Published in final edited form as:

Psychopharmacology (Berl). 2004 December ; 177(1-2): 170–177. doi:10.1007/s00213-004-1936-1.

Progressive ratio performance following challenge with antipsychotics, amphetamine, or NMDA antagonists in adult rats treated perinatally with phencyclidine

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Abstract

Rationale—Previous research has shown that rats exposed perinatally to phencyclidine (PCP) exhibited neuroanatomical abnormalities and altered cognition. In addition to cognitive deficits, schizophrenic patients may also exhibit negative symptoms such as lack of motivation.

Objectives—In this study, we used a progressive ratio (PR) schedule of food reinforcement to assess motivation following early exposure to PCP.

Methods—Male rat pups were injected SC with 10 mg/kg PCP on postnatal days (PN) 7, 9, and 11. On PN 120, they began training in a PR 5 schedule of food reinforcement.

Results—Significant PCP effects on acquisition and baseline performance were not noted. After acquisition of the task, challenges with PCP, dizocilpine, amphetamine, haloperidol, and clozapine resulted in dose-dependent decreases in response rates of similar magnitudes in both groups. In rats that continued to respond at higher doses, PCP, dizocilpine, and clozapine failed to alter breakpoints. In contrast, a 5.6 mg/kg dose of amphetamine selectively increased breakpoints in PCP-treated rats, although very few rats responded at this dose. Haloperidol decreased breakpoints in most rats at non-sedating doses.

Conclusions—These results suggest that a regimen of perinatal PCP administration sufficient to disrupt cognition did not alter motivation for food reinforcement, regardless of whether rats also received challenges with NMDA antagonists or antipsychotics. Interpretation of amphetamine's high dose effects on breakpoints was complicated by the failure of many rats to respond at this dose. Further research is needed to determine whether negative symptoms such as social withdrawal may be modeled within this neurodevelopmental approach to schizophrenia.

Keywords

Clozapine; Dizocilpine; Glutamate; Haloperidol; Motivation; Schizophrenia

Introduction

Perinatal exposure to the *N*-methyl-D-aspartate (NMDA) open channel blocker phencyclidine (PCP) results in neuroanatomical and behavioral abnormalities suggestive of disrupted glutamatergic neurotransmission (Brooks et al. 1997; Ikonomidou et al. 1999; Wang et al. 2001; Wiley et al. 2003). Neuroanatomical abnormalities include increased signs of apoptosis

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in the frontal cortex and increased mRNA for the NR1 subunit of the NMDA receptor (Wang et al. 2001). Behavioral abnormalities include decreased baseline levels of prepulse inhibition of acoustic startle (an animal model of sensorimotor gating, a pre-attentional process), sensitization to PCP-induced locomotor activation, slower acquisition of a delayed spatial alternation task (an animal model of short-term memory), and increased disruption of later performance in the spatial alternation task by PCP-like NMDA antagonists (Wang et al. 2001; Wiley et al. 2003). Similar deficits in sensorimotor gating and short-term memory tasks have been observed in schizophrenia (Braff et al. 1978; Andreasen 1997; Crespo-Facorro et al. 2001), suggesting that perinatal PCP produces later cognitive deficits in rats that resemble some of those occurring in schizophrenia.

Cognitive deficits, as well as other positive and negative symptoms of schizophrenia, can also be mimicked by acute administration of PCP-like drugs to humans (Javitt and Zukin 1991). Negative symptoms that have been observed in schizophrenia include social withdrawal, flat affect, anhedonia, and lack of motivation (e.g. Andreasen and Olsen 1982). Although these negative symptoms have been difficult to model preclinically, some success has been achieved through the use of animal models of anhedonia and social withdrawal (Ellenbroek and Cools 2000). Whereas PCP does not appear to induce anhedonia in models such as sucrose drinking and intracranial self-stimulation (Kornetsky and Esposito 1979; Carlezon and Wise 1993; Turgeon et al. 1998), it does reduce social interaction, particularly after subchronic administration (Schlemmer and Davis 1983; Steinpreis et al. 1994; Sams Dodd 1996). The effects of perinatal PCP in any of these models has not been previously evaluated. Since past studies have effectively used progressive ratio (PR) operant schedules to assess motivation following a wide variety of experimental manipulations (Katz 1990; Schmelzeis and Mittleman 1996; Barr and Phillips 1999; Reilly 1999), we decided to evaluate the usefulness of this procedure as a way to assess possible motivational changes as a consequence of early exposure to PCP. Under this type of schedule, the number of times an animal is required to press a lever in order to obtain a reinforcer (e.g. food or drug) is progressively increased with each successive ratio. Eventually, the animal will reach a ratio at which it will no longer respond (defined as the "breakpoint"). This breakpoint serves as a measure of the animal's motivation to obtain the reinforcer (Markou et al. 1993). We postulated that rats exposed to PCP perinatally would have lower breakpoints in this task than would rats exposed to saline, suggesting lower motivation for food reinforcement in PCP-exposed rats.

Materials and methods

Subjects

Six timed pregnant Sprague-Dawley rats (Harlan, Dublin, Va., USA) were received on gestation day 14 and were individually housed in clear plastic cages in a temperature-controlled (20–22°C) environment with a 12-h light-dark cycle (lights on at 7 a.m.). Plenty of sawdust bedding was available in each cage for nesting. The dams were left undisturbed except for providing food and water until they gave birth approximately 1 week later (postnatal day 0, PN0). On PN2, pups were handled and sexed. Twenty of the male pups were randomly cross-fostered into two groups. Pups in one of the groups were injected with 10 mg/kg PCP SC on PN7, PN9, and PN11 while pups in the other group were treated with SC saline on the same days, as described previously (Wang et al. 2001; Wiley et al. 2003). Following the perinatal injections, the pups remained with their assigned dams until weaning. Subsequently, they were pair-housed with a rat that had received the same treatment. They were weighed and handled at least twice a week and had free access to food and water until PN120, when they began training in the operant task. During subsequent acquisition and testing under the progressive ratio procedure, rats were food-restricted in order to motivate them to consume the food pellet reinforcers; however, since rats were young when they entered the study, they were allowed

to continue to gain weight throughout training until they reached a target weight range of 350-450 g. They had ad libitum water in their home cages. The studies reported in this manuscript were carried out in accordance with guidelines published in guide for the care and use of laboratory animals (National Research Council 1996) and were approved by our Institutional Animal Care and Use Committee.

Apparatus

Rats were trained and tested in standard operant conditioning chambers (Lafayette Instruments Co., Lafayette, Ind., USA) housed in sound-attenuated cubicles. Each chamber had three retractable levers, only one of which (the left) was used for this study. Pellet dispensers delivered 45-mg BIO SERV (Frenchtown, N.J., USA) food pellets to a food cup in the middle of the front wall of the chamber between two of the response levers (right lever retracted) and over the third (retracted) center lever. Fan motors provided ventilation and masking noise for each chamber. House lights located above the food cup were illuminated during training and testing sessions. A micro-computer with Logic "1" interface (MED Associates, Georgia, Vt., USA) and MED-PC software (MED Associates) was used to control schedule contingencies and to record data.

Procedure

Rats initially were trained to lever-press for food reinforcement. Once the lever-press response was acquired (2-3 days), a progressive ratio 5 schedule was instituted. Under this schedule, the rat had to press the lever 5 times in order to receive the first food pellet. For each subsequent reinforcer, the ratio requirement was increased by 5 (i.e. 5, 10, 15, etc.) until the rat failed to respond for 2 min. Failure to respond for 2 min was defined as the "breakpoint" and the session was terminated at the breakpoint. Upon termination of the session at a breakpoint, house lights were extinguished, the lever was retracted, and the rat remained in the chamber until 15 min from the start of the session. When a breakpoint did not occur, maximum session duration was 15 min, at which point the house lights were extinguished and the lever was retracted.

Daily (Monday-Friday) training sessions continued until responding on the progressive ratio schedule was stable (approximately 3 months). Subsequently, drug testing was initiated. Drug tests typically occurred on Tuesdays and Fridays, with continued training on Mondays, Wednesdays, and Thursdays. For each dose-effect curve determination, doses (including vehicle dose) were administered in randomized order according to a modified Latin square design. In addition to investigation of the effects of pharmacological challenges, manipulation of the magnitude of increase of the ratio with each successive reinforcer was altered. With this manipulation, the initial ratio was 5; the step increase was varied additively from 2 to 10 or exponentially (e.g. 2×2, 3×3, 4×4, 5×5, etc.).

Drugs

Phencyclidine HCl (National Institute on Drug Abuse, Rockville, Md., USA), D-amphetamine sulfate (National Institute on Drug Abuse), and dizocilpine maleate [Research Biochemicals International (RBI), Natick, Mass., USA] were mixed in physiological saline. Haloperidol (McNeil Pharmaceutical, Spring House, Pa., USA) was prepared by adding saline to a commercially available 5 mg/ml stock solution containing 1.8 mg methyl paraben, 0.2 mg propylparaben, and lactic acid. Clozapine (RBI) was mixed in a vehicle of absolute ethanol, Emulphor-620 (Rhone-Poulenc, Inc., Princeton, N.J., USA), and saline in a ratio of 1:1:18. Pre-session injection intervals were 10 min for dizocilpine, 15 min for PCP and amphetamine, and 45 min for haloperidol and clozapine. Perinatal PCP and saline were administered SC. All test drugs were administered IP at a volume of 1 ml/kg, with the exception that the 5.6 mg/kg dose of amphetamine was obtained by injection with a 1.87 ml/kg volume of a 3 mg/ml concentration. Doses of all drugs are expressed as mg/kg of the form presented.

Statistical analysis

Four dependent variables were measured: number of reinforcers, response rate, breakpoint, and average interresponse time (IRT). Number of reinforcers was defined as the number of pellets that the rat earned during the entire session. Given the ratio schedule, this value co-varied with the number of responses. Response rates were calculated as number of responses divided by actual session duration. Breakpoint was defined as the first ratio after which a response delay of at least 2 min occurred. For each rat, average IRT was calculated as the mean of the average delay between responses for each ratio (post-ratio latencies between the end of one ratio and the beginning of the next were not considered in calculating the average IRT). Breakpoints and average IRTs were not recorded for rats that responded fewer than 5 times during the session. Separate two-way split-plot analyses of variance (ANOVA) with dose or condition as the within subjects factor and perinatal treatment as the between subjects factor were used to analyze dependent variables for each drug or experimental manipulation. Following significant ANOVAs, Tukey post-hoc tests ($\alpha=0.05$) were used to determine differences between means.

Results

Acquisition of the lever press response and subsequent stabilization of responding on the progressive ratio schedule required approximately 3 months. No systematic differences between the two perinatal treatment groups in rates of acquisition were observed (data not shown).

Challenges with dizocilpine and PCP also failed to reveal differences between treatment groups for any of the measures. While both drugs significantly decreased the number of earned pellets and response rates at the highest doses tested (main effects) [PCP pellets: $F(4,68)=13.2$, $P<0.05$; PCP response rates: $F(4,68)=8.75$, $P<0.05$; dizocilpine pellets: $F(4,60)=8.57$, $P<0.05$; dizocilpine response rates: $F(4,60)=4.99$, $P<0.05$], a significant interaction was not observed (Table 1), suggesting that perinatal treatment with PCP did not differentially affect later response to PCP-like drugs in this model. In contrast to their effects on response rates, neither dizocilpine nor PCP significantly affected breakpoint (Fig. 1, left panels). The 0.1 mg/kg dose of dizocilpine significantly decreased average IRT (main effect; Fig. 1, upper right panel) [$F(4,51)=3.3$, $P<0.05$]; however, the magnitude of this effect was small and it was not dose-dependent.

Tables 2 and 3 show the effects of amphetamine, haloperidol, and clozapine on number of pellets and response rates. Each drug dose-dependently decreased both measures at similar doses (main effects) [amphetamine pellets: $F(6,102)=13.54$, $P<0.05$; amphetamine response rates: $F(6,102)=10.28$, $P<0.05$; haloperidol pellets: $F(4,40)=14.5$, $P<0.05$; haloperidol response rates: $F(4,40)=11.01$, $P<0.05$; clozapine pellets: $F(3,27)=22.14$, $P<0.05$; clozapine response rates: $F(3,27)=16.22$, $P<0.05$]. Amphetamine also significantly affected breakpoint and IRT (Fig. 2, top panels) [amphetamine breakpoint interaction: $F(6,67)=2.71$, $P<0.05$; amphetamine IRT interaction: $F(5,48)=2.51$, $P<0.05$], although the low numbers of subjects responding at the 3 and 5.6 mg/kg doses of amphetamine make meaningful interpretations of the data difficult. In contrast, most subjects continued to respond at higher doses of haloperidol; yet, breakpoints showed significant dose-dependent decreases [main effect: $F(4,35)=18.03$, $P<0.05$] and average IRTs were significantly increased at 0.3 mg/kg haloperidol [main effect: $F(4,33)=3.03$, $P<0.05$] (Fig. 2, middle panels). Clozapine did not significantly affect either measure at doses where responding occurred (Fig. 2, bottom panels).

Figure 3 shows the effects of variation in step value (i.e. increment of ratio after each reinforcer) on number of pellets (upper left panel), response rates (upper right panel), breakpoints (lower left panel), and average IRTs (lower right panel). Increases in the step value of the progressive

ratio systematically and significantly decreased the number of pellets earned [main effect: $F(3,30)=38.54$, $P<0.05$] (Fig. 3, upper left panel) while leaving response rates unaffected (Fig. 3, upper right panel). Breakpoints were significantly increased with exponential increases in the ratio value, but not with additive increases [main effect: $F(3,30)=17.25$, $P<0.05$] (Fig. 3, lower left panel). Average IRTs were not altered at any of the step values (Fig. 3, lower right panel).

Discussion

Social withdrawal, affective flattening, anhedonia and avolition represent hallmark negative symptoms that have been observed in certain cases of schizophrenia (Andreasen and Olsen 1982). Cilia et al. (2001) have suggested that progressive ratio procedures may be useful in modeling avolition associated with schizophrenia. Although perinatal exposure to PCP results in behaviors that mimic cognitive dysfunction and positive symptoms associated with schizophrenia (e.g. hyperactivity and disruption of sensorimotor gating) (Wang et al. 2001; Wiley et al. 2003), the lack of difference between PCP-treated and saline-treated rats in acquisition and baseline responding under a progressive ratio schedule in the present study suggest that this treatment regimen did not alter motivation, as might be expected if perinatal PCP induced behaviors related to negative symptomatology. Several possible explanations of this lack of differential responding are possible. First, neither perinatal PCP nor any other preclinical model of schizophrenia alter physiology and behavior in a manner that is identical to that produced by schizophrenia itself. [Indeed, not all cases of schizophrenia are identical, as some individuals experience prominent positive symptoms with few negative symptoms while others experience primarily negative symptoms (e.g. deficit syndrome; Kirkpatrick et al. 2001)]. Avolition may be a symptom that is not reproduced by this particular experimental manipulation. Second, a significant period of time elapsed between exposure to PCP and training and testing in the progressive ratio procedure. This delay allowed for the possible development of compensatory or restorative mechanisms that may have improved functioning in the PCP-treated animals. If this is the case, however, these compensatory mechanisms differentially affected specific areas of functioning, as cognitive behavior (measured in a delayed spatial alternation task) continued to be disrupted in rats at a comparable interval following an identical regimen of treatment with perinatal PCP (Wiley et al. 2003). Nevertheless, the rats did receive extensive handling during the intervening period between perinatal PCP exposure and training and testing in the progressive ratio procedure and it is possible that this handling may have differentially improved motivational functioning. Indeed, handling has been shown to attenuate responses to isolation rearing (Krebs-Thomson et al. 2001) and to stress (Meaney et al. 1991 for review). Finally, it is possible that the progressive ratio procedure may not represent an adequately sensitive model of avolition such as that observed in schizophrenia. While this possibility cannot be entirely excluded, our data show that the procedure is sensitive to pharmacological and experimental manipulations that have altered motivation in other studies. Specifically, changes in the progressive ratio increment resulted in changes in breakpoints without effects on response rates and most of the drugs affected breakpoints, as discussed in more detail below.

Previously, we had shown that, following acquisition, rats perinatally treated with PCP achieved equal baseline levels of accuracy in a delayed spatial alternation task as did those treated perinatally with saline; however, when these rats were administered dizocilpine or PCP, perinatally PCP-treated rats exhibited greater decreases in accuracy (Wiley et al. 2003). Hence, an underlying deficit in cognitive skills that did not appear under basal conditions was revealed through pharmacological challenge. In the present study, we challenged the rats with several drugs that affect glutamate and dopamine neurotransmission, as these neurotransmitters are likely to be involved in schizophrenia (Carlsson 1988; Moghaddam 1994). None of the drugs differentially affected PCP- and saline-treated rats, suggesting that perinatal treatment with

PCP probably did not dramatically alter later motivation for food reinforcement. Nevertheless, each of the drugs significantly affected some or all of the dependent measures, offering insight into the effects of manipulations of the glutamatergic and dopaminergic systems on motor and motivational variables.

Two NMDA open channel blockers, PCP and dizocilpine, decreased response rates at higher doses under the progressive ratio schedule. These results are consistent with those of other operant studies in which higher doses of PCP-like drugs decreased response rates under fixed ratio and fixed interval schedules or components of multiple schedules (Hudzik and Slifer 1992; McMillan et al. 1992; Poling et al. 1981; Segal et al. 1981). Unlike with some of these studies (Segal et al. 1981; McMillan et al. 1992), however, increases in responding were not observed at lower doses of these drugs. When rats that failed to respond were excluded from calculations of breakpoint for each drug, neither drug altered breakpoint, suggesting that NMDA antagonism via open channel blockade did not affect motivation for food reinforcement. These results are consistent with those of a previous study in which dizocilpine only minimally affected breakpoints for food reinforcement in rhesus monkeys (Buffalo et al. 1994). Further, acute dosing with PCP did not alter responding for intracranial brain stimulation (Spielewoy and Markou 2003), nor did it decrease voluntary sucrose consumption within a few hours after administration (Turgeon and Hoge 2003). Rather, effects on responding for brain stimulation and sucrose consumption were delayed and may have been associated with withdrawal from PCP.

Similar to PCP and dizocilpine, amphetamine also decreased response and reinforcer rates at higher doses. In addition, the 5.6 mg/kg dose of amphetamine increased breakpoint in PCP-treated versus saline-treated rats; however, interpretation of these results is somewhat complicated by the fact that very few rats continued to respond at this dose. Interestingly, though, breakpoints were also enhanced by amphetamine in rats raised in isolation after weaning (Smith et al. 1997), suggesting that amphetamine may accentuate motivation in compromised rats. In humans with schizophrenia, amphetamine selectively improved negative symptoms (Kirkane et al. 2000). Results of tests with amphetamine in previous progressive ratio studies using food reinforcement have been inconsistent: amphetamine decreased breakpoints (Schulze and Paule 1990; Caul and Brindle 2001), increased breakpoints (Poncelet et al. 1983), or produced biphasic effects (Mayorga et al. 2000; Mobini et al. 2000). Given that procedures used in these studies (e.g. increment of ratio, duration of session, training protocol) varied widely, determination of factors that may have contributed to the observed differences is impossible at this time. It is also possible that rats that received the higher doses of amphetamine and that achieved higher breakpoints may have been in stereotypy with the lever, although systematic observations of this behavior were not made.

The patterns of response rate and reinforcer effects produced by the two antipsychotics haloperidol and clozapine were similar in that both drugs dose-dependently decreased response and reinforcer rates with clozapine having the steeper dose-effect function. These results are not surprising, given that higher doses of typical and atypical antipsychotics have been shown to decrease operant response rates under a variety of schedule parameters, including ratio (Sanger and Perrault 1995), interval (Villanueva and Porter 1993), and multiple schedules (Varvel et al. 2002).

Despite their similar effects on response rates, however, the effects of haloperidol and clozapine on breakpoints were notably different. Whereas haloperidol dose-dependently decreased breakpoints at doses at which all or most rats were still responding, clozapine did not affect breakpoints at lower non-sedating doses. A 10 mg/kg dose of clozapine suppressed responding entirely in all but two PCP-treated rats; hence, its effects on breakpoints could not be adequately assessed. Reduced breakpoints under progressive ratio schedules have been consistently

reported with haloperidol (Aberman et al. 1998; Mobini et al. 2000; Caul and Brindle 2001) and with other typical antipsychotics such as chlorpromazine and raclopride (Ferguson and Paule 1996; Aberman et al. 1998; Mobini et al. 2000). The well-documented motor effects of typical antipsychotics (e.g. Tandon and Jibson 2002) most likely contribute to these reductions, as well as to the observed reductions in response rates. Given that haloperidol-induced breakpoint decreases were observed in the present study in all rats that responded and at a dose (0.1 mg/kg) that did not significantly affect response rates, however, it is likely that a decrease in incentive motivation also played a role in this effect. In contrast, clozapine did not decrease breakpoints at non-sedating doses in the present study. In fact, clozapine has been reported to increase breakpoints in other food reinforced progressive ratio procedures with rats (Mobini et al. 2000) and monkeys (Cilia et al. 2001), suggesting that it may increase motivation for food reinforcement. Similar to the clozapine results of the present study, however, a second atypical antipsychotic olanzapine failed to alter breakpoints in the monkey study.

In summary, the results of the present study showed that a modest regimen of perinatal treatment with PCP in male rats did not alter later acquisition or baseline responding in a progressive ratio procedure. To the extent that this model measures motivation, these results suggest that perinatal PCP treatment does not induce the negative symptoms of avolition, although earlier studies have demonstrated that this treatment regimen produces deficits in animal models of gating and cognition. Differences between rats treated perinatally with PCP or saline were not observed following challenges with NMDA antagonists, amphetamine, and a typical and an atypical antipsychotic. These drugs did, however, produce effects consistent with those previously produced in progressive ratio studies with food reinforcement. Notably, whereas NMDA antagonists and amphetamine generally failed to affect breakpoints, haloperidol (but not clozapine) dose-dependently decreased breakpoints. These results suggest that haloperidol may produce effects on motivational variables above and beyond its effects on response rates. Finally, this study represents one of the few in which an attempt has been made to model negative symptoms within a neurodevelopmental model of schizophrenia, an area in which further research is needed.

Acknowledgements

The authors thank Kari LaVecchia for technical assistance in completion of this project. This work was supported by National Institute of Health grants MH-64771 and DA-01442.

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Fig. 1. Effects of dizocilpine (*upper panels*) and PCP (*lower panels*) on breakpoint (*left panels*) and average IRT (*right panels*) in rats treated perinatally with saline (*white squares*) or PCP (*black squares*). In order for data to be included for these measures, rats must have pressed the lever at least 5 times during the session. Each value represents mean ($\pm$ SEM). Number of rats included in mean calculation at each dose is indicated below the points (e.g. 8/9 indicates that data for eight saline-treated and nine PCP-treated rats are included). Unless otherwise indicated, numbers of rats tested at vehicle dose were also tested at other doses. Hash indicates a significant main effect of dose

Fig. 2. Effects of amphetamine (*upper panels*), haloperidol (*middle panels*), and clozapine (*lower panels*) on breakpoint (*left panels*) and average IRT (*right panels*) in rats treated perinatally with saline (*white squares*) or PCP (*black squares*). In order for data to be included for these measures, rats must have pressed the lever at least 5 times during the session. Each value represents mean ($\pm$ SEM). Number of rats included in mean calculation at each dose is indicated below the points (e.g. 8/9 indicates that data for eight saline-treated and nine PCP-treated rats are included). Unless otherwise indicated, numbers of rats tested at vehicle dose were also tested at other doses. Hash indicates a significant main effect of dose. Asterisk indicates a

significant interaction effect in which mean values differ between saline-treated and PCP-treated rats

Fig. 3. Effects of manipulation of the step increase of the progressive ratio on number of pellets (*upper left panel*), response rate (*upper right panel*), breakpoint (*lower left panel*), and average IRT (*lower right panel*) in rats treated perinatally with saline (*white columns*) or PCP (*black columns*). For all step values, the initial ratio was 5. Increases were as indicated (Exp=2×2, 3×3, 4×4, 5×5, etc.). Each value represents the mean ($\pm$ SEM) of five to seven rats for all measures. Hash indicates a significant main effect of step increase

Table 1
Effects of PCP and dizocilpine on number of pellets earned and response rates (responses/s) in rats treated perinatally with saline or PCP

Drug	Dose (mg/kg)	Perinatal drug treatment			
		Number of pellets		Response rate	
		Saline ^a	PCP ^a	Saline ^a	PCP ^a
PCP	0	9.8 (1.98)	13.6 (1.03)	0.58 (0.17)	0.85 (0.13)
	0.1	9.5 (0.75)	10.6 (1.55)	0.51 (0.09)	0.68 (0.12)
	0.3	10.7 (1.99)	12.7 (1.77)	0.63 (0.18)	0.88 (0.16)
	1	9.3 (1.84)	9.6 (1.92)	0.53 (0.16)	0.56 (0.13)
	3	2.3 (1.26) [#]	4.6 (2.19)	0.12 (0.07) [#]	0.28 (0.15)
Dizocilpine	0	8.9 (1.31)	0.55 (0.10)	12.1 (1.95)	0.77 (0.17)
	0.01	12.4 (1.99)	0.77 (0.17)	11.5 (2.49)	0.77 (0.19)
	0.03	12.6 (2.07)	0.69 (0.18)	9.9 (2.17)	0.68 (0.18)
	0.1	12.3 (2.09)	0.73 (0.18)	12.3 (2.25)	0.75 (0.16)
	0.3	3.3 (1.80) [#]	0.23 (0.12)	7.4 (2.35) [#]	0.50 (0.18)

[#] Indicates a significant main effect of dose
^a Each value represents the mean (±SEM) of 8-10 rats

Table 2
Effects of amphetamine on number of pellets earned and response rates (responses/s) in rats treated perinatally with saline or PCP

Drug	Dose (mg/kg)	Perinatal drug treatment			
		Number of pellets		Response rate	
		Saline ^a	PCP ^a	Saline ^a	PCP ^a
Amphetamine	0	10.7 (2.25)	12.3 (1.47)	0.68 (0.21)	0.90 (0.16)
	0.03	10.8 (2.13)	14.8 (1.97)	0.75 (0.20)	0.94 (0.16)
	0.1	11.0 (2.27)	9.2 (1.95)	0.74 (0.19)	0.59 (0.13)
	0.3	12.4 (2.44)	10.2 (1.97)	0.90 (0.20)	0.72 (0.15)
	1	8.6 (2.33)	5.4 (2.29)	0.54 (0.19)	0.33 (0.15)
	3	2.5 (1.24) [#]	3.4 (1.80)	0.13 (0.07) [#]	0.29 (0.14)
	5.6	1.9 (1.43) [#]	2.0 (2.00)	0.14 (0.11) [#]	0.16 (0.16)

[#] Indicates a significant main effect of dose
^a Each value represents the mean (±SEM) of 9-10 rats

Table 3
Effects of haloperidol and clozapine on number of pellets earned and response rates (responses/s) in rats treated perinatally with saline or PCP

Drug	Dose (mg/kg)	Perinatal drug treatment			
		Number of pellets		Response rate	
		Saline ^a	PCP ^a	Saline ^a	PCP ^a
Haloperidol	0	10.1 (2.47)	13.0 (2.30)	0.58 (0.14)	0.77 (0.14)
	0.01	9.1 (1.10)	10.4 (2.93)	0.55 (0.10)	0.70 (0.21)
	0.03	9.1 (1.94)	11.2 (1.85)	0.44 (0.12)	0.58 (0.13)
	0.1	5.3 (1.25) [#]	7.0 (1.05)	0.41 (0.13)	0.45 (0.10)
	0.3	1.3 (0.57) [#]	4.2 (0.86)	0.09 (0.04) [#]	0.21 (0.04)
Clozapine	0	10.3 (2.22)	15.6 (3.26)	0.64 (0.19)	1.06 (0.28)
	1	9.5 (1.38)	15.8 (3.75)	0.56 (0.07)	1.00 (0.28)
	3	8.2 (2.48)	12.6 (4.35)	0.49 (0.19)	0.80 (0.30)
	10	0 (0) [#]	0.4 (0.24)	0.00 (0) [#]	0.02 (0.01)

[#] Indicates a significant main effect of dose
^a Each value represents the mean (±SEM) of 5-6 rats