*Pharmacology Biochemistry & Behavior*, Vol. 39, pp. 947–953. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

# Pharmacokinetic and Pharmacodynamic Properties of Some Phencyclidine Analogs in Rats[1,2]

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Received 6 December 1990

CHO, A. K., M. HIRAMATSU, D. A. SCHMITZ, T. NABESHIMA AND T. KAMEYAMA. *Pharmacokinetic and pharmacodynamic properties of some phencyclidine analogs in rats.* PHARMACOL BIOCHEM BEHAV **39**(4) 947–953, 1991.—The pharmacodynamics and pharmacokinetics of three phencyclidine analogs, differing from phencyclidine (PCP) only in the nature of the amine structure, were determined after intravenous doses of equimolar amounts to rats. The purpose of the study was to assess the role of pharmacokinetics in the in vivo potency of the compounds. The compounds examined were phenylcyclohexyl-pyrrolidine (PCPY), diethylamine (PCDE), ethylamine (PCE), and phencyclohexylamine (PCA). The behavior responses monitored included ataxia and others previously shown to be characteristic of PCP. In contrast to their relative affinities for the MK 801 binding site, the behavioral potencies of PCE, PCDE and PCPY were comparable to PCP. The major discrepancy occurred with PCDE, whose affinity for the NMDA receptor was ½₀th of PCP. The pharmacokinetic studies showed that the discrepancy between in vivo and in vitro activity of PCDE could be partially accounted for by its conversion to PCE, a relatively potent PCP-like agent.

Phencyclidine Behavior Pharmacokinetics Phencyclidine analogs Phencyclidine metabolism NMDA receptor

PHENCYCLIDINE (PCP) was originally developed for its potential as an intravenous anesthetic agent (9), but its hallucinogenic properties eliminated that application and instead, resulted in its extensive abuse. This compound and its derivatives have a complex behavioral pharmacology (15), thought to be meditated, in part, through interaction with the NMDA receptor (8). Interest in PCP has extended to its analogs in part to define its pharmacology (10–12, 16) and in part because of the appearance of analogs in street samples of illicit preparations. Two analogs, differing in the amine moiety, phenylcyclohexylpyrrolidine (PCPY) (3) and N-ethyl-phenylcyclohexylamine (PCE) (13), have been reported in the latter context. At the experimental level, the relative potencies of some of these analogs have been compared in whole animal protocols [e.g., Shannon (12), Vaupel et al. (16), Risner (11), Nabeshima et al. (10)]. They have also been compared in vitro for their affinities to various binding sites attributed to their actions (11,14).

One of the major problems in interpreting in vivo data in terms of receptor interactions is the interposition of pharmacokinetic processes that control drug availability in intact systems. This report describes results of a study of the comparative pharmacokinetics and behavioral responses of three phencyclidine derivatives differing only in the structure of the amine (Fig. 1) in rats. Plasma levels of the parent compound and a common active metabolite, phenylcyclohexylamine (PCA), were determined and the relationship between the bioavailabilities of these compounds and their relative pharmacological potencies was assessed.

## METHOD

### *Chemicals*

Phenylcyclohexyldiethylamine hydrochloride and phenylcyclohexylethylamine hydrochloride were obtained from the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD). Phenylcyclohexylpyrrolidine (PCPY) was synthesized in our laboratory by procedures published elsewhere (2). 1-(2H5-Phenyl)cyclohexylamine hydrochloride was synthesized from 2H5 bromobenzene according to the procedure of Geneste et al. (6) and 1-phenyl-1-(2-2H-piperidino) cyclohexane was prepared from 2-2H-piperidine according to the procedure of Maddox et al. (9). The purity of each compound was established by elemental analysis, gas chromatography, and mass spectrometry. All other chemicals used were reagent grade and obtained from commercial sources.

### *Animals*

Male Sprague-Dawley derived rats (Charles River Breeding Laboratories, Wilmington, MA) weighing 230 to 360 g were

[1]This research was supported by USPHS research grant DA 02411.
[2]Portions of this research have been presented at the Satellite Symposium of the 17th Congress of Collegium Internationale Neuro-Psychopharmacologicum: NMDA Related Agents: Biochemistry, Pharmacology and Behavior, Sept. 15–17, 1990, Nagoya, Japan.

ABBREVIATIONS

| | |
|---|---|
| PCP | Phencyclidine |
| PCPY | Phenylcyclohexylpyrrolidine |
| PCDE | Phenylcyclohexyldiethylamine |
| PCE | Phenylcyclohexylethylamine |
| PCA | Phenylcyclohexylamine |
| AUC | Area under the curve |
| GC/MS | Gas chromatography/Mass spectrometry |
| NMDA | N-Methyl-D-aspartate |

used. Vascular-Access-Ports (model SLA; Norfolk Medical Products, Skokie, IL) were implanted 24 hours before the experiment by procedure described elsewhere (4). In brief, the rats were anesthetized with ether and incisions were made to allow attachment of the port to the back of the neck. The attached catheter was passed subcutaneously to the ventral side of the neck where it was inserted into the right external jugular vein and advanced into the atrium. The neck wound was then sutured and the animals allowed to recover for at least 24 hours. On the morning of the experiment, the ports were flushed with heparinized saline and the drug injected into the port. The port was immediately flushed with heparinized saline. Blood samples (0.5 ml) were taken from the port at 5, 10, 20, 30, 60, 120, 180, 300 and 420 minutes, by first drawing 0.6 ml of blood, collecting the actual sample (0.5 ml) then reinjecting the first collection. The port was again washed with 0.5 ml heparinized saline. The blood samples were centrifuged at 15,000 rpm for 3 min and then the plasma was collected and stored at −80°C until assayed.

*Analysis of Plasma*

Internal standard (deuterium labelled amines) and 100 microliters of 60% perchloric acid were added to 200 μl of plasma and the mixture centrifuged for 3 minutes. The supernatant was transferred to a 20 ml round bottom tube containing 1 ml of 1.5 M sodium carbonate (pH 9.5) and 5 ml of methylenedichloride. The mixture was shaken for 10 minutes and then centrifuged for 10 minutes at 2000 rpm. The organic layer was transferred to a 12 ml conical tube and the solvent evaporated under a stream of nitrogen to a volume of about 150 microliters. The sample was then transferred to a microvial for GC/MS analysis.

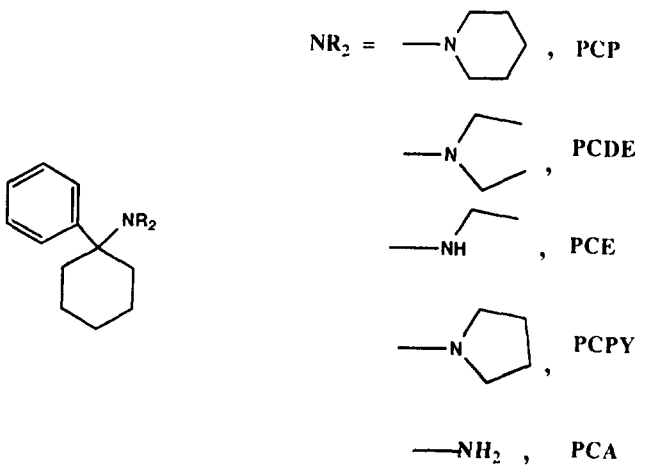


FIG. 1. Phencyclidine and its analogs.

TABLE 1

| Amine | M/Z Value Used for SIM | Retention Time (min) |
|---|---|---|
| | GC Condition 1 | |
| PCA | 132.1 | 3.28 |
| PCA-d5 | 137.0 | 3.27 |
| PCDE-d2 | 190.0 | 4.04 |
| PCDE | 188.1 | 4.04 |
| PCE | 160.05 | 3.57 |
| | GC Condition 2 | |
| PCA | 132.1 | 3.29 |
| PCA-d5 | 137.0 | 3.27 |
| PCPY | 186.1 | 4.69 |
| PCP | 200.5 | 5.16 |
| PCP-d2 | 202.1 | 5.15 |

The retention times and the mass used in the selected ion monitoring GCMS analysis of the PCP analogs were examined. The GC conditions are described in the Method section.

A Hewlett Packard 5971A GC/MS system was used in the selected ion mode with deuterium labelled compounds as internal standards. A methyl silicone (0.33 micron film thickness) capillary column, 12.5 m in length and 0.2 mm i.d., was used. The oven was heated in a temperature ramp of 80 to 210°C with a rate of 35°C/min or 90 to 210 with a 30°C/min rate. The injection port temperature was set at 190°C, the transfer line temperature at 280°C and the mass analyzer at 180°C. The ionizing voltage of the mass selective detector (MSD) was 70 ev. The m/z values and the retention times of the compounds are shown in Table 1. Recoveries of the amines through the extraction procedure, determined from spiked samples, ranged from 85% (PCHM) to quantitative for PCP and varied by less than 10%.

*Pharmacokinetic Analysis*

The values for the areas under the plasma-time curves were calculated by the trapezoidal method. Since the times of plasma analysis were not coincident with the times for behavioral evaluation, the plasma concentrations were interpolated from the curves after fitting to a three exponent equation by nonlinear regression using the BMDP Statistical Program (5).

*Behavioral Assays*

In parallel behavioral experiments, rats were placed individually into 30 × 36 × 17 cm high plastic rat cages and allowed to acclimate at least 30 minutes before testing began. After drug administration, rating for stereotyped behaviors and ataxia were taken for ten periods of 3 min each as follows: 10–13, 20–23, 30–33, 60–63, 90–93, 120–123, 150–153, 180–183, 210–213, and 240–243 min.

To evaluate stereotyped behaviors and ataxia, the behavioral scoring system developed by Nabeshima et al. (10) for stereotypy and Sturgeon et al. (5) for ataxia were employed with minor modification. Briefly, the stereotyped rating scale is as

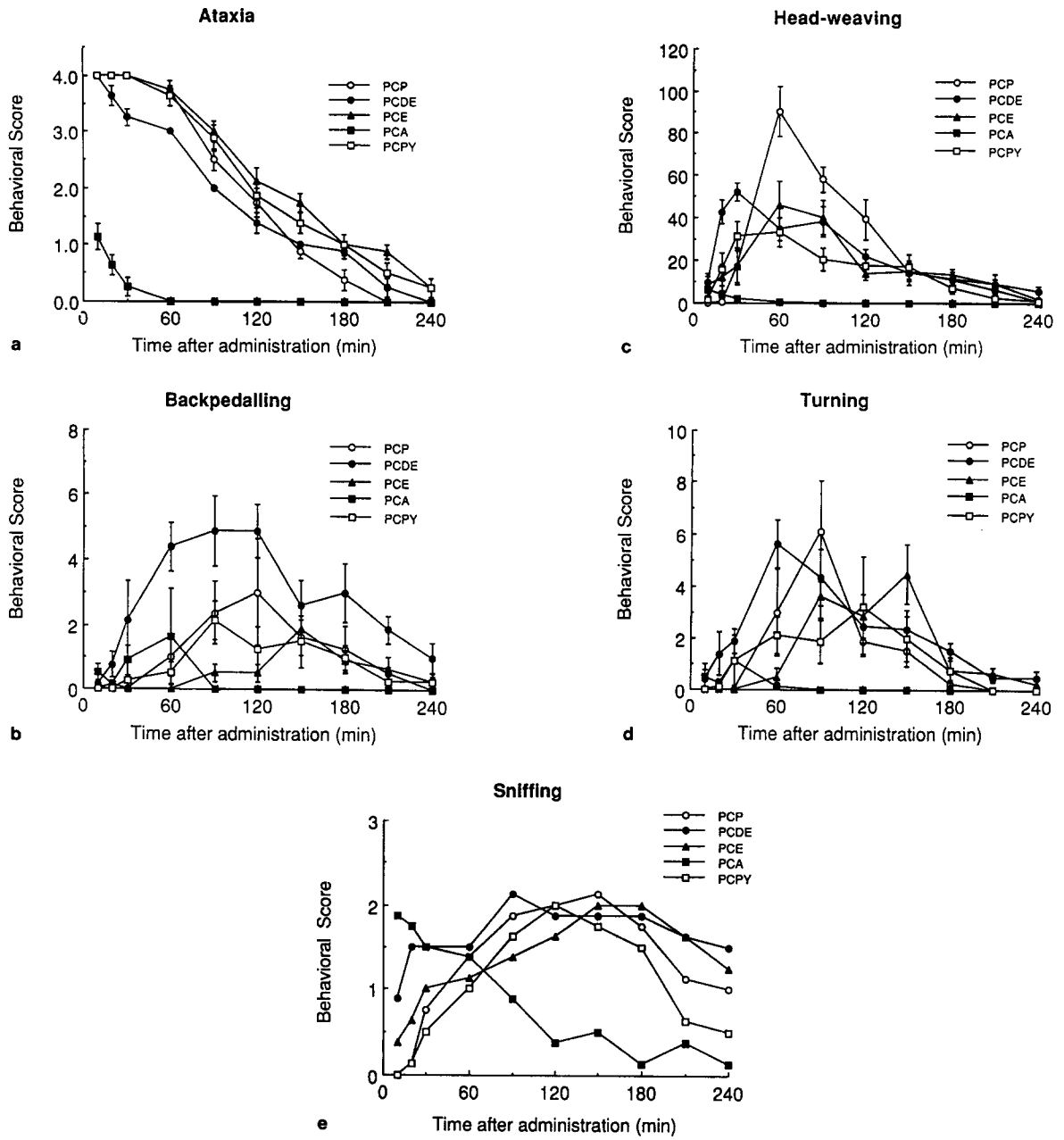


FIG. 2. Behavioral responses to phencyclidine and its analogs. Animals were given intravenous doses of 35.7 micromoles/kg and the behavior monitored at the times indicated using the scale described in the Method section. (The values represent the means ± S.E. for 8 animals.)

follows: sniffing (0: absent; 1: occasional; 2: frequent; 3: constant); head-weaving (the number of times an animal made side-to-side or lateral head-movements); turning (the number of times the animal circled laterally to left or right over 360° within a relatively small area); backpedalling (the number of times the animal made backward locomotion). The ataxia rating scale is (0) inactive or coordinated movements; (1) awkward or jerky movements or loss of balance while rearing; (2) frequent falling or partial impairment of antigravity reflexes; (3) the inability to move beyond a small area and to support body weight; (4) inability to move except for twitching movements.

The experiments were conducted between 10 a.m. and 6 p.m. in a quiet laboratory. All results are expressed as the means ± S.E.M.

## RESULTS

### *Pharmacological Response*

The structures of the compounds studied and their abbreviations are shown in Fig. 1. The drugs were administered intrave-

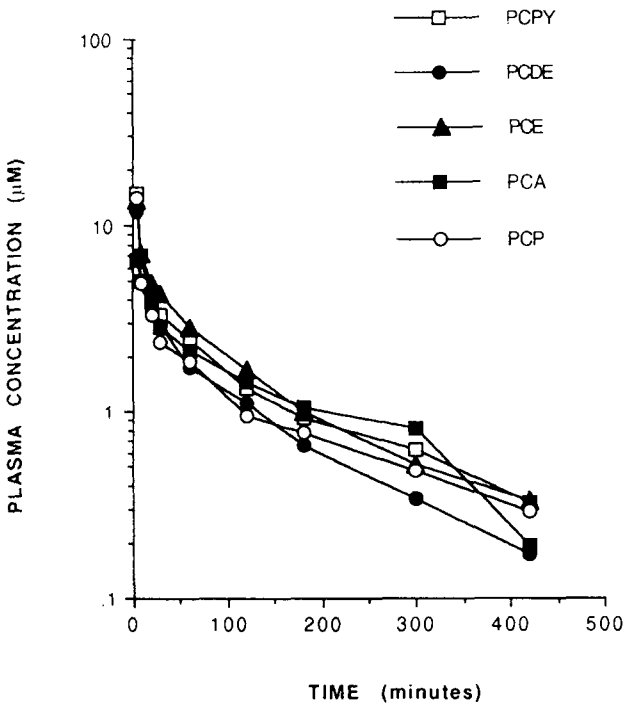


FIG. 3. Plasma concentrations of phencyclidine analogs. Animals were given intravenous doses of 35.7 micromoles/kg and the blood collected at the indicated times through vascular access ports. The plasma was collected and analyzed by GC/MS procedures described in the Method section. PCA formed after administration of the tertiary and secondary amines was also measured but is not shown. (The values expressed as the means ± S.E. for at least 5 animals.)

nously at equimolar (36 micromole/kg) doses, equivalent to 10 mg/kg of phencyclidine, a dose sufficient to induce a major behavioral response (4). The behavioral responses to the compounds were monitored (Fig. 2) over a four-hour time period thereby providing time response curves (Fig. 2). The total response for each compound, assessed as the area under the time response curves (AUC) is summarized in Table 2. PCE was slightly more potent than the tertiary amines, with respect to ataxia but all, except PCA, induced maximal to supramaximal ataxia responses. This response is thought to be mediated by NMDA receptor blockade (7). PCA, on the other hand, was very weak in its ability to induce ataxia. PCDE had greater potency in eliciting the backpedalling and turning response when compared to the other derivatives.

*Plasma Concentrations*

The plasma concentration of each compound was monitored for 7 hours after intravenous dosage and the time courses are shown in Fig. 3. Although not obvious, the 5-minute concentrations for the 3 testing amines varied from 11.8 (PCDE) to 14.7 (PCP). The concentration of PCA, a common, active metabolite was also monitored and found to be quite low compared to the administered amine. The plasma decay curves were very similar indicating that the distributional properties of the compounds were also similar. As PCDE is metabolized to PCE (14), the concentrations of PCE and PCA were measured together with PCDE (Fig. 4). PCE levels after PCDE were quite high and exceeded those of PCDE after 2 hours. A previous study demonstrated that a linear relationship existed between plasma PCP concentration and ataxia (4). A similar analysis was made of the data obtained in this study and the results are shown in Fig. 5.

TABLE 2

SUMMARIES OF PHARMACOLOGICAL RESPONSES

| Drug | | Ratio to PCP |
|---|---|---|
| | Ataxia (AUC) | |
| PCP | 437.5 ± 17.7 | 1.00 |
| PCDE | 396.3 ± 10.5 | 0.91 |
| PCE | 538.8 ± 22.5 | 1.23 |
| PCA | 22.5 ± 5.9 | 0.05 |
| PCPY | 501.25 ± 30.1 | 1.14 |
| | Backpedalling (AUC) | |
| PCP | 293.8 ± 126.6 | 1.00 |
| PCDE | 715.0 ± 121.5 | 2.43 |
| PCE | 135.0 ± 30.5 | 0.46 |
| PCA | 72.5 ± 42.3 | 0.25 |
| PCPY | 207.50 ± 70.70 | 0.71 |
| | Sniffling (AUC) | |
| PCP | 338.8 ± 16.1 | 1.00 |
| PCDE | 402.5 ± 29.3 | 1.19 |
| PCE | 341.3 ± 20.2 | 1.01 |
| PCA | 176.9 ± 17.9 | 0.52 |
| PCPY | 273.75 ± 10.76 | 0.81 |
| | Head weaving (AUC) | |
| PCP | 6968.8 ± 400.9 | 1.00 |
| PCDE | 5523.1 ± 512.0 | 0.79 |
| PCE | 4683.8 ± 692.0 | 0.67 |
| PCA | 157.5 ± 30.8 | 0.02 |
| PCPY | 3760.0 ± 613.39 | 0.54 |
| | Turning (AUC) | |
| PCP | 382.5 ± 74.7 | 1.00 |
| PCDE | 568.8 ± 103.7 | 1.49 |
| PCE | 390.0 ± 88.9 | 1.02 |
| PCA | 33.8 ± 23.3 | 0.09 |
| PCPY | 323.75 ± 120.90 | 0.85 |

TABLE 3

IN VITRO PHARMACOLOGY

| | Relative Affinities | |
|---|---|---|
| Drug | Rat* NMDA | Rat† σReceptor |
| PCP | 1.00 | 1.00 |
| PCDE | 0.058 | 0.194 |
| PCPY | 0.379 | 0.828 |
| PCE | 0.598 | 0.313 |
| PCA | 0.110 | 0.061 |

The relative affinities of the compounds to the receptors indicated were measured by competitive binding assays.

*Relative affinities for MK 801 binding site (14).

†Relative affinities for di-o-tolyl guanidine binding (14).

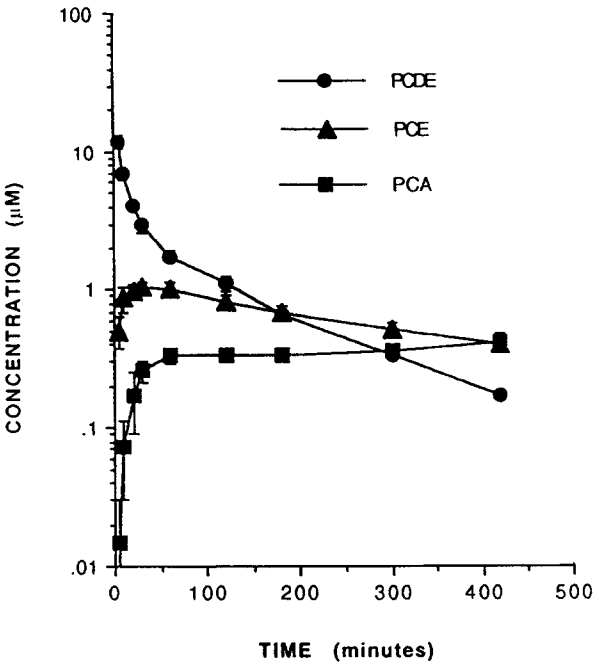


FIG. 4. Plasma concentrations of PCDE and its metabolites. Animals were given intravenous doses of 35.7 micromoles/kg of PCDE and blood collected at the indicated times through a vascular access port as described in the Method section. The concentrations of the three compounds was measured by GC/MS. The values are the means of 6 samples ± S.E.

TABLE 4

BIOAVAILABILITY

| Drug | Bioavailability | Pharmacol. Availability | Total Availability | Ratio |
|---|---|---|---|---|
| PCP | 438.82 ± 65.89 | 438.82 | 450.34 | 1.00 |
| PCDE | 437.11 ± 56.02 | 25.35 | 211.18 | 0.47 |
| PCPY | 567.06 ± 59.23 | 214.91 | 222.02 | 0.49 |
| PCE | 625.68 ± 109.03 | 374.14 | 400.32 | 0.88 |
| PCA | 534.45 ± 25.54 | 58.79 | 58.43 | 0.13 |
| PCE/PCDE | 285.03 ± 22.40 | 170.43 | | |
| PCA/PCP | 104.71 ± 20.54 | 11.52 | | |
| PCA/PCDE | 140.42 ± | 5.99 | 15.4 | |
| PCA/PCE | 238.04 ± 18.29 | 26.18 | | |
| PCA/PCPY | 64.72 ± 11.38 | 7.11 | | |

The bioavailability of each compound was determined from the areas under the plasma concentration time data for each compound. The values are given ± S.E. for a minimum of 5 animals. These areas were multiplied by the relative affinities of the compound for the NMDA receptor to obtain the pharmacological availability shown in column three. Total availability is the sum of pharmacological availabilities; that due to the parent compound and the measured, active metabolites.

The relative potencies based on visual estimations of plasma concentrations at an ataxia response of 2 showed the order, PCP>PCPY>PCE>PCDE. PCA was extremely weak and did not elicit a maximal response at this dosage. This analysis could not be made for the other responses because of the dominance of ataxia. When the animals are ataxic, the other responses are suppressed. When the PCE plasma concentration vs. ataxia curves after administration of PCE and after PCDE were compared, there was a change in slope ($p<0.01$, test for parallelism) (Fig. 6). The potency of PCE appears to increase in the presence of PCDE, suggesting that it potentiates the actions of PCE.

*Relative Bioavailability*

Since the compounds were administered in equimolar doses, a comparison of the areas under the plasma time curves should provide a relative bioavailability, or the proportion of the administered dose available for action (Table 4). Although the bioavailabilities do not differ significantly (NS at $p<0.05$, $F=2.27$), there is a trend for great availability of PCE and PCPY. Thus it is possible that the greater ataxia responses for PCPY and PCE relative to PCP may reflect, in part, their greater bioavailability.

*Relationship of Behavior to NMDA Receptor Blockade*

The actions of PCP and its congeners have been proposed to involve their interaction with the NMDA specific glutamate receptor (1). Behavioral studies with a structurally distinct NMDA ligand, MK 801, have revealed that ataxia and headweaving, but not backpedalling, are among the dominant responses (7). If the behavioral actions of these PCP congeners also reflect actions on this receptor system, the responses should parallel plasma concentration, since they are assumed to be a linear function of the concentration of the drug at the receptor. A correction of the plasma concentration reflecting differences in receptor affinities, is also necessary. Relative affinities summarized in Table 3 for

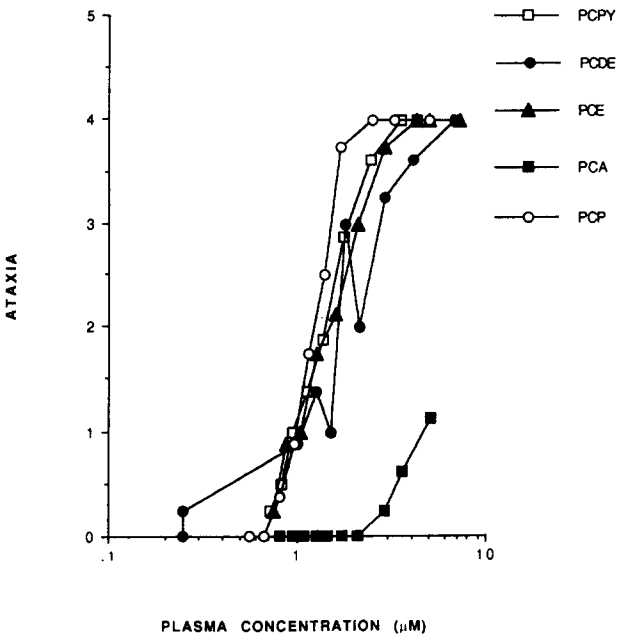


FIG. 5. Ataxia vs. plasma concentration. Plasma concentrations at the times of ataxia measurement are plotted against the ataxia score and reflect the changes in response due to falling concentrations. The concentrations at the times not determined were interpolated from a curve generated by nonlinear regression analysis of the plasma concentration vs. time data.

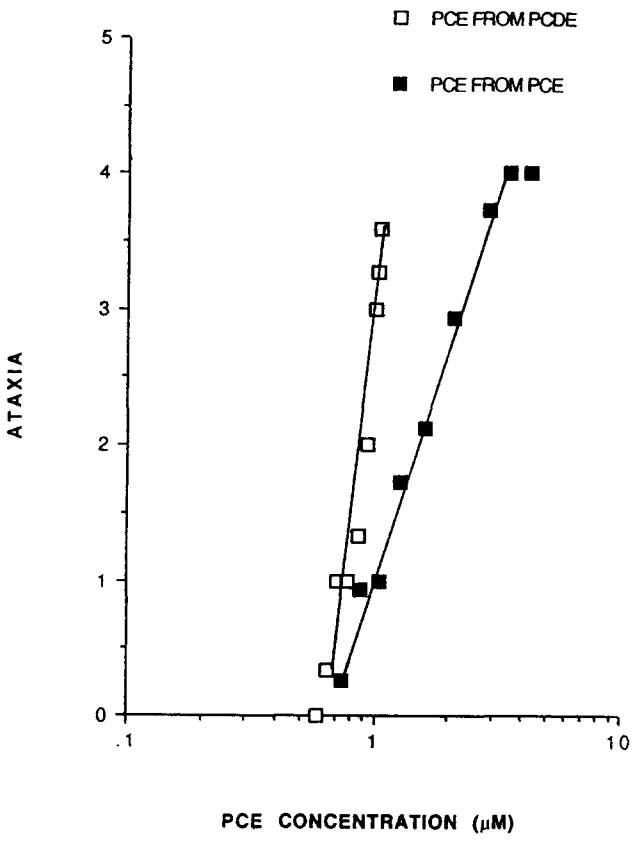


FIG. 6. Ataxia vs. plasma concentration of PCE. Ataxia scores are plotted against the plasma concentrations of PCE after direct injection of PCE and after injection of PCDE.

the NMDA receptor were determined in a separate study (14) and were used to make the corrections in Table 4. The results show that response to PCDE is anomalous compared to its receptor affinity. Thus, unlike PCA which also has a low receptor affinity, PCDE elicits a strong ataxia response. Part of the response must be due to the metabolically formed PCE.

## DISCUSSION

The primary site of phencyclidine action has been proposed to be the NMDA specific glutamate receptor. The compound is thought to bind to a site in the interior of this complex ion channel and noncompetitively block stimulation by glutamate agonists (17). Ataxia is the dominant response observed in rats after phencyclidine (4) and the NMDA receptor ligand, MK 801 (7). This response is dose dependent for PCP (4), and for MK 801, but the latter is twenty times more potent (7). Studies with PCP showed a linear correlation between the log of plasma concentration and ataxia response (4), so that plasma concentration is a good predictor of drug available to the receptor. The analogs studied here show the same linear relationship between plasma concentration and ataxia response when examined between the threshold of ataxia and its maxima. The intercepts of these lines with 2, the half maximal ataxia response, should reflect the potencies of the agents. Except for PCA, all of these compounds are capable of inducing a maximal response which occurs at higher concentrations as the potency decreases. Although the weak response from PCA is predicted from its low receptor affinity, the response from PCDE is far greater than would be expected since it has a lower receptor affinity than PCA.

A partial explanation is based on the metabolism of PCDE to PCE. As shown in Fig. 4, substantial amounts of PCE are generated after PCDE. The bioavailability of PCE after PCDE is about 45% relative to an IV injection of PCE, so that a large part of the administered PCDE dose is converted to this active metabolite. In an attempt to quantitate the availability of drug and the response obtained, the bioavailability of the compounds were multiplied by their relative affinities for the NMDA receptor. The results are shown in Table 4 as a set of "pharmacological availabilities." To obtain the total pharmacological equivalents from the measured compounds, the sum of the pharmacological availabilities for the parent compound, PCA and, in the case of PCDE, PCE were added. The relative values obtained from this calculation (Table 4) would predict that PCP and PCE would be similar and the others much weaker in eliciting NMDA receptor-mediated effects. These predicted values differ from the observed order shown in Table 2. Thus this analysis predicts the activity of the compounds but with some errors reflecting other pharmacokinetic or pharmacodynamic issues not included in this simplistic model. Inherent in the model is the assumption that all of the compounds block the channel with an efficacy that parallels their affinity. This may not be a valid assumption and may also account for the discrepancy between predicted and observed responses. On the basis of receptor affinity, a low activity for PCDE would be predicted but formation of the active metabolite, PCE, results in a major response. However, as the slope of the plasma concentrations vs. response curve to PCE changes when PCDE is administered, an interaction between PCDE and its active metabolite appears to be occurring. The NMDA receptor system is extremely complex and has numerous modulating binding sites (17). Given this complexity and the noncompetitive nature of the interaction between PCP type compounds and glutamate, the mechanistic possibilities for potentiation are numerous and need to be assessed in another, more simple system.

PCDE also differs from the other compounds in its ability to induce backpedalling and to a lesser extent, turning (see Fig. 2). These responses have been attributed to interaction of PCP with the 5-HT system (7,10). Thus PCDE appears to be less specific with a greater involvement with the 5HT system.

The quantitative interpretation of the in vivo actions of drugs such as PCP in terms of interactions with specific receptors requires knowledge of the amount of drug available at the site of action. This study is an attempt to relate drug levels to action based on affinities for a specific receptor and bioavailabilities. This simple pharmacokinetic approach has partially accounted for the discrepancies between observed in vivo potencies and those predicted from receptor affinities. The results also suggest that parent drug may affect the pharmacodynamics of active metabolites. Studies of this type and the experiments they suggest are necessary to understand the relationship between in vitro and in vivo pharmacology.

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