

Subchronic Phencyclidine Administration Reduces Mesoprefrontal Dopamine Utilization and Impairs Prefrontal Cortical-Dependent Cognition in the Rat

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Repeated ingestion of phencyclidine by humans induces enduring schizophrenic symptomatology, particularly cognitive dysfunction. In the presently described series of experiments, the neurochemical and cognitive consequences of subchronic phencyclidine administration in the rat were explored. Repeated phencyclidine exposure led to a selective reduction in basal and stress-evoked dopamine utilization in the prefrontal cortex. In addition, rats previously subchronically-treated with phencyclidine were impaired on performance of a spatial working memory task in a delay-dependent manner. Importantly, these dopaminergic and cognitive deficits were observed after withdrawal from phencyclidine, and as such, the neurochemical and

behavioral effects were due to drug-induced neurobiological changes rather than direct drug effects. These biochemical and behavioral data show that repeated phencyclidine administration induces prefrontal cortical cognitive deficits in rats, as in humans, and offer a biochemical perspective of the neural substrate underlying this cognitive impairment: inhibition of mesocortical dopamine neurons. Thus, these data may have relevance to psychiatric disorders involving prefrontal cortical dopaminergic hypoactivity and cognitive dysfunction, as has been hypothesized in schizophrenia.

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Several lines of research suggest that schizophrenia may involve dysfunction of the prefrontal cortex, and possibly, its dopaminergic innervation (reviewed in Carlsson 1988; Goldman-Rakic 1991; Kahn and Davis 1995). The prefrontal cortex receives a prominent dopa-

mine projection (Thierry et al. 1973; Williams and Goldman-Rakic 1993), and dopamine appears to be a critical neuromodulatory influence on the cognitive functions of this region, particularly working memory. Regionally-restricted dopamine depletion or dopamine receptor blockade can impair performance of working memory tasks in monkeys (Brozoski et al. 1979; Sawaguchi and Goldman-Rakic 1991) and rats (Bubser and Schmidt 1990). In addition, increased dopamine transmission in the prefrontal cortex, induced by a pharmacological stressor, can impair spatial working memory (Murphy et al. 1996), possibly by degrading memory-related firing of prefrontal cortical neurons (Williams and Goldman-Rakic 1995).

Prefrontal cortical cognitive dysfunction, including working memory deficits, have been demonstrated in

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schizophrenia (Fey 1951; Goldman-Rakic 1991; Park and Holzman 1992; Goldberg and Gold 1995), and these deficits may be related to a dopaminergic dysfunction, which has been hypothesized to be involved in schizophrenia (Carlsson 1988; Davis et al. 1990; Robbins 1990; Grace 1991; Deutch 1992). Evidence in support of dopamine dysfunction in schizophrenia include the high affinity of most typical antipsychotic drugs for the dopamine D2 receptor (Seeman 1992; Deutch et al. 1992) and the activation of dopaminergic transmission by acute administration of such psychotomimetic drugs as amphetamine (During et al. 1987), cocaine (Sorg and Kalivas 1993), Δ^9 -tetrahydrocannabinol (Bowers and Morton 1994) and phencyclidine (PCP; Deutch et al. 1987; Bowers and Morton 1994; Hondo et al. 1994; Hertel et al. 1996; Jentsch et al. 1997).

Given acutely, PCP and the PCP congener, ketamine, induce hyperactivity, paranoia, hallucinations, formal thought disorder and cognitive impairments in normal human subjects (Luby et al. 1959; Davies and Beech 1960; Pearlson 1981; Javitt and Zukin 1991; Krystal et al. 1994; Malhotra et al. 1996). Cognitive deficits have also been observed in PCP- or ketamine-treated rats (Danysz et al. 1988; Alessandri et al. 1989; Verma and Moghaddam 1996) and monkeys (Boyce et al. 1991). The cognitive dysfunction induced by acute PCP or ketamine challenge may be mediated by increased dopamine release and utilization in the prefrontal cortex as hyperdopaminergic states of the prefrontal cortex are correlated with impaired spatial working memory (Murphy et al. 1996; Verma and Moghaddam 1996).

Repeated exposure to PCP can more reliably induce robust and enduring cognitive deficits in humans (Pearlson 1981; Cosgrove and Newell 1991). The development of a profound and enduring psychotomimetic reaction after repeated PCP exposure suggests that long-lasting neurobiological changes which mimic some features of the neuroetiology of schizophrenia may occur.

Schizophrenic subjects have been shown to have a failure of metabolic activation of frontal cortical regions during performance of prefrontal-dependent tasks (Ingvar and Franzen 1974; Weinberger et al. 1986, 1988; Weinberger and Berman 1996), and this effect is similarly observed in PCP-abusing humans (Hertzman et al. 1990; Wu et al. 1991). Interestingly, the hypofrontality associated with schizophrenia may be related to a dopaminergic dysfunction (Weinberger et al. 1988; Dolan et al. 1995).

Whereas acute PCP administration activates dopamine systems, contributing to a hyperdopaminergic hypothesis of schizophrenia, the neurochemical effects of repeated PCP exposure remain unexplored. In the present set of experiments, the neurochemical and cognitive consequences of subchronic PCP administration in the rodent were characterized. Specifically, whether

repeated exposure to PCP alters prefrontal cortical dopamine and cognitive function was investigated. The present evidence suggests that subchronic PCP administration induces a selective prefrontal cortical dopaminergic deficit and an associated cognitive dysfunction.

METHODS

Animals

Male Sprague-Dawley CAMM rats (Charles River Labs, Portage, MI) were used as subjects. The rats were maintained on a 12-hour light-dark cycle with the light phase being 7:00 A.M. to 7:00 P.M. Rats used for biochemical studies were fed and watered *ad libitum*, while those used for cognitive testing were food-restricted for the duration of the experiment to maximize the palatability of food rewards used in the cognitive testing. Animals performing the cognitive task were fed approximately 5 g of food a day immediately following testing; water was always available in the home cage.

Drugs

Phencyclidine hydrochloride (Research Biochemicals Inc., Natick, MA) was dissolved in sterile saline and injected at 1 ml/kg intraperitoneally (i.p.). Drug weights were calculated as the salt.

Studies of Basal Neurotransmitter Metabolism

In experiments studying basal utilization, animals were subchronically treated with either saline (1 ml/kg once or twice a day for 7 or 14 days) or PCP (10 mg/kg once a day for 7 to 14 days, or 5 mg/kg twice a day for 7 days). Twenty-four hours after the final treatment, they were removed from their home cage and sacrificed. No intermediate challenge or stressor was delivered.

Stress Experiment

In some studies, rats were challenged with a mild foot-shock stress after receiving subchronic treatments. Animals were subchronically treated with either once-a-day injections of saline (1 ml/kg) or PCP (10 mg/kg) for 14 days, and 1 or 2 days after the final administration, they were placed in standard grid-floor shock boxes illuminated with red-light. Background noises were masked with white noise broadcast in the chamber. Either no shock (sham) or shock (10 random 0.5 second 0.3 mA shocks over 20 minutes) was delivered. This regimen was chosen to selectively activate dopamine utilization in the prefrontal cortex. Rats were sacrificed immediately following the stress session. Shock boxes were cleaned with 70% ETOH between rats to remove olfactory cues.

Biochemistry

All rats weighed 250–275 g at the time of sacrifice. Sacrifices were performed during the animals' light phase. Rats were euthanized by rapid decapitation, their brains were quickly removed, and brain regions were dissected out on a chilled platform. Samples were immediately frozen on dry ice and stored at -70°C until assayed.

Tissues were prepared using dihydroxybenzylamine as an internal control. Samples were homogenized in 400 μl of ice-cold 0.1 M perchloric acid and centrifuged at 46000 g, 200 μl of the supernatant was analyzed directly with HPLC using electrochemical detection with a glassy carbon electrode at + 0.7 V (BAS, West Lafayette, IN) and a reversed-phase column (3 μm C18 beads, 100 Å diameter, 10 cm length; BAS, West Lafayette, IN). Pellets were analyzed for protein content according to Lowry et al. (1951). The remaining 200 μl of supernate was processed for levels of 3-methoxy-4-hydroxyphenylglycol (MHPG; free + conjugate) by mass spectrometry/gas chromatography according to Elsworth et al. (1983).

Mobile phase used for HPLC was an 8% solution of acetonitrile containing 0.6% tetrahydrofuran, 0.1% diethylamine, 0.025 mM EDTA, 2.3 mM 1-octane-sulfonic acid, 30 mM sodium citrate and 13.7 mM sodium dihydrogen phosphate (final pH 3.1).

Measurements of utilization were made as the ratio of tissue concentration (in ng/mg protein) of the primary metabolite, dihydroxy-O-phenylacetic acid (DOPAC) or MHPG to the parent amine (dopamine or norepinephrine, respectively).

Cognitive Testing

Rats were tested 5 days a week during the light phase by an experienced tester who tested the rats at the same time every day to preclude circadian effects. The individual rat testers were always blind to any drug treatments.

As noted above, all rats were food-restricted for the duration of the experiment; each rat was fed approximately 5 g of rat chow immediately after testing each day. No rat experienced weight loss during the experiment; in fact, all rats gained 5–10% of their body weight each week until they reached their adult weights of 450–500 g. Highly palatable miniature chocolate chips were used as a reward during testing.

White noise was broadcast in the testing room during daily experiments to prevent external noises from disturbing performance of the task. A standard black T-maze was used for delayed alternation testing.

Delayed Alternation Testing

Training and testing was performed with modification of the methods described previously in Murphy et al.

(1996). In the present experiment, a variable-delayed alternation was utilized in order to construct delay functions for each rat. After a rat had been trained, it began testing under a single-delay condition. This delay was increased until the animal stabilized at 80% performance for 3 days. Then a delay curve was constructed by presenting the animal with five separate delays spanning from '0' sec (as a control) to twice the duration of their current delay (e.g., 0, 20, 40, 60, 80 sec) over a 20-trial session (each delay encountered 4 times throughout the session). This variable-delay task was administered for two days. Then, the animal received once-a-day subchronic saline (1 ml/kg) or PCP (10 mg/kg) injections for 14 days. Two days after the final injections, performance under the 20-trial variable-delay task was reassessed. Following reassessment, the rats continued to be tested under the variable-delay conditions; however, no rat was studied in the cognitive paradigm more than 10 days after cessation of PCP treatments.

Statistics

For biochemical and cognitive studies, group comparisons were performed with one-way analysis of variance (ANOVA) followed by Scheffe's *F*-test for *post-hoc* analysis. Comparisons of stress responsivity in saline- and PCP-treated animals utilized two-way ANOVA (with drug and shock conditions as factors) followed by appropriate *post-hoc* tests. Analyses were performed with Statview II (Abacus Concepts, Berkeley, CA) on a Macintosh IIcx. All data is presented as mean \pm S.E.M.

RESULTS

Basal Monoamine Utilization after Subchronic PCP Treatment

Basal dopamine utilization (as assessed by the ratio of tissue levels of DOPAC to dopamine) in the prefrontal cortex was significantly reduced 24 hour after the last injection of PCP when 10 mg/kg once a day for 14 days ($74.3 \pm 5.8\%$ of control; $F_{(1,7)} = 8.7$; $p \leq .05$) and 5 mg/kg twice a day for 7 days ($66.8 \pm 5.2\%$ of control; $F_{(1,15)} = 9.9$; $p \leq 0.01$) but not 10 mg/kg once a day for 7 days ($95.8 \pm 9.4\%$ of control; $F_{(1,15)} = 0.1$; $p > .05$) was administered (Figure 1). None of these treatment regimens significantly altered basal dopamine utilization in the nucleus accumbens or dorsolateral striatum (Figure 1). Importantly, all changes in dopamine utilization are metabolite driven, as no significant effect of subchronic PCP administration on absolute dopamine levels was detected (Table 1). In addition, no difference in basal norepinephrine (MHPG/norepinephrine) metabolism was detected in the prefrontal cortex of rats subchronically treated with saline versus PCP ($123.3 \pm 13.2\%$ of control; $F_{(1,7)} = 2.1$; $p > .05$).

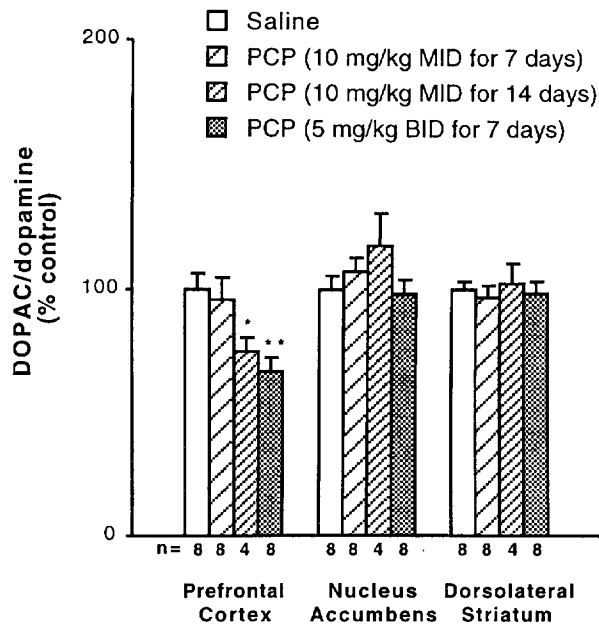


Figure 1. Subchronic exposure to PCP reduces basal dopamine utilization in the prefrontal cortex, but not subcortical regions of the rat brain. Twice a day administration appears to better induce the inhibition. Data represent mean \pm SEM. Significantly reduced relative to saline-treated controls: * $p \leq .05$; ** $p \leq .01$.

Stress-Evoked Dopamine Metabolism in Prefrontal Cortex after Subchronic PCP Treatment

In order to further investigate the nature of the PCP-induced prefrontal cortical dopaminergic dysfunction, animals previously subchronically treated with either PCP or saline were challenged with mild foot-shock, a stressor which evokes increased dopamine release and turnover in the prefrontal cortex of normal animals. Subjects were treated once a day for 14 days with saline or PCP (10 mg/kg), stressed 24 or 48 hrs after the final drug administration and sacrificed immediately following the stress session. No differences between the 24 and 48

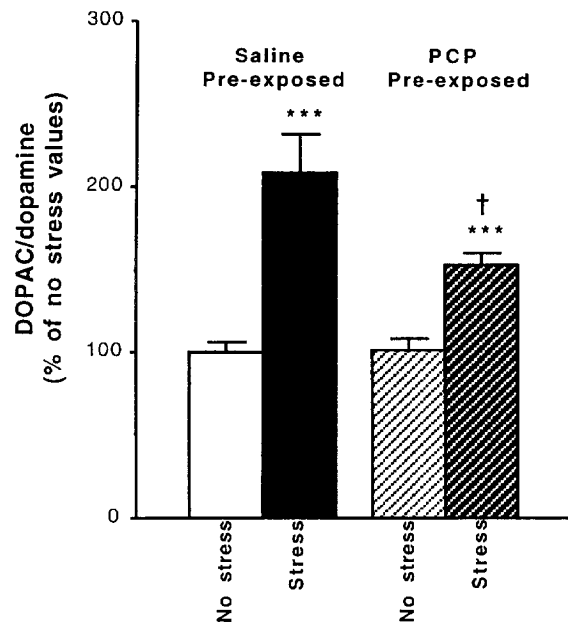


Figure 2. A mild foot-shock stress increases dopamine utilization in the prefrontal cortex of both saline- and PCP-treated controls; however, the response of the mesocortical dopamine system (assessed as the % increase relative to no stress values) is reduced in PCP-pre-exposed animals relative to saline-treated controls. The absolute DOPAC/dopamine ratios are: saline/no stress = 0.27 ± 0.02 , saline/stress = 0.57 ± 0.07 , PCP/no stress = 0.23 ± 0.01 , PCP/stress = 0.35 ± 0.02 . Data represent mean \pm SEM. $n = 8$ for all observations. ***Significantly increased relative to no stress values: $p \leq .001$. †Significantly reduced relative to saline-pre-exposed/stress values: $p \leq .05$.

hour post-drug groups were measured, so these data were combined for analysis.

Animals subchronically treated with saline responded to the stress with an increase in dopamine utilization to $208.0 \pm 23.1\%$ of control (saline-preexposed/no stress) levels (Figure 2; $F_{(1,15)} = 20.3$; $p \leq .001$). In addition, PCP-pretreated animals exhibited a significant stress-induced activation of frontal cortical dopamine metabo-

Table 1. Dopamine Levels in Rat Brain Are Unchanged After Repeated PCP Administration

	Saline	PCP (10 mg/kg MID for 7 days)	PCP (10mg/kg MID for 14 days)	PCP (5 mg/kg BID for 7 days)
Prefrontal cortex	00.43 ± 0.06 ($n = 12$)	00.32 ± 0.03^a ($n = 8$)	00.60 ± 0.03^b ($n = 4$)	00.36 ± 0.03 ($n = 8$)
Nucleus accumbens	38.68 ± 4.28 ($n = 12$)	28.94 ± 2.16 ($n = 8$)	53.18 ± 6.74 ($n = 4$)	33.34 ± 4.03 ($n = 8$)
Dorsolateral striatum	79.61 ± 3.64 ($n = 12$)	76.71 ± 4.57 ($n = 8$)	75.05 ± 8.73 ($n = 4$)	80.76 ± 5.18 ($n = 8$)

No difference in basal dopamine levels (ng/mg protein) in saline- and PCP-treated animals indicate that all observed changes in dopamine utilization are metabolite driven. Data represent mean \pm SEM.

^aNot significantly different: $F_{(1,18)} = 2.27$; $p = .15$.

^bNot significantly different: $F_{(1,14)} = 2.25$; $p = .153$.

Table 2. Stress Fails to Alter Dopamine Levels in Saline- or PCP-Treated Rat Prefrontal Cortex

	No Shock	Shock
Saline pre-exposed	0.53 ± 0.06	0.46 ± 0.08
PCP pre-exposed	0.56 ± 0.05	0.50 ± 0.04

No difference in basal dopamine levels (ng/mg protein) due to saline- or PCP-treatment or to no shock/shock condition in the prefrontal cortex of the rat. Data represent mean ± SEM. n = 8 for all measures.

lism (Figure 2; $152.7 \pm 7.9\%$ of PCP-preexposed/no stress values, $F_{(1,15)} = 22.1$; $p \leq .001$). However, the response to an acute stressor (calculated as the % increase in dopamine utilization after stress relative to no stress condition) was significantly reduced in PCP-preexposed animals relative to saline-exposed animals (i.e., there was a significant interaction between drug treatment and no-shock/shock condition: $F_{(1,28)} = 4.6$; $p < .05$). These effects were metabolite driven as no changes in basal dopamine values were induced by PCP or shock condition (Table 2). No increase in nucleus accumbens dopamine utilization in either saline- or PCP-pretreated animals was observed at the shock intensity used in this study (data not shown).

Cognitive Effects of Subchronic PCP Exposure

Before drug treatment, no significant differences in choice accuracy were detected between the saline-treated and PCP-treated groups ($F_{(1,11)} = 0.7$; $p > .05$); however a delay-dependent reduction in accuracy was observed across both groups ($F_{(4,29)} = 4.3$; $p \leq .01$). Subchronic PCP exposure led to impairments of performance on a

spatial delayed alternation task, relative to saline-treated controls ($F_{(1,11)} = 2.7$; $p \leq .05$), and this impairment was delay-dependent ($F_{(4,29)} = 11.5$; $p < .001$), i.e., impairments were evident at longer delays, with no deficits at the '0' sec delay condition (Figure 3).

DISCUSSION

The results of the present series of experiments demonstrate that repeated exposure to PCP leads to an inhibition of basal and stress-evoked dopamine utilization in the prefrontal cortex of the rat. These changes in responsiveness are not accompanied by a change in absolute dopamine concentrations, suggesting that an anatomical lesion of the dopaminergic innervation does not occur after repeated PCP exposure. In addition, norepinephrine utilization in the prefrontal cortex and dopamine utilization in other brain regions were not different in saline- and PCP-pre-exposed animals, suggesting that the reduction in dopamine utilization in the prefrontal cortex is not as a result of generalized alterations in catecholamine metabolism. Thus, it appears that the reduction in prefrontal cortical dopamine utilization is indicative of a reduced activity of mesoprefrontal dopamine neurons, i.e., a partial *functional* lesion of the mesocortical dopamine projection in rats.

Cognitive Correlates of Dopaminergic Dysfunction

The prefrontal cortex and its dopaminergic innervation are involved in working memory processes in rodents and primates (Goldman-Rakic 1987). Prefrontal cortical

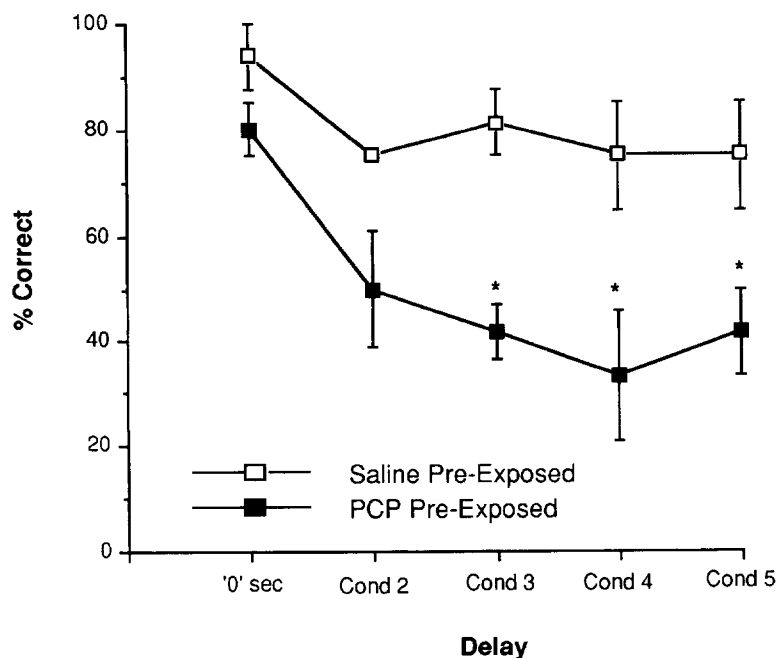


Figure 3. Rats subchronically exposed to PCP have delay-dependent working memory impairments relative to saline-treated controls as assessed by performance of a delayed alternation task. Data represent mean ± SEM. n = 6 for all observations. * Significantly impaired relative to saline-treated controls: $p \leq .05$.

ablation in monkeys (Goldman et al. 1971), regionally-specific destruction of dopamine terminals in the prefrontal cortex of rats and monkeys with 6-hydroxydopamine (Brozoski et al. 1979; Bubser and Schmidt 1990) and local prefrontal cortical dopamine D1 receptor blockade (Sawaguchi and Goldman-Rakic 1991) all induce performance deficits on tasks dependent on working memory. We thus hypothesized that the subchronic PCP-induced reduction in dopaminergic utilization in the frontal cortex would be accompanied by a working memory deficit. This hypothesis was confirmed, as rats subchronically treated with PCP exhibited performance impairments on spatial delayed alternation, a task dependent on intact working memory function. These deficits were delay-dependent, suggesting that the performance impairments were due to a cognitive, and not a non-specific, dysfunction.

Selective Inhibition of the Mesocortical Dopamine Projection

Subchronic PCP administration exerts preferential, if not selective, effects on the mesocortical dopamine innervation. In contrast to the depression of dopamine utilization in the prefrontal cortex, no such effect was observed in other dopamine-rich forebrain sites, such as the dorsolateral striatum or nucleus accumbens. In addition, no changes in norepinephrine turnover were measured in the medial prefrontal cortex after repeated PCP exposure. These data are consistent with previous findings regarding the selective pharmacological modulation of the prefrontal cortical dopamine projection (Deutch and Roth 1990).

Relevance to Subcortical Dopamine Systems

Recent work suggests that the prefrontal cortex exerts potent regulatory effects over the mesolimbic and nigrostriatal dopamine systems (Deutch 1992; Murase et al. 1993; Taber and Fibiger 1993, 1995). The dopaminergic innervation of the prefrontal cortex appears to have an inhibitory influence on subcortical dopamine systems, i.e., reductions in prefrontal cortical dopamine levels result in heightened activation of mesolimbic dopamine neurons by stress or haloperidol in the rat (Deutch et al. 1990; Rosin et al. 1992) or increased high K⁺-evoked dopamine release in the marmoset caudate nucleus (Roberts et al. 1994), whereas augmentation of extracellular dopamine levels in prefrontal cortex, with local amphetamine or cocaine application, reduces dopamine release in the caudate of the monkey (Kolachana et al. 1995). Thus, subchronic PCP-induced inhibition of frontal cortical dopamine function may be associated with a heightened activity of subcortical structures. This hypothesis awaits further experimentation; however, preliminary evidence suggests that subchronic PCP-treated rats, un-

der the present treatment regimen, are hyperresponsive to the locomotor-stimulating effects of amphetamine (unpublished observations), possibly indicating a heightened mesolimbic response to amphetamine.

Relevance to Schizophrenia

Whereas early studies of the acute effects of psychostimulants like PCP contributed to a hyperdopaminergic hypothesis of schizophrenia, more recent data have suggested that cortical dopaminergic hypoactivity (underlying cognitive deficits and some other negative symptoms of schizophrenia) and subcortical dopamine hyperactivity (underlying some positive symptoms of schizophrenia) may be involved in the disorder. Negative symptoms, including but not limited to cognitive deficits, appear to be unaffected by typical antipsychotic drugs (Lee et al. 1994), which possess potent dopamine D2 receptor antagonist properties (Seeman 1992; Deutch et al. 1992). Direct or indirect dopamine receptor agonists such as amphetamine (Angrist et al. 1982; van Kammen and Boronow 1988; Daniel et al. 1991) and apomorphine (Daniel et al. 1989; Dolan et al. 1995) may ameliorate hypofrontality or negative symptoms in schizophrenia, while exacerbating positive symptoms (Angrist and Gerson 1970, 1977; Angrist et al. 1980). Also, schizophrenic subjects exhibit deficits on Wisconsin Card Sort performance and failure of task-related activation of the dorsolateral prefrontal cortex, and these deficits are inversely correlated with cerebrospinal fluid homovanillic acid levels (Weinberger et al. 1986, 1988), suggesting that central dopaminergic deficits may be involved in the cognitive deficits. Finally, reduced dopaminergic innervation of the prefrontal cortex has been shown in schizophrenia (Akil and Lewis 1996). Thus, the prefrontal cortical dopaminergic hypofunction and cognitive deficits induced by repeated PCP administration may more successfully model a cortical dopaminergic and cognitive deficit in schizophrenia.

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