Subchronic Phencyclidine Administration Increases Mesolimbic Dopaminergic System Responsivity and Augments Stress- and Psychostimulant-Induced Hyperlocomotion

J. David Jentsch, B.A., Jane R. Taylor, Ph.D., and Robert H. Roth, Ph.D.

Previous studies have shown that repeated exposures to phencyclidine (PCP) induces prefrontal cortical dopaminergic and cognitive deficits in rats and monkeys, producing a possible model of schizophrenic frontal cortical dysfunction. In the current study, the effects of subchronic PCP exposure on forebrain dopaminergic function and behavior were further explored. Prefrontal cortical dopamine utilization was reduced 3 weeks after subchronic PCP administration, and the cortical dopaminergic deficit was mimicked by repeated dizocilpine exposure. In contrast, stress- and amphetamine-induced hyperlocomotion, behavior believed to be mediated by activation of mesolimbic dopamine transmission, was enhanced after PCP exposures. Furthermore, haloperidol-induced increases in nucleus accumbens dopamine utilization were larger in magnitude in PCP-treated rats relative to control subjects. These data are the first to demonstrate that repeated exposures to PCP causes prefrontal cortical dopaminergic hypoactivity and subcortical dopaminergic hyper-responsivity in rats, perhaps mimicking alterations in dopaminergic transmission that underlie the behavioral pathology of schizophrenia. ***[Neuropsychopharmacology 19:105–113, 1998]*** *© 1998 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

KEY WORDS: *Psychotomimetic; Schizophrenia; Working memory; Nucleus accumbens; Prefrontal cortex; Dizocilpine*

Phencyclidine (PCP) has psychotomimetic properties in man (Javitt and Zukin 1991); that is, administration of PCP or its congeners ketamine or dizocilpine can induce schizophrenic-like symptomatology in people (Luby et al. 1959; Krystal et al. 1994; Bunney et al. 1994) and precipitate psychosis in schizophrenics (Ital et al. 1967; Lahti et al. 1994). These compounds can stimulate both positive and negative symptoms of schizophrenia (Javitt and Zukin), including cognitive dysfunction (Cosgrove and Newell 1991). As such, PCP administration has been suggested to represent a drug-induced model of schizophrenia (Javitt and Zukin; Steinpreis 1996).

The ability of PCP to simulate the symptomatology of schizophrenia in humans has led to the proposal that the behavioral pathologies evident in schizophrenia and PCP-exposed humans are caused by dysfunction of common neural substrates (Luby et al. 1959; Javitt and Zukin 1991). The effects of PCP on brain dopamine systems has received particular attention (Meltzer et al. 1980; Bowers and Hoffman 1984; Deutch et al. 1987; Hertel et al. 1996; Jentsch et al. 1997a) since alterations in dopaminergic systems have been hypothesized in schizophrenia (reviewed in Davis et al. 1991; Deutch 1992).

From the Neuropsychopharmacology Research Unit (JDJ, RHR), Section of Neurobiology (JDJ), and Departments of Pharmacology (RHR) and Psychiatry (JRT, RHR), Yale University School of Medicine, New Haven, Connecticut, USA.

Address correspondence to: J. David Jentsch, Section of Neurobiology, Yale University School of Medicine, P.O. Box 208001, New Haven, CT 06520-8001.

Received October 2, 1997; revised December 1, 1997; accepted December 8, 1997.

NEUROPSYCHOPHARMACOLOGY 1998–VOL. 19, NO. 2

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/98/$19.00
PII S0893-133X(98)00004-9

Recent work has shown that long-term administration of PCP causes enduring cognitive dysfunction and cortical dopamine deficits in rats and monkeys (Jentsch et al. 1997b,c). These data correspond to reports of cognitive disturbances in schizophrenic subjects (Fey 1951; Goldman-Rakic 1991; Park and Holzman 1992), and recent *in vivo* imaging studies of the schizophrenic brain have revealed a failure of activation of frontal cortex during cognitive performance (termed "hypofrontality" by Weinberger and Berman 1996), effects that may be mediated by dopaminergic dysfunction (Weinberger et al. 1988; Daniel et al. 1989, 1991; Dolan et al. 1995). These data are also consistent with studies in nonhuman primates that have revealed that lesions of the prefrontal cortical dopamine innervation lead to working memory impairments (Brozoski et al. 1979), a cognitive process closely associated with this brain region (Goldman-Rakic 1987).

Moreover, prefrontal cortical dopaminergic deficiencies may result in enhancement of activity of subcortical dopamine systems. Destruction of prefrontal cortical dopamine terminals has been shown to augment the response of the mesolimbic dopamine systems to stress (Deutch et al. 1990), amphetamine sensitization (Banks and Gratton 1994), high K^+-stimulation (Roberts et al. 1994), or haloperidol administration (Rosin et al. 1994). These data have supported an emerging neurochemical hypothesis of schizophrenia: cortical dopaminergic hypoactivity and subcortical dopaminergic hyperactivity (Robbins 1990; Grace 1991; Deutch 1992). Recent in vivo studies of the schizophrenic brain have revealed evidence for the subcortical component of this hypothesis; heightened responsivity to the dopamine-releasing properties of amphetamine has been shown in the striata of schizophrenic subjects (Laruelle et al. 1996). Subcortical dopaminergic hyper-responsivity may, thus, be expressed along with cortical dopaminergic hypoactivity in subchronic PCP-treated subjects. This hypothesis is preliminarily supported by the finding that chronic ketamine administration leads to increased apomorphine-induced stereotypy in rats (Lannes et al. 1991).

In the present report, we describe the results of experiments designed to test the hypothesis that long-term administration of PCP results in subcortical dopaminergic hyperactivity along with enduring deficits in cortical dopaminergic transmission. We tested whether subchronic PCP administration augmented the locomotor response to amphetamine and stress and to haloperidol-stimulated increases in mesolimbic dopamine utilization. Furthermore, we extended our previous findings by examining whether the PCP-induced mesocortical dopamine deficits were enduring and due, specifically, to NMDA receptor blockade. Together, these data are the first to demonstrate that long-term administration of PCP induces both enduring cortical dopamine hypoactivity and subcortical dopamine hyper-responsivity in rats, possibly mimicking the neurochemical pathology of idiopathic schizophrenia.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (CAMM, Wayne, NJ) were used. They were maintained on a 12-h light–dark cycle with the light phase being 7:00 A.M. to 7:00 P.M. Rats used for biochemical and locomotor studies were fed and watered *ad libitum*. All study protocols were approved by the Yale University Animal Care and Use Committee.

Drugs

Phencyclidine hydrochloride, dizocilpine [(+)-MK-801 hydrogen maleate] and *d*-amphetamine sulfate (Research Biochemicals Inc., Natick, MA) were dissolved in sterile saline and injected in volumes of 1 ml/kg IP. Drug weights were calculated as the salt. Injectable haloperidol (as the lactate; 5 mg/ml; Solopak Laboratories, Inc, Elk Grove Village, IN) was diluted in sterile saline to a volume of 1 ml/kg and delivered IP.

Studies of Basal Neurotransmitter Utilization

In experiments studying basal (or nonstimulated) dopamine utilization, animals were subchronically treated with either saline (1 ml/kg twice daily for 7 days), PCP (5 mg/kg twice daily for 7 days) or dizocilpine (0.5 mg/kg twice daily for 7 days) or received only a single administration of these drugs. For repeated treatments, injections were given at approximately 9 A.M. and 8 P.M. One or three weeks (as specified below) after the final treatment, they were removed from their home cage and sacrificed. No intermediate challenges or stressors were delivered.

Haloperidol Challenge

Rats were subchronically treated with either saline (1 ml/kg twice daily for 7 days) or PCP (5 mg/kg twice daily for 7 days), and 7 days after the final administration, they were given either haloperidol (0.25 mg/kg) or saline (1 ml/kg) and sacrificed 30 min later. This treatment regimen resulted in 4 groups: subchronic saline–saline challenge, saline–haloperidol, PCP–saline, and PCP–haloperidol. This dose of haloperidol was chosen to submaximally increase dopamine utilization in the nucleus accumbens.

Biochemistry

All rats were 250 to 275 grams 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 selected brain regions were dissected out from 2-mm thick coronal sections on a chilled platform. Samples were immediately frozen on dry ice and stored at −70°C until assayed.

Catecholamine measurements were made with high-performance liquid chromatography (HPLC) using electrochemical detection according to methods detailed in Jentsch et al. (1997a). Measurements of utilization were made as the ratio of tissue concentration (in ng/mg protein) of the primary metabolite, dihydroxy-O-phenylacetic acid (DOPAC), to the parent amine, dopamine; i.e., DOPAC:dopamine.

Locomotor Testing

The locomotor boxes were identical to the home cages but were in a sound-attenuated room with standard ambient light. Activity was monitored with an automated 16 photocell array (Omnitech Digiscan Micro-Monitor, Columbus, Ohio, USA), which was set to count photocell beam interruptions per 10 min bin period.

For locomotor experiments, rats were initially subchronically treated with saline (1 ml/kg) or PCP (5 mg/kg) twice daily for 7 days. Seven days after the final injection, they were assessed for rates of locomotion in response to a novel environment for 30 min. All rats then received a saline injection (1 ml/kg) as a mild stressor and were monitored for an additional 60 min. Two days later, the subjects were returned to the locomotor boxes. After a 30 min habituation period, amphetamine (1 mg/kg) was administered, and activity was measured for 60 min postdrug.

Statistics

For basal biochemical studies, group comparisons were performed with one-way analysis of variance (ANOVA) followed by Scheffe's *F*-test for post-hoc analysis. Comparisons of haloperidol responsivity in saline- and PCP-treated animals utilized two-way ANOVA (with chronic treatment and acute challenge conditions as factors). Significant effects were further examined by factorial ANOVA with Scheffe's *F*-test. Analyses of locomotor data utilized ANOVA with repeated measures, the repeated measures being time. Analyses were performed with Statview II (Abacus Concepts, Berkeley, California, USA) on a Macintosh IIcx. All data are expressed as mean ± SEM.

RESULTS

Subchronic PCP-Induced Cortical Dopamine Utilization Deficits: Enduring Nature and Dependency on Repeat Treatment and N-methyl-D-aspartate (NMDA) Receptor Blockade

The enduring nature of the PCP-induced cortical dopamine deficit was explored in the current study by examining dopamine utilization in the forebrains of rats 3 weeks after drug administration. Rats were subchronically treated with saline (1 ml/kg) or PCP (5 mg/kg) twice daily for 7 days, and 3 weeks after the final administration, they were removed from their cages and sacrificed with no intervening stressor or challenge. Dopamine utilization in the prefrontal cortex of the PCP-treated rats was reduced relative to saline-treated controls (Figure 1; $F(1,29) = 24.97$, $p < .0001$). In contrast, no difference in nucleus accumbens dopamine utilization between the two groups was detected (Figure 1; $F(1,31) = 0.37$, $p = .85$).

To determine whether this was an effect mediated by the NMDA receptor-blocking properties of PCP, a cohort of rats were subchronically treated with dizocilpine (0.5 mg/kg twice daily for 7 days) or saline (identical regimen). Sacrifice occurred 1 week after the final administration as a direct comparison with previous observations that subchronic PCP treatment reduced prefrontal cortical dopamine utilization at 1 week. As with PCP, dizocilpine induced a reduction in prefrontal cortical dopamine utilization relative to saline controls ($F(1,22) = 10.14$, $p < .01$).

It is possible the observed effects following repeated exposure are mediated by long-term effects of a single administration; therefore, a cohort of rats received either a single injection of PCP (5 mg/kg) or saline (1 ml/kg) and were sacrificed 2 weeks later. This time point corresponds to the same interval from first treatment to sacrifice in the 1 week subchronic group. No differences in dopamine utilization were detected in the prefrontal cortices of PCP- vs. saline-treated controls ($F(1,23) = 0.002$, $p = .96$).

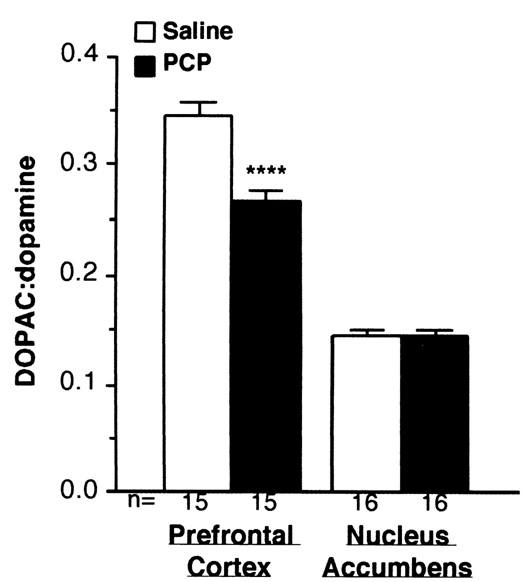

Figure 1. Subchronic exposure to PCP induces a reduction in prefrontal cortical dopamine utilization that is still evident 3 weeks after cessation of drug treatment, indicating that this effect is enduring. No drug-elicited changes in nucleus accumbens dopamine utilization were observed. ****$p < .0001$ by analysis of variance and Scheffe's *F*-test. Data represent mean ± SEM.

Table 1. Absolute Dopamine Concentrations in Rat Prefrontal Cortex after PCP or Dizocilpine Administration

	Saline	Acute PCP	Subchronic PCP	Subchronic Dizocilpine
Prefrontal cortex	0.54 ± 0.08	0.60 ± 0.13	0.64 ± 0.17	0.68 ± 0.22

Values represent mean ± SEM dopamine concentrations (ng/mg protein). No differences were measured, indicating that all observed changes in DOPAC:dopamine ratios were metabolite driven.

The ratio of DOPAC:dopamine can be affected by changes in either DOPAC or dopamine concentrations. Importantly, changes in the ratio that are driven by substantial alterations in dopamine concentrations alone are not necessarily indicative of altered dopamine utilization, *per se*. Thus, it is important to note that all reported differences in dopamine utilization occurred in the absence of large or significant changes in dopamine levels (see Table 1). The effects are primarily attributable to alterations in metabolite (DOPAC) accumulation.

Stress- and Amphetamine-Induced Hyperlocomotion in Subchronic Saline- vs. PCP-Treated Rats

The locomotor response to mild stress (exposure to a novel environment or saline injection) or amphetamine was determined in PCP-treated and control rats to examine whether PCP administration led to hyper-responsivity to the behavioral effects of stress- and amphetamine-induced mesolimbic dopamine activation. Subjects were subchronically treated with saline (1 ml/kg twice daily for 7 days) or PCP (5 mg/kg twice daily for 7 days) and were tested 1 week after the final drug treatment. Rats were placed in a novel environment and monitored for 30 min. ANOVA-repeated measures (time being the repeated measure) showed a significant effect of chronic treatment across the 30-min sampling session; subchronic PCP-treated rats were significantly more locomotive than saline-treated controls (Figure 2; $F(1,30) = 4.82$, $p < .05$). All subjects were then given an IP injection of saline (1 ml/kg) as a mild stressor. Again, ANOVA-repeated measures revealed a significant effect of chronic treatment. PCP-treated subjects were more locomotive in response to the injection than were saline-treated rats (Figure 2; $F(1,30) = 5.50$, $p < .05$).

Two days later, rats were returned to the chambers. No difference between saline- and PCP-treated subjects were detected by ANOVA-repeated measures in the initial 30-min baseline period (Figure 2; $F(1,30) = 1.02$, $p = .32$). In contrast, subchronic PCP treatment augmented amphetamine-induced (1 mg/kg) hyperlocomotion, as indicated by a greater increase in locomotor activity in PCP-treated rats as compared with controls (Figure 2; $F(1,30) = 6.04$, $p < .05$ by ANOVA-repeated measures).

Haloperidol-Induced Increases in Nucleus Accumbens Dopamine Utilization

No significant differences between basal nucleus accumbens dopamine utilization were detected in subchronic saline vs. PCP-treated rats (Figure 3; $F(1,14) = 2.71$, $p = .13$). Haloperidol (0.25 mg/kg) increased dopamine utilization in the nucleus accumbens of both

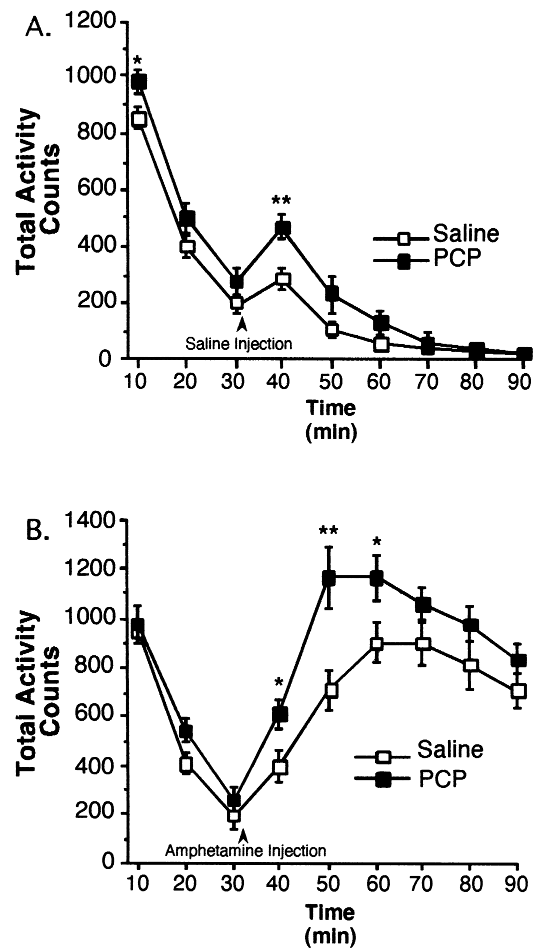

Figure 2. **(A)** Rats repeatedly treated with PCP are more hyperlocomotive in response to exposure to a novel environment or saline injection (mild stress) than saline-treated counterparts. **(B)** Subchronic PCP-treated rats are more hyperlocomotive in response to amphetamine administration than saline-treated controls. $^*p < .05$, $^{**}p < .01$ by analysis of variance and Scheffe's F-test. Data represent mean ± SEM.

saline- (Figure 3; $F(1,14) = 380.00$, $p < .0001$) and PCP-treated (Figure 3; $F(1,14) = 1788.21$, $p < .0001$) rats 30 min postadministration. Furthermore, two-way ANOVA using chronic treatment (saline vs. PCP) and acute challenge (saline vs. haloperidol) as factors revealed a significant interaction between these two conditions ($F(1,28) = 24.18$, $p < .0001$), and this effect was attributable to greater haloperidol-induced increases in dopamine utilization in PCP-treated relative to saline-treated rats (Figure 3; $F(1,14) = 22.02$, $p < .001$).

DISCUSSION

These data provide evidence for prolonged hypoactivity of mesocortical dopamine neurons and hyper-responsivity of mesolimbic dopamine neurons after subchronic PCP exposure. Previously, we showed that subchronic PCP exposure impaired spatial working memory and led to reductions in basal and stress-evoked dopamine utilization in the prefrontal cortex of the rat (Jentsch et al. 1997b), and here, we demonstrate that this biochemical effect is enduring (at least 3 weeks), dependent upon repeated exposure to the drug, and induced by long-term NMDA receptor blockade. Furthermore, we show augmented locomotor response to mild stress and amphetamine (using behavioral measures) and haloperidol administration (using *ex vivo* biochemical measures) in rats after subchronic PCP exposure.

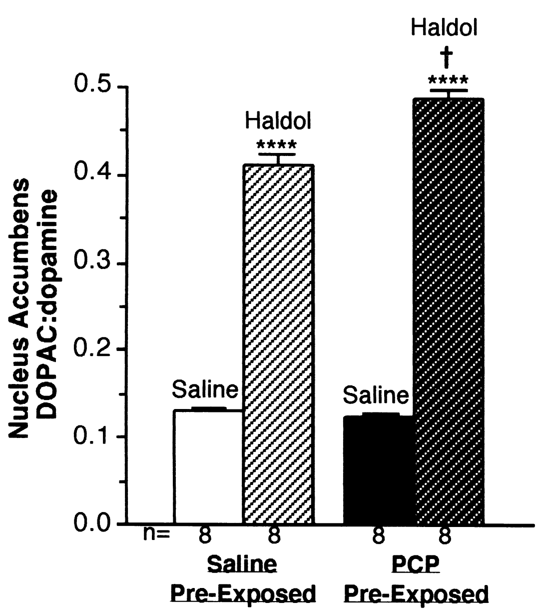

Figure 3. Haloperidol induces increases in nucleus accumbens dopamine utilization in rats repeatedly treated with either saline or PCP; however, this increase is greater in PCP-treated rats than controls. ****Increased relative to saline challenge: $p < .0001$ by analysis of variance and Scheffe's *F*-test. †Greater increase than in subchronic saline-treated rats: $p < .01$ by ANOVA and Scheffe's *F*-test. Data represent mean ± SEM.

Although the behavioral effects of amphetamine administration and the neurochemical effects of haloperidol administration are not directly comparable, together they provide evidence for mesolimbic dopaminergic hyper-responsivity. The neurochemical effects of mild stress exposure or systemic amphetamine administration on dopamine transmission in the nucleus accumbens are complicated by the fact that these conditions likely increase prefrontal cortical dopamine transmission to some degree in rats repeatedly exposed to PCP, even if the response is reduced as compared to controls (Jentsch et al. 1997b). Thus, these situations may lead to a partial reversal of the cortical dopamine dysfunction that presumably propagates the subcortical hyperactivity. Instead, we studied the neurochemical effects of haloperidol administration, because it preferentially activates mesostriatal dopamine neurons, sparing mesocortical neurons, and thus, is less likely to reverse the cortical dopamine deficit.

These data are consistent with the previous finding that repeated exposure to ketamine, a PCP congener, enhances apomorphine-induced stereotypy in rats (Lannes et al. 1991). Augmented behavioral effects of a direct dopamine receptor agonist would suggest that postsynaptic dopaminergic function may likewise be enhanced and that dorsal striatal function may also be enhanced, because stereotypy is most closely associated with the nigrostriatal dopaminergic innervation of dorsal striatum.

These data are the first to demonstrate that subchronic exposure to PCP induces frontal cortical cognitive deficits and hyper-responsivity to stress or amphetamine, moreover, they suggest that cortical dopaminergic hypoactivity and mesolimbic dopaminergic hyperactivity may subserve these effects, respectively. Thus, subchronic PCP exposure provides further functional evidence for dysfunction of cortical and subcortical dopamine systems in schizophrenia (Davis et al. 1991; Grace 1991; Deutch 1992).

Anatomic and Pharmacologic Specificity of the Effects of PCP

The dopaminergic abnormalities in this model seem to be attributable to dysregulation of dopaminergic systems rather than morphologic or anatomic changes in dopamine neurons, *per se*. Repeated exposure to PCP has not been reported to induce anatomic damage to dopamine neurons within the ventral mesencephalon (Ellison 1995), and we have not observed PCP-induced reductions in cortical dopamine levels, a presumed indication of loss of dopaminergic terminals (Jentsch et al. 1997b,c). Furthermore, we have not seen any indication of neuronal death, as revealed by suppressed silver staining, following this PCP treatment regimen (unpublished findings). In contrast, chronic (not intermittent) PCP administration or acute, high-dose PCP treatment has been shown to damage neurons within the corticolimbic axis (reviewed in Ellison). It remains possible that the ascending dopamine neurons may have altered regulation or responsivity because of dysfunctional ventral midbrain afferents.

In the current study, it was shown that dizocilpine mimics the effects of PCP after repeated administration. In addition to its action at NMDA receptors, however, PCP has significant affinity for the membrane dopamine transporter and sigma receptors. Of course, the similar effects of the selective noncompetitive NMDA receptor antagonist dizocilpine suggest that this receptor contributes heavily to the observed inhibition of cortical dopamine transmission, but it may be that other sites of action of PCP are contributory to its long-term dopaminergic effects.

Validity of the Subchronic PCP-Based Animal Model of Schizophrenia

The validity of subchronic PCP administration as an animal model of schizophrenia is supported by several findings. First, extensive literature shows that PCP is a drug with the ability to simulate schizophrenic-like episodes in humans (Luby et al. 1959; Javitt and Zukin 1991). Chronic PCP abuse in humans can cause enduring presentation of schizophrenic-like symptoms (Pearlson 1981; Javitt and Zukin), and this is the exposure condition most closely mimicked in the current study. Thus, in humans, PCP administration seems to represent a drug-induced model of some aspects of schizophrenia.

Behaviorally, subchronic PCP administration induces spatial working memory deficits in rats (Jentsch et al. 1997b) and behavioral disinhibition and perseveration in monkeys (Jentsch et al. 1997c). Schizophrenics have been reported to have these same symptoms: working memory impairments (Park and Holzmann 1992), behavioral disinhibition, and perseveration (Fey 1951; Weinberger et al. 1986). Furthermore, we now demonstrate hyper-responsivity to the stimulant qualities of stress and amphetamine in PCP-treated rats, and schizophrenic subjects can show increased psychotic symptoms in response to stress and amphetamine (Angrist and Gershon 1977). Finally, abnormal social interactions have previously been characterized in rats after subchronic PCP administration (Sams-Dodd 1996) another classic symptom of schizophrenia.

Neurobiologically, this model seems to mimic some observations of alterations in the schizophrenic brain. *In vivo* studies of cerebral glucose utilization in the schizophrenic brain have shown failure of metabolic activation of the frontal cortex during impaired performance of cognitive tasks in schizophrenia (Weinberger et al. 1986; Andreasen et al. 1992; Weinberger and Berman, 1996), and this prefrontal cortical hypoactivity has been observed in chronic PCP abusers, also (Hertzman et al. 1990; Wu et al. 1991). The degree of hypofrontality in schizophrenia has been shown to be inversely correlated with cerebrospinal fluid levels of homovanillic acid (the major metabolite of dopamine in humans [Weinberger et al. 1988]), and hypofrontality is alleviated after administration of the catecholamine-releasing drug amphetamine (Daniel et al. 1991) or direct dopamine receptor agonist apomorphine (Daniel et al. 1989; Dolan et al. 1995), suggesting that dopamine deficiencies in the cortex underlie the metabolic failure. This is analogous to the PCP-induced cognitive and dopamine deficits in the prefrontal cortex. Furthermore, hyperactivation of dopamine release (as measured by *in vivo* displacement of a dopamine D2 receptor ligand) by amphetamine has been reported in the schizophrenic striatal complex (Laruelle et al. 1996), and PCP-treated rats are hyper-responsive to amphetamine, presuming an increased mesolimbic dopamine response to this drug. Finally, a recent study reported decreases in dopamine D1 receptor mRNA in the frontal cortex of rats repeatedly treated with MK-801 (Healy and Meador-Woodruff 1996). These findings directly correspond with *in vivo* imaging studies of dopamine receptors that have revealed decreased prefrontal cortical dopamine D1 receptors in the schizophrenic brain (Okubo et al. 1997).

Overall, it seems that repeated exposure to PCP mimics many of the behavioral and biochemical sequelae of schizophrenia, findings that are tantamount to both face and construct validity for the PCP model of schizophrenia. Furthermore, several studies have generated data to suggest that the PCP model may have predictive validity, showing a qualitatively similar response to drug treatment as schizophrenia (Steinpreis et al. 1994; Sams-Dodd 1996; Jentsch et al. 1997c).

Relationship to Other Animal Models of Schizophrenia

Other models have been developed in an attempt to mimic schizophrenia in animals, the most interesting being neonatal hippocampal lesions in the rat (Lipska et al. 1993). This model has the unusual and distinctive feature of being developmentally valid. Schizophrenia is a disease that generally surfaces postpubertally, and the effects of neonatal ventral hippocampal damage seem to emerge only after puberty in rats (Lipska et al. 1993). Using this model, Lipska and colleagues have also demonstrated abnormal locomotor, stereotypic, sensorimotor-gating, and dopaminergic responses to stress, amphetamine, or apomorphine (Lipska and Weinberger 1993; Lipska et al. 1993; Lipska and Weinberger 1994; Lipska et al. 1995a,b), akin to the current findings. In addition, preliminary evidence for memory deficits in neonatally lesioned rats has been reported (Chambers et al. 1996); however, it is not clear that these deficits are dependent upon prefrontal function or are qualitatively similar to those observed in schizophrenic subjects. Finally, reduced social interactions have been reported in neonatally hippocampus-lesioned rats (Sams-Dodd et al. 1997).

Unlike findings with PCP, there is no clear validation of the ventral hippocampal lesion model in humans. Temporal lobe abnormalities have been consistently reported in schizophrenia (Kerwin and Murray 1992), but neonatal ibotenic acid lesions of the rat ventral hippocampus do not mimic either the degree or extent of temporal lobe abnormalities reported in schizophrenia or the lateralization of the purported anatomic defects (in the left, but not right, temporal lobe) (Shenton et al. 1992). In addition, although imaging studies have argued for a relationship between temporal activation and psychotic symptoms (Gur et al. 1989; Liddle et al. 1992), several studies have failed to correlate medial temporal lobe abnormalities with neuropsychological impairments in schizophrenic subjects (Goldberg and Weinberger 1988; Seidman et al. 1994). Of course, future imaging and neuropsychological studies may provide information regarding the precise role of hippocampal dysfunction in schizophrenic symptomatology; moreover, this model could reflect some important features of schizophrenia, if not the circumscribed disorder.

Another important animal model of schizophrenia relies on induction of selective anatomic and neurochemical lesions of the dorsolateral prefrontal cortex in monkeys. Damage to the dorsolateral prefrontal cortex or lesions of the prefrontal cortical dopamine innervation can both induce deficits reminiscent of schizophrenic negative symptoms and working memory dysfunction in monkeys (Brozoski et al. 1979; Goldman-Rakic 1987, 1991). Furthermore, damage to cortical dopamine terminals has been shown to induce mesolimbic dopaminergic hyper-responsivity in rats and monkeys (Deutch et al. 1990; Rosin et al. 1994; Roberts et al. 1994). This model, in many ways, implicates similar neuropathology in schizophrenia as does the PCP model. The lesion model, however, may not be as useful as the PCP model, because 6-hydroxydopamine lesions of the monkey frontal cortex are fraught with technical difficulties (e.g., craniotomy, local edema, nonselectivity of the lesion). In contrast, we have shown profound and enduring cortical dopamine transmission deficits in monkeys after subchronic PCP administration, a completely noninvasive procedure (Jentsch et al. 1997c).

Conclusion

The behavioral and neurochemical data, taken together, strongly argue for validity of subchronic PCP administration as an animal model of schizophrenia. This model may, therefore, provide a mechanism for the investigation of the pathophysiology of schizophrenia and be predictive of pharmacological response of schizophrenic subjects to antipsychotic drugs. Indeed, our recent work has demonstrated that cognitive deficits in subchronic PCP-treated monkeys are alleviated by clozapine (Jentsch et al. 1997c) but exacerbated by haloperidol (our unpublished data). These data correspond with some clinical reports of the effects of clozapine and haloperidol on schizophrenic cognitive dysfunction (Lee et al. 1994).

Studies of PCP in both humans and animals extend the hypotheses that schizophrenia is a disease that may be subserved by frontal cortical dopaminergic hypoactivity and mesolimbic hyper-responsivity. In tandem with clinical data suggesting cortical hypodopaminergia in schizophrenia, these neurochemical and behavioral effects of PCP suggest that selective pharmacological strategies targeted at alleviating cortical dopaminergic dysfunction may be an effective treatment for schizophrenia. Perhaps most exciting is the possibility of using what is known about the unique pharmacologic regulation of mesocortical dopamine neurons (Deutch and Roth 1990) to advance future novel and highly selective treatments for schizophrenia that involve augmentation of mesoprefrontal cortical dopamine neuron function.

ACKNOWLEDGMENTS

Thanks to Kenneth Youngren for his critical reading of this manuscript and Dung Le, Anh Tran, and Kristina Kudelko for their technical support. Supported, in part, by U.S. PHS grants MH-14092 and MH-57483 (RHR) and the Scottish Rite Schizophrenia Research Program, N.M.J., U.S.A. (JDJ). Portions of these data have been presented in abstract form (Jentsch and Roth 1996; Jentsch et al. 1997d).

REFERENCES

Andreasen NC, Rezai K, Alliger R, Swayze VW, Flaum M, Kirchner P, Cohen G, O'Leary DS (1992): Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Arch Gen Psychiatry 49:943–958

Angrist B, Gershon S (1977): Clinical response to several dopamine agonists in schizophrenic and nonschizophrenic subjects. Adv Biochem Pharmacol 16:667–680

Banks KE, Gratton A (1994): Possible involvement of medial prefrontal cortex in amphetamine-induced sensitization of mesolimbic dopamine function. Eur J Pharmacol 282: 157–167

Bowers MB, Hoffman FJ (1984): Homovanillic acid in rat caudate and prefrontal cortex following phencyclidine and amphetamine. Psychopharmacol 84:136–137

Brozoski TJ, Brown RM, Rosvold HE, Goldman PS (1979):

Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205: 929–931

Bunney BG, Bunney WE, Jr, Carlsson A (1994): Schizophrenia and glutamate. In Bloom FE, Kupfer DJ (eds), Psychopharmacology, the Fourth Generation of Progress. New York, Raven, pp 1205–1214

Chambers RA, Moore J, McEvoy JP, Levin ED (1996): Cognitive effects of neonatal hippocampal lesions in a rat model of schizophrenia. Neuropsychopharmacology 15:587–594

Cosgrove J, Newell TG (1991): Recovery of neuropsychological functions during reduction in use of phencyclidine. J Clin Psychol 47:159–169

Daniel DG, Berman KF, Weinberger DR (1989): The effect of apomorphine on regional cerebral blood flow in schizophrenia. J Neuropsych 1:377–384

Daniel DG, Weinberger DR, Jones DW, Zigun JR, Coppola R, Handel S, Bigelow LB, Goldberg TE, Berman KF, Kleinman JE (1991): The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. J Neurosci 11:1907–1917

Davis KL, Kahn RS, Ko G, Davidson M (1991): Dopamine in schizophrenia: A review and reconceptualization. Am J Psychiatry 148:1474–1486

Deutch AY (1992): The regulation of subcortical dopamine systems by the prefrontal cortex: Interactions of central dopamine systems and the pathogenesis of schizophrenia. J Neural Transm 36:61–89

Deutch AY, Clark WA, Roth RH (1990): Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res 521:311–315

Deutch AY, Roth RH (1990): The determinants of stress-induced activation of the prefrontal cortical dopamine system. In Vylings HBM, Eden CGV, DeBruim JPC, Corner MA, Feenstra MGP (eds), The Prefrontal Cortex: Its Structure, Function, and Pathology. Amsterdam, Elsevier, pp 367–403

Deutch AY, Tam SY, Freeman AS, Bowers MB, Roth RH (1987): Mesolimbic and mesocortical dopamine activation induced by phencyclidine: Contrasting pattern to striatal response. Eur J Pharmacol 134:257–264

Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RSJ, Grasby PM (1995): Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. Nature 378:180–182

Ellison G (1995): The N-methyl-D-aspartate antagonists phencyclidine, ketamine, and dizocilpine as both behavioral and anatomical models of the dementias. Brain Res Rev 20:250–267

Fey ET (1951): The performance of young schizophrenics and young normals on the Wisconsin Card Sorting Test. J Consult Psychol 15:311–319

Goldberg TE, Weinberger DR (1988): Probing prefrontal function in schizophrenia with neuropsychological paradigms. Schizophr Bull 14:179–183

Goldman-Rakic PS (1987): Circuitry of the frontal cortex and the regulation of behavior by representational knowledge. In Plum F, Mountcastle V (eds), Handbook of Physiology, Volume V, The Nervous System. Bethesda, MD, American Physiological Society, pp 373–417

Goldman-Rakic PS (1991): Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In Carroll BJ, Barret JE (eds), Psychopathology and the Brain. New York, Raven, pp 1–23

Grace AA (1991): Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. Neurosci 41:1–24

Gur RE, Resnick SM, Gur RC (1989): Laterality and frontality of cerebral blood flow and metabolism in schizophrenia: Relationship to symptom specificity. Psychiatry Res 27:325–334

Healy DJ, Meador-Woodruff JH (1996): Differential regulation, by MK-801, of dopamine receptor gene expression in rat nigrostriatal and mesocorticolimbic systems. Brain Res 708:38–44

Hertel P, Mathe JM, Nomikos GG, Iurlo M, Mathe AA, Svensson TH (1996): Effects of d-amphetamine and phencyclidine on behavior and extracellular concentrations of neurotensin and dopamine in the ventral striatum and the medial prefrontal cortex of the rat. Behav Brain Res 72:103–114

Hertzman M, Reba RC, Kotlyarove EV (1990): Single photon emission computerized tomography in phencyclidine and related drug abuse. Am J Psychiatry 147:255–256

Ital T, Keskiner A, Kiremitci N, Holden JMC (1967): Effect of phencyclidine in chronic schizophrenics. Can Psychiatric Assoc J 12:209–212

Javitt DC, Zukin SR (1991): Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148: 1301–1308

Jentsch JD, Roth RH (1996): Differential effects of acute and repeated phencyclidine administration on prefrontal cortical dopamine: relevance to schizophrenia. Soc Neurosci Abstr 22:1320

Jentsch JD, Elsworth JD, Redmond DE, Jr, Roth RH (1997a): Phencyclidine increase forebrain monoamine metabolism in rats and monkeys: Modulation by the isomers of HA966. J Neurosci 17:1769–1776

Jentsch JD, Tran A, Le D, Youngren KD, Roth RH (1997b): Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. Neuropsychopharmacology 17:92–99

Jentsch JD, Redmond DE Jr, Elsworth JD, Taylor JR, Youngren KD, Roth RH (1997c): Enduring cognitive dysfunction and cortical dopamine deficits in monkeys after long-term administration of phencyclidine. Science 277:953–955

Jentsch JD, Taylor JR, Elsworth JD, Redmond DE, Jr, Tran A, Le D, Kudelko KT, Roth RH (1997d): Prefrontal cortical cognitive and dopamine deficits in rats and monkeys after subchronic PCP exposure. Soc Neurosci Abstr 23:1930

Kerwin RW, Murray RM (1992): A developmental perspective on the pathology and neurochemistry of the temporal lobe in schizophrenia. Schizophr Res 7:1–12

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers BM, Charney DS (1994): Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: Psychotomimetic, perceptual, cognitive and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Lahti AC, Koffel B, Laporte D, Tamminga CA (1994): Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19

Lannes B, Micheletti G, Warter J-M, Kempf E, Di Scala G (1991): Behavioral, pharmacological, and biochemical effects of acute and chronic administration of ketamine in the rat. Neurosci Lett 128:177–181

Laruelle M, Abi-Dargham A, Van Dyck C, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Finugado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB (1996): Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci USA 93:9235–9240

Lee MA, Thompson PA, Meltzer HY (1994): Effects of clozapine on cognitive function in schizophrenia. J Clin Psychiatry 55:82–87

Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RSJ (1992): Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 160:179–186

Lipska BK, Jaskiw GE, Weinberger DR (1993): Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal hippocampal damage: A potential animal model of schizophrenia. Neuropsychopharmacology 9:67–75

Lipska BK, Weinberger DR (1993): Delayed effects of neonatal hippocampal damage on haloperidol-induced catalepsy and apomorphine-induced stereotypic behaviors in the rat. Dev Brain Res 75:75–222

Lipska BK, Weinberger DR (1994): Subchronic treatment with haloperidol or clozapine in rats with neonatal excitotoxic hippocampal damage. Neuropsychopharmacology 10:199–205

Lipska BK, Chrapusta SJ, Egan MF, Weinberger DR (1995a): Neonatal excitotoxic ventral hippocampal damage alters dopamine response to mild chronic stress and haloperidol treatment. Synapse 20:125–130

Lipska BK, Swerdlow NR, Geyer MA, Jaskiw GE, Braff DL, Weinberger DR (1995b): Neonatal excitotoxic hippocampal damage in rats causes postpubertal changes in prepulse inhibition of startle and its disruption by apomorphine. Psychopharmacology 122:35–43

Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelly R (1959): Study of a new schizophrenic-like drug—Sernyl. Arch Neurol Psychiatry 81:363–369

Meltzer HY, Sturgeon RD, Simonovic M, Fessler RG (1980): Phencyclidine as an indirect dopamine agonist. Psychopharmacol Bull 16:62–65

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M (1997): Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 385:634–636

Park S, Holzman PS (1992): Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry 49:975–982

Pearlson GD (1981): Psychiatric and medical syndromes associated with phencyclidine (PCP) abuse. The Johns Hopkins Med J 148:25–33

Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ, Robbins TW (1994): 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analogue of the Wisconsin Card Sort Test: Possible interactions with subcortical dopamine. J Neurosci 14:2531–2544

Robbins TW (1990): The case for frontostriatal dysfunction in schizophrenia. Schizophr Bull 16:391–402

Rosin DL, Clark WA, Goldstein M, Roth RH, Deutch AY (1994): Effects of 6-hydroxydopamine lesions of the prefrontal cortex on tyrosine hydroxylase activity in subcortical dopamine systems in the rat. Neuroscience 48:831–839

Sams-Dodd F (1996): Phencyclidine-induced stereotyped behavior and social isolation in rats: A possible animal model of schizophrenia. Behav Pharmacol 7:3–23

Sams-Dodd F, Lipska BK, Weinberger DR (1997): Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behavior in adulthood. Psychopharmacology 132:303–310

Seidman LJ, Yurgelun-Todd D, Kremen WS, Woods BT, Goldstein JM, Faraone SV, Tsuang MT (1994): Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. Biol Psychiatry 35:235–246

Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, et al. (1992): Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. New Engl J Med 327:604–612

Steinpreis RE (1996): The behavioral and neurochemical effects of phencyclidine in humans and animals: Some implications for modeling psychosis. Behav Brain Res 74:45–55

Steinpreis RE, Sokolowski JD, Papanikolaou A, Salamone JD (1994): The effects of haloperidol and clozapine on PCP- and amphetamine-induced suppression of social behavior in the rat. Pharmacol Biochem Behav 47:579–585

Weinberger DR, Berman KF (1996): Prefrontal function in schizophrenia: Confounds and controversies. Phil Trans R Soc Lond B 351:1495–1503

Weinberger DR, Berman KF, Zec RF (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 43:114–125

Weinberger DR, Berman KF, Illowsky BP (1988): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a monoaminergic mechanism. Arch Gen Psychiatry 45:609–615

Wu JC, Buchsbaum MS, Bunney WE (1991): Positron emission tomography study of phencyclidine users as a possible drug model of schizophrenia. Jpn J Psychopharmacol 11:47–48