley, 1998; Klamer et al., 2004c; Fejgin et al., in press; Palsson et al., 2007). In addition, a recent study suggests an increase in NO production following PCP administration, since mice treated acutely with PCP (5 mg/kg) showed a significant increase in cGMP content in the medial PFC as measured by microdialysis. This PCP-induced increase in cGMP was blocked by pretreatment with L-NAME (40 mg/kg). Furthermore, blocking the NO-dependent cGMP production with local injection of an inhibitor of soluble guanylyl cyclase into the medial PFC significantly attenuated the PCP-induced disruption of pre-pulse inhibition in mice (Fejgin et al., in press). Data using a microelectrochemical sensor for measuring NO levels *in vivo* (Brown and Lowry, 2003), in awake and freely moving rats, suggest that there is a transient and long-lasting increase in NO levels in the medial PFC following acute PCP (2 mg/kg) administration (Lowry JP et al. in collaboration, unpublished data). Thus, there is accumulating evidence supporting the hypothesis of a stimulatory effect of PCP on NO production following acute treatment.

PCP and its analogue ketamine have been shown to cause an increase in glutamate and dopamine levels in the PFC of the rat (Adams and Moghaddam, 1998; Moghaddam et al., 1997). Based on these findings it is possible that the increased glutamate efflux in the PFC leads to stimulation of *e.g.* calcium permeable α-amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) receptors (Yin et al., 1994). Furthermore, besides having affinity for the NMDA receptor, PCP also binds to 5-HT2 receptors and dopamine D2 receptors (Kapur and Seeman, 2002). It is therefore possible that these non-NMDA receptors and/or secondary effects of neurotransmitters, such as *e.g.* glutamate and dopamine, also are involved in the present effects of PCP on water maze behaviour.

Clinical findings, such as those by Yilmaz et al. (2007), have demonstrated increased levels of NO in serum of patients with schizophrenia in comparison with controls. Further, (Deutsch et al., 1997) treated patients with chronic schizophrenia with methylene blue, an inhibitor of NO production, as an adjuvant to conventional antipsychotics and found a decrease in overall psychopathology in these patients. The present and previous findings indicate a dysregulated NO system as part of the pathophysiology of schizophrenia (Baba et al., 2004; Bernstein et al., 2005; Reif et al., 2006). Hence, pharmacological manipulation of NO activity may be a fruitful approach when trying to alleviate cognitive dysfunctions in schizophrenia.

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