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Subchronic phencyclidine exposure potentiates the behavioral and c-Fos response to stressful stimuli in rats

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Abstract

Prior exposure to subchronic phencyclidine (PCP) produces behaviors argued to model schizophrenia in rats, including alterations in the behavioral responses to stress-inducing stimuli. Prior exposure to a single injection of PCP also produces a number of schizophrenia-like behaviors in rats, suggesting that a single injection of PCP is able to model schizophrenia-like behaviors as well. We examined the effects of prior exposure to either a single injection or subchronic PCP on stress-induced behavior and c-Fos-like immunoreactivity (FLI). Twenty-four hours after a single injection of PCP (15 mg/kg) or subchronic PCP (10 mg/kg for 14 days) or saline, male rats were exposed to either novel environment, forced swim, or left in their home cages. A single injection of PCP produced only small effects on stress-induced behavior and FLI: a drug × time interaction on the number of cage crossings in the novel environment and a drug × condition interaction on FLI in the shell of the nucleus accumbens. However, subchronic PCP decreased cage crosses and rears in the novel environment and increased immobility in the forced swim test. The increased immobility in the forced swim test was accompanied by increased striatal FLI. These data suggest that while a single injection of PCP produces only minimal alterations in the response to stressful stimuli, subchronic PCP produces a quantitatively greater effect. In addition, the observation that PCP pretreatment increased striatal FLI induced by forced swim but not novelty suggest that PCP alters the behavioral responses to these stressors via different neurochemical mechanisms.

Keywords: Forced swim test; Novel environment; Schizophrenia; Striatum; Prefrontal cortex; Nucleus accumbens

1. Introduction

Phencyclidine (PCP) produces a schizophrenia-like state in humans and has thus been investigated for its ability to model schizophrenia-like behaviors in animals (Javitt and Zukin, 1991). Withdrawal from single and/or subchronic injections of PCP has been reported to produce a variety of schizophrenia-like behaviors including increased behavioral response to amphetamine (Jentsch et al., 1998; Turgeon and Roche, 1999), decreased social interaction (Lee et al., 2005; Sams-Dodd, 1998), disrupted latent inhibition (Turgeon et al., 1998), and decreased reward function (Spielewoy and Markou, 2003; Turgeon and Hoge, 2003). In addition, subchronic PCP has been reported to increase the behavioral response to stressful stimuli in animals. PCP pretreatment increases the behavioral response to a novel environment in rats (Jentsch et al., 1998) and increases immobilities in the forced swim test in mice (Abdel-Naby Sayed et al., 2001; Noda et al., 1995, 1997, 2000), a depression-related test which also functions as a stressor. These PCP-induced changes in the response to stressful stimuli may provide a model for abnormalities in the stress response that have been noted in schizophrenia (Yeap and Thakore, 2005).

While previous experiments looking at the effects of PCP exposure on the response to stressful stimuli have examined the effects of withdrawal from subchronic PCP administration, prior exposure to a single injection of PCP has also been found to produce behavioral changes argued to model schizophrenia in animals. In comparison to controls, prior exposure to a single injection of PCP (15 mg/kg) increased the behavioral response to amphetamine (Turgeon and Roche, 1999), increased escape latency in a water maze (Okuyama et al., 1995) and produced decreases in voluntary sucrose consumption (Turgeon and

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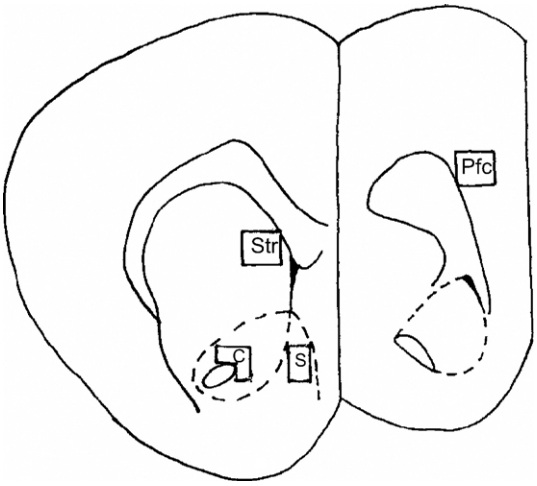

Fig. 1. Areas in which FLI positive cells were counted. The area of the regions counted in the striatum (Str) and the prefrontal cortex (Pfc) was 640 μm × 480 μm, the area in the nucleus accumbens shell (S) was 320 μm × 480 μm, and the area in the nucleus accumbens core (C) was 640 μm across the top, 480 μm across the long side, 240 μm across the short side and 320 μm across the bottom.

Hoge, 2003) as well as increases in self-stimulation thresholds (5 and 10 mg/kg; Spielewoy and Markou, 2003), suggesting decreased reward function. However, there do appear to be differences in the ability of prior exposure to subchronic and single injections of PCP to induce behaviors argued to model schizophrenia in animals. For example, repeated injections of 10 mg/kg PCP produced excessive atypical grooming in rats (Audet et al., 2006) and increases in forced swim test immobilities in mice (Noda et al., 1995) not seen after a single injection. Given the evidence that a single injection of 15 mg/kg PCP is able to produce some schizophrenia-like behaviors and that the reports failing to show effects of a single dose of PCP used only 10 mg/kg, it is not clear whether the failure to see schizophrenia-like effects following a single dose is due to an inadequate number of exposures or an inadequate dose of PCP. Should withdrawal from a single injection of PCP produce some but not all of schizophrenia-like effects seen following withdrawal from subchronic PCP, this would suggest that these behavioral effects are mediated by different neurochemical sequelae of PCP exposure. An elucidation of the differential induction of schizophrenia-like behaviors following withdrawal from single versus subchronic PCP will allow for the identification of relevant neurochemical changes underlying the behavioral effects of PCP. Therefore, we examined the effects of prior exposure to single (15 mg/kg) and subchronic (10 mg/kg daily for 14 days) injections of PCP on the behavioral response to a two stressors: novel environment and forced swim.

Previous research in our laboratory has implicated the striatum as a region of interest in examining the behavioral effects of PCP. We have found changes in striatal c-Fos-like immunoreactivity (FLI) associated with PCP-induced increases

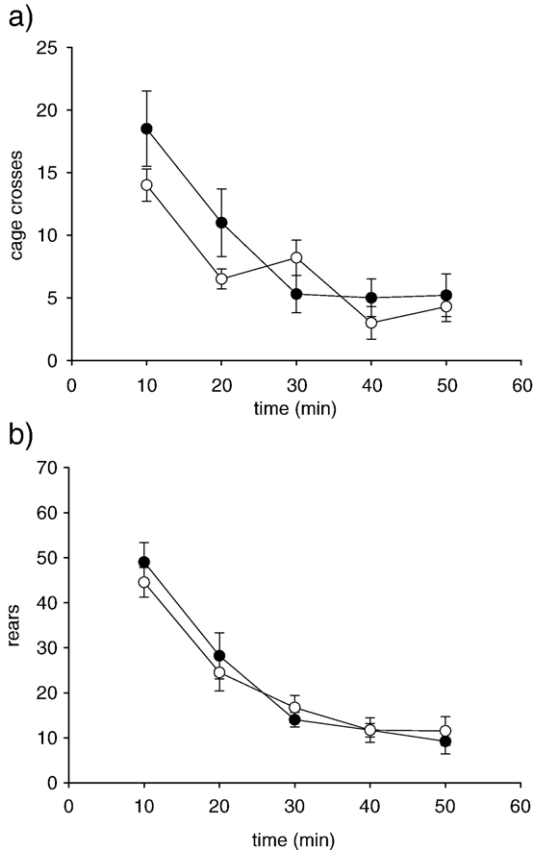

Fig. 2. Effects of prior exposure to a single injection of PCP on behavior in a novel environment. PCP did not alter the number of cage-crosses (a) or rears (b) in the first 50 min in the novel environment.

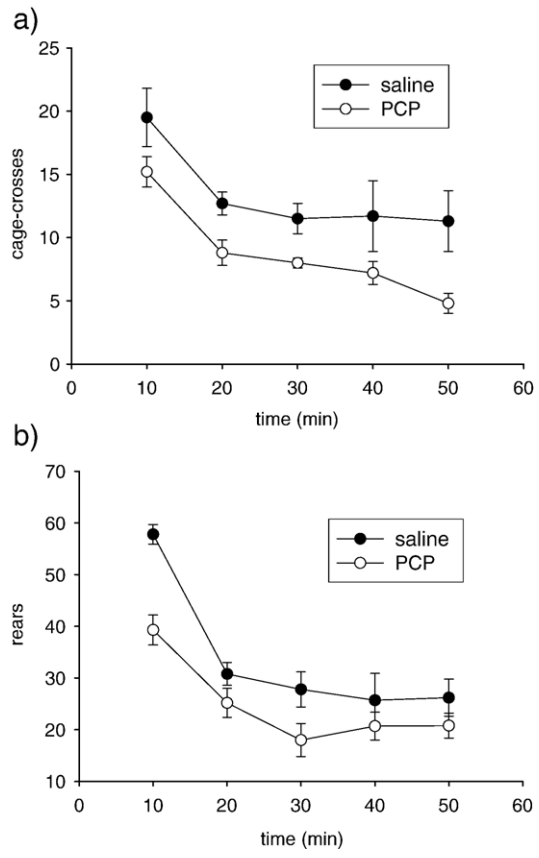

Fig. 3. Effects of prior exposure to subchronic PCP on behavior in a novel environment. PCP decreased the number of cage-crosses (a) and rears (b) in the first 50 min in the novel environment.

in amphetamine-induced behavior (Turgeon and Roche, 1999) as well as latent inhibition in a conditioned taste aversion paradigm (Turgeon and Reichstein, 2002) which can be modulated by PCP (Turgeon et al., 1998). Finally, subchronic PCP has been shown to increase striatal FLI in both stressed and non-stressed mice (Abdel-Naby Sayed et al., 2001).

The prefrontal cortex is also thought to be involved in the effects of PCP pretreatment. Jentsch, et al. have reported decreases in dopamine utilization in the PFC following subchronic PCP treatment (Jentsch et al., 1997, 1998) and lesions to the PFC have been reported to increase stress-induced increases in nucleus accumbens DA (Deutch et al., 1990). In addition, we have found decreases in PFC FLI 24 hours after a single injection of PCP (Turgeon and Roche, 1999). Subchronic PCP also increases FLI in the cingulate cortex in both stressed and non-stressed mice (Abdel-Naby Sayed et al., 2001).

While we have not previously found evidence for PCP-induced alterations in nucleus accumbens FLI, a range of stressors have been found to influence nucleus accumbens Fos induction. Injection stress increases FLI in the nucleus accumbens (Barrot et al., 1999), and both novelty (Badiani et al., 1998) and swim stress (Cullinan et al., 1995) increase *c-fos* mRNA in the nucleus accumbens. These observations suggest that the nucleus accumbens may be a region of interest as well. In order to assess the possible involvement of these areas in PCP induced changes in the stress response, we examined FLI induction in the striatum, PFC, and nucleus accumbens following exposure to the novel environment, the swim test, and in unstressed controls.

2. Experimental procedures

2.1. Animals and drugs

Thirty-six male Sprague-Dawley rats were used in each experiment. Rats were individually housed in hanging wire cages, maintained on a 12-hour reverse light-dark cycle and allowed access to food and water ad libitum. In the single injection experiment, rats were injected with PCP (15 mg/kg, ip) or saline. In the subchronic experiment, rats were injected with PCP (10 mg/kg, ip) or saline daily for 14 days. Twenty four hours following the last injection, animals were exposed to a novel environment, the forced swim test (FST), or no stress such that 6 groups were generated for each experiment: saline-no stress, PCP-no stress, saline-novel, PCP-novel, saline-FST, and PCP-FST ($n=6$ per group). All methods were approved by the Institutional Animal Care and Use Committee at Amherst College.

2.2. Behavioral testing

The novel environment consisted of a Plexiglas aquarium (60 cm × 32 cm) with wood shavings on the floor. The aquarium

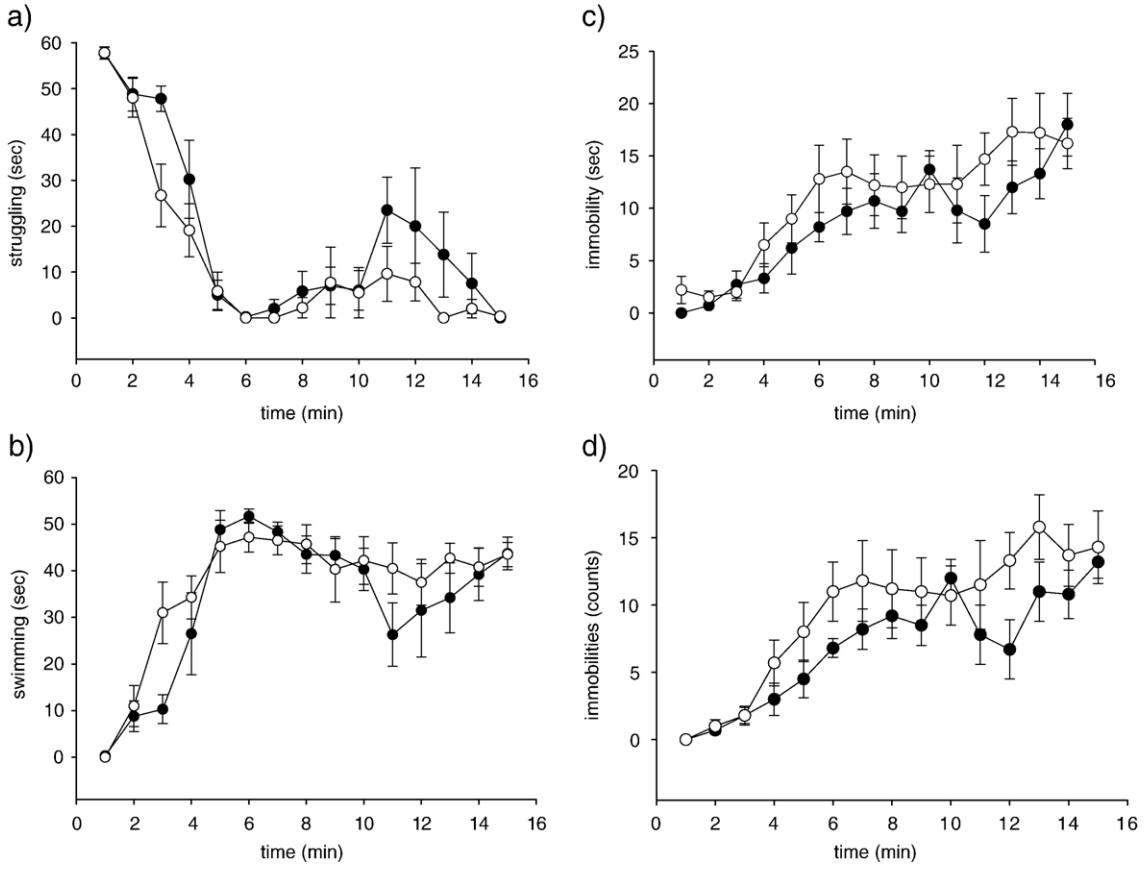

Fig. 4. Effects of prior exposure to a single injection of PCP on behavior in a forced swim test. PCP did not alter the amount of time spent struggling (a), swimming (b), or immobile (c) or the number of immobilities (d).

was located in a separate room with dark walls and a red light. Animals were placed in the aquarium for 110 min and then perfused 120 min after the onset of the stress. Videotapes of the animals behavior during the first 50 min in the novel environment were coded for number of cage-crosses and number of rears by an experimenter blind to the treatment condition. A cage-cross was defined as a movement in which the rat began behind a point six inches from one end of the aquarium and ended across a mark six inches from the other end. A rear was defined as a movement in which the rat stood on his hind legs and his front paws rose above a mark 13 cm from the bottom of the aquarium. Due to video tape error, data for 1 rat in the subchronic PCP group were lost; however, this animal remained in the immunohistochemical analysis.

The forced swim test was conducted in a clear Plexiglass cylinder 60.5 cm high and 29 cm in diameter, filled with 30 cm of water at 25 °C. Rats were videotaped for 15 min, placed under a warm air blower for 20 min, returned to their home cages, and then perfused 2 h after the onset of the swim test. Videotapes were coded by an experimenter blind to treatment condition for the amount of time spent swimming, struggling, and immobile. In addition, immobility was assessed by counting the number of times the rat sank under water and had to swim to return to the surface. Due to video tape error, data for 1 rat in the subchronic PCP group and 2 rats in the subchronic saline group were lost; however, these animals remained in the immunohistochemical analysis.

2.3. Perfusion

Rats were anesthetized with 0.5 ml (im) of a cocktail containing ketamine (50 mg/ml) and xylazine (10 mg/ml) followed by 0.5 ml pentobarbital (100 mg/ml, ip) and perfused transcardially with cold 0.9% saline followed by 4% paraformaldehyde. Brains were post-fixed in paraformaldehyde overnight, and cryoprotected in 30% sucrose for 24 h. Brains were then sliced into 50 μm coronal sections using a freezing microtome and stored in PBS until processing for c-Fos immunohistochemistry.

2.4. Immunohistochemistry

Sections were processed for Fos-like immunoreactivity (FLI) using a rabbit polyclonal c-Fos antiserum (1:1000, Santa Cruz Biotechnology). Tissue was pre-incubated for 30 min in PBS with 2% normal goat serum and then incubated overnight in the primary antibody. Tissue was then washed with phosphate buffered saline (PBS) three times for 20 min each and incubated in biotinylated goat anti-rabbit secondary antibody at a 1:200

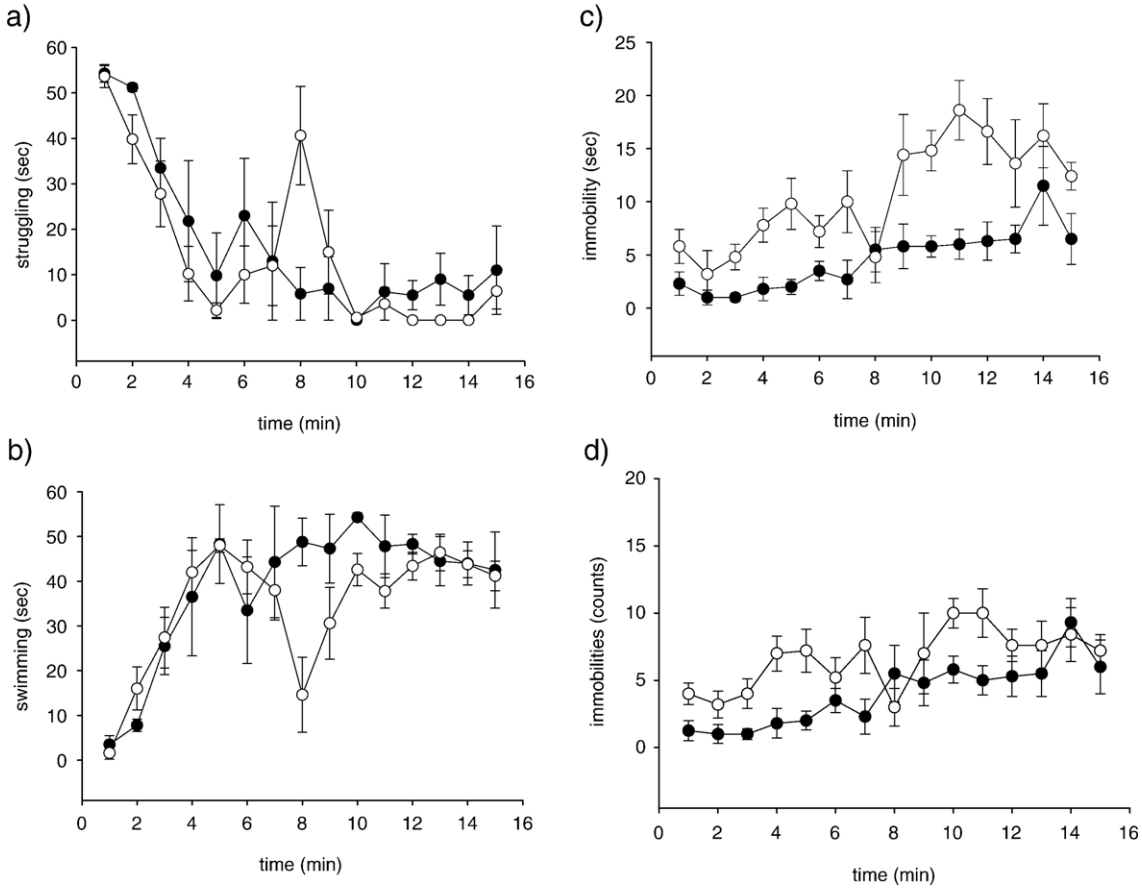

Fig. 5. Effects of prior exposure subchronic PCP on behavior in a forced swim test. PCP did not alter the amount of time spent struggling (a) or swimming (b); however, PCP did increase the amount of time spent immobile (c) and the number of immobilities (d).

dilution. Following three twenty minute washes in PBS, tissue was incubated for 1 h in avidin–biotin–horseradish peroxidase conjugate from goat. Tissue was washed three times in PBS, once in 50 mM Tris buffer (pH 7.6) for 15 min and then developed using a DAB substrate kit (Vector Laboratories, Burlingame, CA).

Immunoreactivity was quantified using a microscope with the field projected onto a television screen at 10× magnification. Sections were chosen between the levels of plates 9 to 13 in the atlas of Paxinos and Watson (1986). The number of immunoreactive cells in the prefrontal cortex, striatum, and nucleus accumbens were counted in the regions depicted in Fig. 1 by an experimenter blind to the treatment group. Due to inadequate sections at the level of the nucleus accumbens, data for one rat in the single injection saline-novel group were not obtained for this area. For each brain, six half brain sections were averaged. The values presented represent the average number of immunoreactive cells in one half brain section.

2.5. Statistics

All behavioral results were analyzed using repeated measures ANOVA with time as the within subjects variable and drug as the between subjects variable. All FLI data were analyzed using a 2×3 ANOVA with drug (saline, PCP) and condition (home, novel, swim) as between subjects variables. In addition, two-tailed *t*-tests were used to examine the effects of PCP on FLI under individual conditions in the presence of marginally significant effects of drug in the PFC following single dose PCP and drug and drug×condition in the striatum following subchronic PCP given prior observations that a single dose of PCP decreases PFC FLI in unchallenged rats and that alterations in PCP-induced behavioral responses to amphetamine are accompanied by increases in striatal FLI (Turgeon and Roche, 1999).

3. Results

3.1. Novel environment

Only a small effect on the behavioral response to the novel environment was noted in the single injection experiment (Fig. 2). Repeated measures ANOVAs revealed significant effects of time on cage-crosses ($F(4,40)=35.9$, $p<0.001$) and rears ($F(4,40)=75.0$, $p<0.001$). In addition, there was a significant time×drug interaction effect on the number of cage-crosses ($F(4,40)=3.4$, $p<0.05$).

Prior exposure to subchronic PCP decreased the behavioral response to the novel environment (Fig. 3). Repeated measures ANOVAs revealed significant effects of time ($F(4,36)=13.7$, $p<0.001$) and drug ($F(1,9)=8.6$, $p<0.05$) on the number of cage-crosses. There were also significant effects of time ($F(4,36)=$

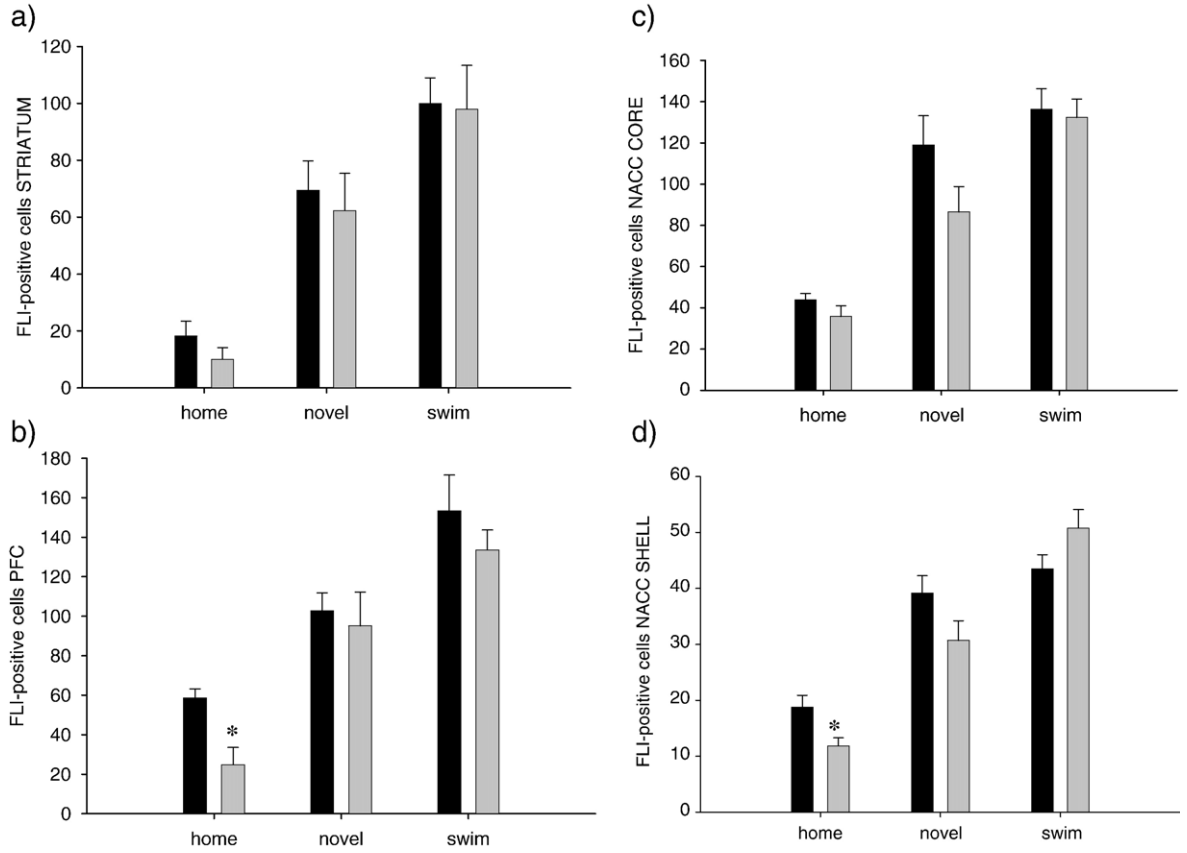

Fig. 6. Effects of prior exposure to a single injection of PCP on the number of FLI positive neurons in the striatum (a), prefrontal cortex (b), nucleus accumbens core (c), and nucleus accumbens shell (d). PCP pretreatment decreased the number of FLI positive cells in the prefrontal cortex and nucleus accumbens shell in unstressed (home) animals (*$p<0.05$ vs saline, *t*-test).

41.7, $p<0.001$) and drug ($F(1,9)=5.2$, $p<0.05$) on the number of rears.

3.2. Swim test

Prior exposure to a single dose of PCP did not affect the behavioral response to the swim test (Fig. 4). Repeated measures ANOVAs on the time spent struggling, swimming, and immobile and the number of immobility counts revealed significant effects of time on all measures (struggling: $F(14,140)=28.9$, $p<0.001$, swimming: $F(14,140)=22.5$, $p<0.001$, immobility: $F(14,140)=15.9$, $p<0.001$, immobility counts: $F(14,140)=21.4$, $p<0.001$) but no effects of drug and no drug×time interaction effects.

Prior exposure to subchronic PCP did not significantly affect the time spent swimming or struggling but did increase the amount of time spent immobile and the number of immobilities (Fig. 5). Repeated measures ANOVAs on the time spent struggling, swimming, and immobile revealed significant effects of time on all measures (struggling: $F(14,98)=11.9$, $p<0.001$, swimming: $F(14,98)=9.3$, $p<0.001$, immobility: $F(14,98)=7.6$, $p<0.001$, immobility counts: $F(14,98)=6.3$, $p<0.001$). There were no main effects of drug on either swimming or struggling; however there were significant effects of drug on time spent immobile ($F(1,7)=10.2$, $p<0.05$) and number of immobilities ($F(1,7)=8.2$, $p<0.05$).

3.3. FLI

3.3.1. Single PCP pretreatment

Exposure to stress increased FLI in all regions examined (Fig. 6) as revealed by significant effects of condition in the striatum ($F(2,30)=34.2$, $p<0.001$), PFC ($F(2,30)=34.5$, $p<0.001$), nucleus accumbens core ($F(2,29)=53.5$, $p<0.001$) and shell ($F(2,29=69.9$, $p<0.001$). In addition, a significant drug×condition interaction effect was observed in the shell ($F(2,29)=5.1$, $p<0.05$) and a marginal effect of drug was noted in the PFC ($F(2,30)=4.1$, $p=0.05$). *T*-tests revealed that PCP significantly decreased FLI in the home cage condition in the PFC ($t(10)=3.4$, $p<0.01$) and the shell ($t(10)=2.7$, $p<0.05$).

3.3.2. Repeated PCP pretreatment

Exposure to stress increased FLI in all regions examined (Fig. 7) as revealed by significant effects of condition in the striatum ($F(2,30)=33.3$, $p<0.001$), PFC ($F(2,30)=15.2$, $p<0.001$), nucleus accumbens core ($F(2,29)=22.8$, $p<0.001$) and shell ($F(2,29=39.2$, $p<0.001$). In addition, marginal effects of drug ($F(2,30)=3.7$, $p=0.06$) and drug×condition ($F(2,30)=3.1$,

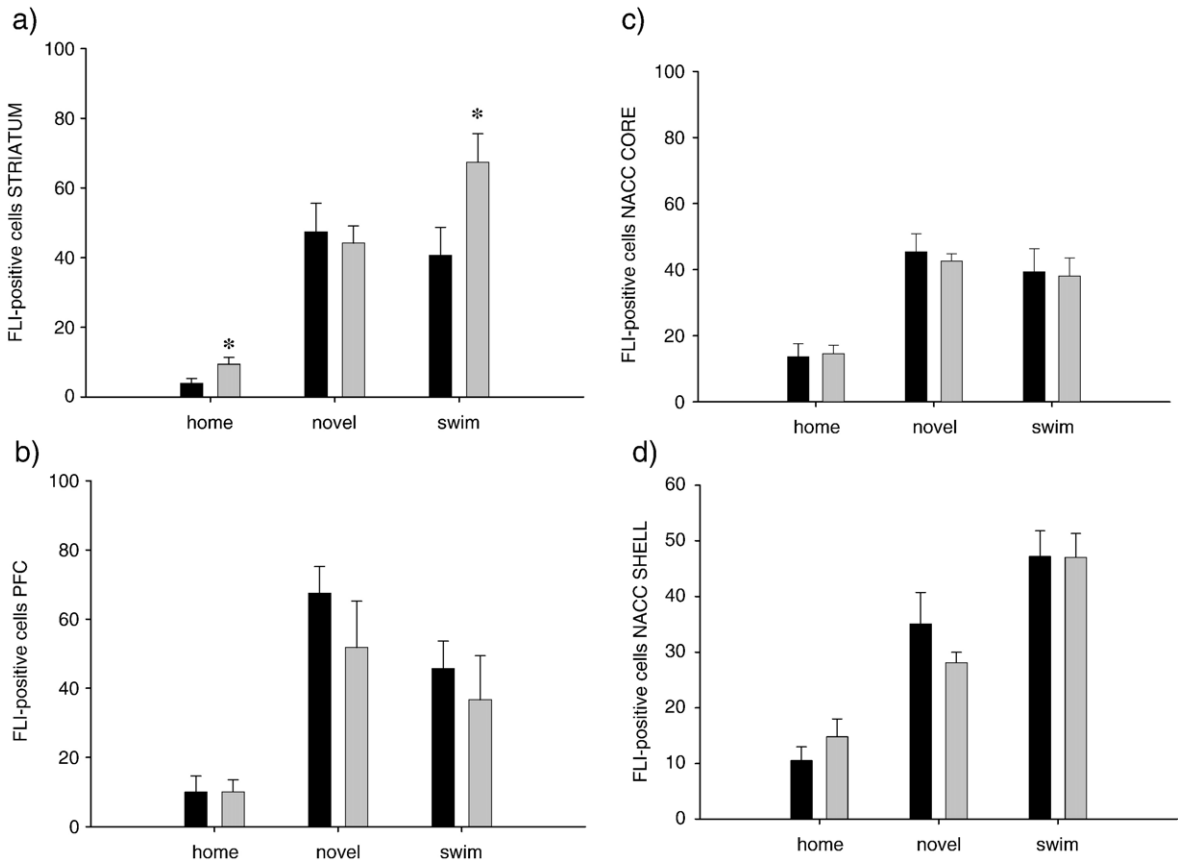

Fig. 7. Effects of prior exposure to subchronic PCP on the number of FLI positive neurons in the striatum (a), prefrontal cortex (b), nucleus accumbens core (c), and nucleus accumbens shell (d). PCP pretreatment increased the number of FLI positive cells in the striatum in unstressed (home) and swim stressed animals (*$p<0.05$ vs saline, *t*-test).

$p=0.059$) were observed in the striatum. *T*-tests revealed that PCP significantly increased striatal FLI in the home condition ($t(10)=2.29$, $p<0.05$; two-tailed) and the swim condition ($t(10)=2.33$, $p<0.05$; two-tailed).

4. Discussion

Prior exposure to a single injection of PCP has been shown to produce a number of behavioral changes approximating those seen in schizophrenia, including cognitive impairment (Okuyama et al., 1995), increased behavioral response to amphetamine (Turgeon and Roche, 1999), and decreased sucrose consumption (Turgeon and Hoge, 2003). The present experiments sought to determine whether withdrawal following a single injection of PCP could produce alterations in the behavioral response to stressful stimuli. The effects of withdrawal from subchronic PCP were also examined as a positive control. In addition, regional changes in FLI expression accompanying behavior were investigated in order to gain insight into the neurobiological correlates of PCP-induced changes in behavior. The results suggest that while withdrawal from subchronic exposure to PCP did alter the behavioral and neurochemical response to both novelty and forced swim, withdrawal following a single injection of PCP produced only minimal effects. In addition, the subchronic PCP-induced increases in immobility in the forced swim test were accompanied by increases in striatal FLI.

Exposure to subchronic PCP decreased the behavioral response to the novel environment and increased immobilities in the forced swim test. Struggling and swimming were not altered by subchronic PCP, suggesting that the PCP-induced changes are not due to a generalized decrease in behavior. The effect of a single exposure to PCP on the behavioral response to the novel environment was limited to a time × drug interaction effect and there were no significant effects in the forced swim test. The time × drug interaction effect on cage-crossings following a single exposure to PCP appears to be driven by slightly lower numbers of crossings in the PCP group during first 20 min in the novel environment which is not maintained during the rest of the session. In addition, while insignificant, the PCP group in the single exposure experiment had more time spent immobile and more immobilities than the saline-treated group. Thus a single exposure to PCP appears to produce qualitatively similar but insignificant alterations in behavior compared to those seen following subchronic PCP.

The forced swim test data are in agreement with data from mouse studies which show increased immobility following repeated, but not single exposures to PCP (Noda et al., 1995). Likewise, the observation that subchronic PCP decreases cage-crossing and rears in the novel environment is consistent with the observation that the same PCP administration protocol decreases the number of activity counts in a novel environment in mice (Abdel-Naby Sayed et al., 2001). However, this finding contradicts a prior report that subchronic PCP increases the behavioral response to novelty in rats (Jentsch et al., 1998). The prior study differed from the current study in a few respects; they examined behavior a week after the end of drug treatment rather than 24 h and while they administered the same total dose of PCP, they administered PCP twice daily for 7 days rather than once daily for 14 days as in the current study. However, both of these administration patterns decreased prefrontal cortex dopamine turnover 24 h (Jentsch et al., 1997) and 3 weeks (Jentsch et al., 1998) after the last injection, an effect argued to underlie PCP-induced increases in the response to novelty (Jentsch et al., 1998). The observation that these two methods of administration produce opposite effects on behavior suggests that the PCP-induced decrease in PFC dopamine turnover observed in the prior study may not be related to the altered behavioral response to novelty.

PCP-induced decreases in the behavioral response to a novel environment and increases in immobility in the forced swim test may reflect increased anxiety. Decreases in rearing behavior in an open field, but increases in line crossing, have been associated with increased anxiety as assessed with an elevated plus maze (Butterweck et al., 2003). In addition, rats bred for high anxiety exhibit decreased distance traveled in an open field and increased immobilities in the forced swim test (Liebsch et al., 1998). Prior studies examining the effects of subchronic PCP treatment have failed to find evidence for changes in anxiety behavior as assessed by the elevated plus maze (Schwabe et al., 2006), and open field and light/dark emergence (Lee et al., 2005). However, both of these studies administered lower total doses of PCP than the dose administered in the current study; therefore it remains possible that the pattern of administration in the present study might produce alterations in anxiety.

Alternatively, decreases in exploration of a novel environment and increases in immobility in the forced swim test have been argued to model avolition associated with depression (Ellenbroek and Cools, 2000; File and Tucker, 1986; Noda et al., 1995, 1997, 2000) the symptoms of which are common to aspects of negative schizophrenic symptomatology (Ellenbroek and Cools, 2000; Markou and Kenny, 2002). This combination of behaviors, along with decreased sucrose consumption which is also seen following PCP (Turgeon and Hoge, 2003), has been seen in response to chronic stress (Strekalova et al., 2004) in an animal model for depression. Thus the behavioral effects seen in the current study may reflect the induction of depressive-like symptoms by subchronic PCP.

The FLI data reveal clear stress-induced increases in all regions examined. These data are in agreement with prior reports indicating swim stress-induced *c-fos* mRNA in these regions (Cullinan et al., 1995) and FLI in the rat medial prefrontal cortex (Duncan et al., 1993), and in the mouse amygdala, pontine nucleus, striatum, thalamus, and cortex (Abdel-Naby Sayed et al., 2001). Open field exposure/novelty has also been found to elevate *c-fos* mRNA in the nucleus accumbens (Badiani et al., 1998), the striatum (Badiani et al., 1998; Emmert and Merman, 1999), and the medial prefrontal cortex (Handa et al., 1993).

Subchronic treatment with PCP enhanced striatal FLI seen following swim stress, but not novelty stress. This observation suggests that the mechanisms by which PCP produces alterations in the behavioral responses to novelty and swim may differ. Forced swim and novelty do produce different effects on

striatal neurochemistry. Exposure to the forced swim test has been found to increase striatal dopamine turnover (Connor et al., 1999) and serotonin levels (Kirby and Lucki, 1997; Kirby et al., 1997) whereas novelty does not (Bardo et al., 1990; Piazza et al., 1991). Immobilities appear more likely to reflect striatal dopamine activity as both immobilities and striatal dopamine turnover are decreased by the norepinephrine reuptake inhibitor reboxetine (Connor et al., 1999) whereas fluoxetine-induced increases in striatal serotonin levels are not correlated with immobilities (Kirby and Lucki, 1997). In addition, swim stress-induced FLI is seen in a number of limbic regions (although striatum was not reported) and is reduced by antidepressants acting on noradrenergic, but not serontonergic systems (Duncan et al., 1996). Taken together, these data suggest that PCP may be altering the catecholamine response to forced swim.

Repeated PCP exposure has also been found to increase NMDA receptor subunit expression in the striatum (Hanania et al., 1999). NMDA receptor antagonists block the induction of *c-fos* mRNA by amphetamine (Badiani et al., 1998), suggesting that PCP-induced increases in functional NMDA receptors could underlie the increases in FLI seen in response to amphetamine (Turgeon and Roche, 1999) and perhaps those observed here in response to forced swim as well. Consistent with our observation that pretreatment with subchronic PCP does not alter novelty-induced striatal FLI, novelty-induced striatal *c-fos* mRNA is not sensitive to NMDA receptor antagonists (Ferguson et al., 2003) and striatal glutamate is not altered in response to novelty (Ho et al., 2000; Badiani et al., 2000). While striatal glutamate levels in response to forced swim have not been assessed to our knowledge, NMDA receptor antagonists have been found to decrease immobilities in a forced swim test (Trullas and Skolnick, 1990), suggesting that increases in NMDA receptor activity could underlie the increased immobility seen following repeated exposure to PCP.

In addition to the changes observed in the striatum following subchronic PCP, a single exposure to PCP decreased PFC FLI in home group. This result is in agreement with our previous observation that prior exposure to a single dose of PCP decreases background levels of FLI in the PFC (Turgeon and Roche, 1999). We argued that this decrease in PFC FLI might reflect PCP-induced decreases in prefrontal cortex dopamine utilization similar to those seen following subchronic PCP exposure (Jentsch et al., 1997). However, unlike the effect on dopamine utilization which is seen following subchronic PCP, we do not see a similar effect on FLI following subchronic PCP exposure. The lack of effect in the subchronic exposure may be due to a floor effect as FLI levels are low in both saline and PCP treated home cage groups. However, the absence of an effect following subchronic exposure argues against the change in PFC FLI seen following a single exposure to PCP as reflective of a change in dopamine utilization.

A single exposure to PCP also produced a significant drug × condition interaction effect on FLI in the NAcc shell driven by a PCP-induced decrease in the home condition, a trend toward a decrease in the novel condition and a trend toward an increase in the FST condition. The NAcc shell was the region found to be the most senstitive to FLI changes and extracellular dopamine changes induced by injection stress (Barrot et al., 1999). The observation that PCP differentially effects stress-induced FLI in the NAcc may stem from similar differences in the neurochemical effects of novelty vs swim stress to those discussed above for the striatum.

In summary, prior exposure to a single injection of PCP, while able to model some schizophrenia-like behaviors in animals, does not produce significant alterations in the response to stressful stimuli. The effects of subchronic PCP on the behavioral response to novelty and swim stress may reflect PCP-induced neurochemical changes that model depressive-like symptoms of schizophrenia. In addition, the differential effects of subchronic PCP on striatal FLI induced by novelty and forced swim suggest that PCP alters the behavioral responses to these stressors via different neurochemical mechanisms.

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References

Abdel-Naby Sayed M, Noda Y, Hamdy MM, Mamiya T, Nagai T, Furukawa H, et al. Enhancement of immobility induced by repeated phencyclidine injection: association with c-Fos protein in the mouse brain. Behav Brain Res 2001;124:71–6.

Audet M-C, Goulet S, Dore FY. Repeated subchronic exposure to phencyclidine elicits excessive atypical grooming in rats. Behav Brain Res 2006;167:103–10.

Badiani A, Oates MM, Day HEW, Watson SJ, Akil H, Robinson TE. Amphetamine-induced behavior, dopamine release, and c-Fos expression: modulation by environmental novelty. J Neurosci 1998;12:10579–93.

Badiani A, Oates MM, Fraioli S, Browman KE, Ostrander MM, Wolf ME, et al. Environmental modulation of the response to amphetamine: dissociation between changes in behavior and changes in dopamine and glutamate overflow in the rat striatal complex. Psychopharmacology 2000;151:166–74.

Bardo MT, Bowling SL, Peirce RC. Changes in locomotion and dopamine neurotransmission following amphetamine, haloperidol, and exposure to novel environmental stimuli. Psychopharmacology 1990;101:338–43.

Barrot M, Marinelli M, Abrous DN, Rouge-Pont F, Le Moal M, Piazza PV. Functional heterogeneity in dopamine release and in the expression of Fos-like proteins within the rat striatal complex. Eur J Neurosci 1999;11:1155–66.

Butterweck V, Prinz S, Schwaninger M. The role of interleukin-6 in stress-induced hyperthermia and emotional behavior in mice. Behav Brain Res 2003;144:49–56.

Connor TJ, Kelliher P, Harkin A, Kelly JP, Leonard BE. Reboxetine attenuates forced swim test-indued behavioral and neurochemical alterations in the rat. Eur J Pharmacol 1999;379:125–33.

Cullinan WE, Herman JP, Battaglia DF, Akil H, Watson SJ. Pattern and time course of immediate early gene expression in rat brain following acute stress. Neuroscience 1995;64:477–505.

Deutch AY, Clark WA, Roth RH. Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res 1990;521:311–5.

Duncan GE, Johnson KB, Breese GR. Topographic patterns of brain activity in response to swim stress: assessment by 2-deoxyglucose uptake and expression of Fos-like immunoreactivity. J Neurosci 1993;13:3932–43.

Duncan GE, Knapp DJ, Johnson KB, Breese GR. Functional classification of antidepressants based on antagonism of swim stress-induced fos-like immunoreactivity. J Pharmacol Exp Ther 1996;277:1076–89.

Ellenbroek BA, Cools AR. Animal models for the negative symptoms of schizophrenia. Behav Pharmacol 2000;11:223–33.

Emmert MH, Herman JP. Differential forebrain *c-fos* mRNA induction by ether inhalation and novelty: evidence for distinctive stress pathways. Brain Res 1999;845:60–7.

Ferguson SM, Norton CS, Satson SJ, Akil H, Robinson TE. Amphetamine-evoked *c-fos* mRNA expression in the caudate-putamen: the effects of DA and NMDA receptor antagonists vary as a function of neuronal phenotype and environmental context. J Neurochem 2003;86:33–44.

File SE, Tucker JC. Behavioral consequences of antidepressant treatment in rodents. Neurosci Biobehav Rev 1986;10:123–34.

Hanania T, Hillman GR, Johnson KM. Augmentation of locomotor activity by chronic phencyclidine is associated with an increase in striatal NMDA receptor function and an upregulation of the NR1 receptor subunit. Synapse 1999;31:229–39.

Handa RJ, Nunley KM, Bollnow MR. Induction of *c-fos* mRNA in the brain and anterior pituitary gland by a novel environment. NeuroReport 1993;4:1079–82.

Ho Y-J, Chang Y-C, Liu T-M, Tai M-Y, Wong C-S, Tsai Y-F. Striatal glutamate release during novelty exposure-induced hyperactivity in olfactory bulbectomized rats. Neurosci Lett 2000;287:117–20.

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiat 1991;148:1301–8.

Jentsch J, Taylor J, Roth R. Subchronic phencyclidine administration increases mesolimbic dopaminergic system responsivity and augments stress-and psychostimulant-induced hyperlocomotion. Neuropsychopharmacology 1998;19:105–13.

Jentsch JD, Tran A, Dung Le BA, Youngren KD, Phil M, Roth RH. Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. Neuropsychopharmacology 1997;17:92–9.

Kirby LG, Lucki I. Interaction between the forced swimming test and fluoxetine treatment on extracellular 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in the rat. J Pharmacol Exp Ther 1997;282:967–76.

Kirby LG, Chou-Green JM, Davis K, Lucki I. The effects of different stressors on extracellular 5-hydroxytryptamine and 5-hydroxyindoleacetic acid. Brain Res 1997;760:218–30.

Lee PR, Brady DL, Shapiro RA, Dorsa DM, Koenig JI. Social interaction deficits caused by chronic phencyclidine administration are reversed by oxytocin. Neuropsychopharmacology 2005;30:1883–94.

Liebsch G, Montkowski A, Holsboer F, Landgraf R. Behavioural profiles of two Wistar rat lines selectively bred for high or low anxiety-related behaviour. Behav Brain Res 1998;94:301–10.

Markou A, Kenny PJ. Neuroadaptations to chronic exposure to drugs of abuse: relevance to depressive symptomatology seen across psychiatric diagnostic categories. Neurotox Res 2002;4:297–313.

Noda Y, Yamada K, Furukawa H, Nabeshima T. Enhancement of immobility in a forced swimming test by subacute or repeated treatment with phencyclidine: a new model of schizophrenia. Br J Pharmacol 1995;116:2531–7.

Noda Y, Takayoshi M, Furukawa H, Nabeshima T. Effects of antidepressants on phencyclidine-induced enhancement of immobility in a forced swimming test in mice. Euro J Pharmcol 1997;324:135–40.

Noda Y, Kamei H, Mamiya MS, Furukawa H, Nabeshima T. Repeated phencyclidine treatment induces negative symptom-like behavior in forced swimming test in mice: imbalance of prefrontal serotonergic and dopaminergic functions. Neuropsychopharm 2000;23:375–87.

Okuyama S, Ogawa S-I, Nakazato A, Tomizawa K. Effect of NE-100, a novel sigma receptor ligand, on phencyclidine-induced delayed cognitive dysfunction in rats. Neurosci Lett 1995;189:60–2.

Paxinos G, Watson C. The Brain in Stereotaxic Coordinates. 2nd Ed. Sydney: Academic Press; 1986.

Piazza PV, Rouge-Pont F, Deminiere JM, Kharoubi M, Le Moal M, Simon H. Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats predisposed to develop amphetamine self-administration. Brain Res. 1991;567:169–74.

Sams-Dodd F. Effects of continuous d-amphetamine and phencyclidine administration on social behaviour, stereotyped behaviour, and locomotor activity in rats. Neuropsychopharmacology 1998;19:18–25.

Schwabe K, Klein S, Koch M. Behavioural effects of neonatal lesions of the medial prefrontal cortex and subchronic pubertal treatment with phencyclidine of adult rats. Behav Brain Res 2006;168:150–60.

Spieleway C, Markou A. Withdrawal from chronic phencyclidine treatment induces long-lasting depression in brain reward function. Neuropsychopharmacology 2003;28:1106–16.

Strekalova T, Spanagel R, Bartsch D, Henn F, Gass P. Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. Neuropsychopharmacology 2004;29:2007–17.

Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol 1990;185:1–10.

Turgeon SM, Roche JK. The delayed effects of phencyclidine enhance amphetamine-induced behavior and striatal c-Fos expression in the rat. Neuroscience 1999;91:1265–75.

Turgeon SM, Reichstein DA. Decreased striatal c-Fos accompanies latent inhibition in a conditioned taste aversion paradigm. Brain Res 2002;924:120–3.

Turgeon SM, Hoge SG. Prior exposure to phencyclidine decreases voluntary sucrose consumption and operant performance for food reward. Pharmacol Biochem Behav 2003;76:393–400.

Turgeon SM, Auerbach EA, Heller MA. The delayed effects of phencyclidine (PCP) disrupt latent inhibition in a conditioned taste aversion paradigm. Pharmacol Biochem Behav 1998;60:553–8.

Yeap S, Thakore JH. Stress axis dysfunction in schizophrenia. Eur Psychiatr 2005;20:8307–12.