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Short communication

DISCRIMINATIVE STIMULUS EFFECTS OF MONOHYDROXYLATED PHENCYCLIDINE METABOLITES IN RHESUS MONKEYS

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Rhesus monkeys were trained to discriminate saline from an injection of ketamine. In tests of stimulus generalization, phencyclidine (PCP) produced dose-related ketamine-appropriate responding in each monkey. Two monohydroxylated PCP metabolites also produced ketamine-like discriminative effects, although only at considerably higher doses than did PCP. A third monohydroxylated PCP metabolite produced only sham-appropriate responding. The results suggest that these PCP metabolites contribute little to the behavioral actions of PCP in the monkey.

Phencyclidine Ketamine Phencyclidine metabolites Rhesus monkeys Discriminative stimulus effects

1. Introduction

Phencyclidine (PCP) was developed as an anesthetic agent but was withdrawn from clinical use because of disturbing side-effects, such as drunkenness, mental impairment, and psychotomimetic phenomena (Domino, 1964). More recently, a long-lasting toxic psychosis has been observed following single high doses of PCP (e.g., Luisada, 1978). PCP has been detected both in the brain and in urinary excretion for at least several days following its administration (e.g., Misra et al., 1979). It is of interest, therefore, to evaluate the effects of these proposed metabolites to determine whether they contribute to the overall spectrum of effects produced by PCP.

Various monohydroxylated PCP metabolites, including 4-phenyl-4-piperidinocyclohexanol (PPC) and 1-(1-phenylcylohexyl)-4-hydroxy-piperidine (PCHP) have been identified in a number of species (for review, see Jasinski et al., 1981). The present experiment evaluated the capacity of PPC and PCHP to produce discriminative stimulus effects similar to ketamine, a compound closely related to PCP in structure and pharmacologic activity, in rhesus monkeys. A third monohydroxylated PCP metabolite, 1-[1-(4-hydroxyphenyl)-cyclohexanol]-piperidine (HPCP) (Domino, personal communications) was also evaluated. The discriminative stimulus effects of ketamine in rhesus monkeys are shared by PCP but not by a number of drugs from other pharmacological classes (Solomon et al., unpublished observations). Thus, this procedure appears to be an appropriate assay for evaluating PCP-like discriminative stimulus effects. The time course of the discriminative control of behavior exerted by ketamine and by PCP were also studied in the present experiment.

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2. Materials and methods

The subjects were three rhesus monkeys (*Macaca mulatta*) (754, 794 and 808) that had participated in a previous study of the discriminative effects of ketamine (Solomon et al., unpublished observations). The monkeys were maintained at 80% of their free-feeding weights. Each experimental chamber contained two response levers, a food receptacle, and an array of colored 7-W stimulus lights. Continuous ventilation and masking noise were provided by an exhaust fan and a speaker. Banana-flavored food pellets were delivered to the food receptacle by a pellet dispenser mounted outside the chamber. Programming and recording of experimental sessions were accomplished with a computer and cumulative recorders.

The procedure has been described in detail previously (Solomon et al., unpublished observations). Daily training sessions consisted of a series of discrete trials, each preceded by a 10 min blackout period which was initiated by either a sham injection or a s.c. injection of ketamine (1.0 or 1.8 mg/kg). In each trial, 100 consecutive responses on the correct lever (e.g., the right lever after sham and the left lever after ketamine) produced food. Each trial ended after 5 min, whether or not food had been delivered. Training sessions began with 0-4 sham trials and ended after 2 ketamine trials. Ketamine was administered prior to the first ketamine trial; the second ketamine trial was preceded by a sham injection. A discrimination was considered to be established when a monkey emitted at least 90% correct responses in every trial during five consecutive sessions.

In test sessions, each trial was preceded by a s.c. drug injection of the test compound which increased the total dose injected within the session by 1/4 or 1/2 log-unit steps. During each trial of a test session, 100 consecutive responses on either the sham or the ketamine-appropriate lever produced food. Training and test sessions were conducted in alternation six days per week. If the performance criteria were not exhibited in a training session (e.g., at least 90% correct responses in each trial), test sessions were not conducted until performance criteria were achieved in two consecutive training sessions.

At each dose of the test compounds, the data were calculated as the percentage of responses on the ketamine-appropriate lever. In addition, the rates of responding, irrespective of the lever on which the responses occurred, were calculated in responses/s.

The drugs used in this study were ketamine hydrochloride (Warner-Lambert, Ann Arbor, MI), phencyclidine hydrochloride (National Institute on Drug Abuse, Bethesda, MD NIDA), 1-(1-phenylcyclohexyl)-4-hydroxypiperidine hydrochloride, 4-phenyl-4-piperidinocyclohexanol (NIDA), and 1-[1-(4-hydroxylphenyl)-cyclohexyl]-piperidine hydrochloride (Warner-Lambert).

4-Phenyl-4-piperidinocyclohexanol was dissolved in sterile water to which a few drops of lactic acid were added and the pH of the final solution adjusted to above 4 with sodium hydroxide. All other drugs were dissolved in sterile 0.9% sodium chloride solution. Doses are expressed in the forms described above.

3. Results

The time course of the behavioral effects of ketamine (1.8 mg/kg, closed symbols) and PCP (0.18 mg/kg, open symbols) are shown in fig. 1. One min after their injection, both ketamine and PCP produced only saline-appropriate responding. After 5 min, an average of 62 and 72% ketamine-appropriate responding was produced by PCP and ketamine, respectively. Responding almost entirely on the ketamine-appropriate lever occurred at 10 and 25 min following the administration of ketamine. Ketamine-appropriate responding following PCP administration was 90% or greater at all time intervals between 25 and 90 min (upper panel fig. 1). The amount of ketamine-appropriate responding produced by both drugs then decreased in a time-dependent manner until only sham-appropriate responding was observed 85 min after ketamine and 180 min after PCP administration (upper panel, fig. 1). Following ketamine, response rates were lowest at 5 min and had, subsequently, increased by 25 min; no large changes in response rates were observed at later time intervals (lower panel, fig. 1). The lowest response rate following

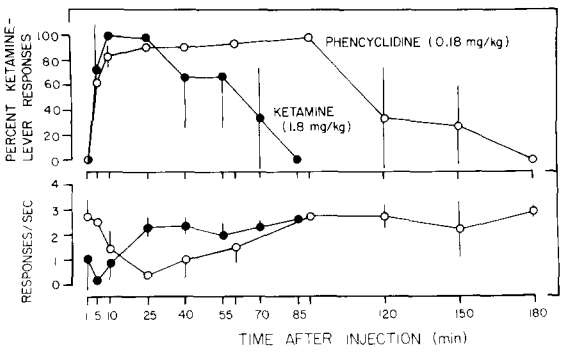

Fig. 1. Time course of the discriminative control of behavior exerted by the smallest doses of ketamine (1.8 mg/kg, closed symbols) and PCP (0.18 mg/kg, open symbols) that produced ketamine-like discriminative stimulus effects in each rhesus monkey (Solomon et al., 1982). *Upper panel ordinates*: responses on ketamine lever, percent of total responses. *Lower panel ordinates*: response rate, responses/s. *Abscissae*: time after injection, min. The data are the mean of single observations in each of three monkeys and were obtained in sessions that consisted of several discrete trials initiated at various times following drug injection; all trials, except the first trial of each experimental session, were preceded by a sham injection. Lines through the points indicate ±1 S.E.M.

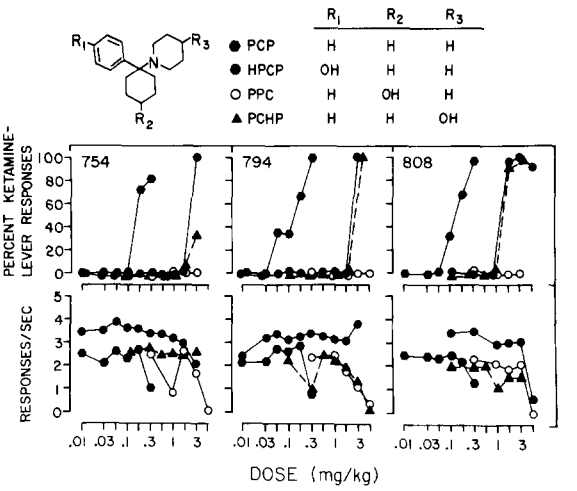

Fig. 2. Discriminative stimulus effects of PCP and three monohydroxylated PCP metabolites (*upper panels*) and the effects of these drugs on response rates (*lower panels*) in three rhesus monkeys. *Ordinates*: as in fig. 1. *Abscissae*: cumulative s.c. dose of drug, mg/kg. For PCP, each point represents the mean of three separate determinations in each animal. All other points represent data from a single determination in each animal.

PCP occurred at 25 min, after which these rates increased through 90 min and were then relatively constant across later time intervals (lower panel, fig. 1). Thus, in comparison to ketamine, the discriminative control of behavior exerted by PCP and its effects on rates of responding were characterized by a somewhat slower onset and a longer duration of action.

The chemical structure of PCP and three monohydroxylated PCP metabolites and the discriminative stimulus effects and rate-decreasing effects they produced are shown in fig. 2. In each monkey, PCP (closed hexagons) produced dose-related ketamine-appropriate responding which reached a maximum at 0.3 mg/kg (upper panels, fig. 2). Rates of responding at the highest dose of PCP were approximately 50% of those rates observed at lower doses (lower panels, fig. 2). In addition, profound ataxia, salivation, and nystagmus were noted in each animal following the sessions in which PCP was administered.

The monohydroxylated metabolite PCHP (closed triangles) also produced dose-related ketamine-appropriate responding in each animal. Responding on the ketamine-appropriate key reached nearly 100% at 3 mg/kg in two monkeys (794 and 808; upper panels, fig. 2). In these animals, the rates of responding at the highest doses of PCHP were somewhat decreased in comparison to the response rates at smaller doses of the compound (lower panels, fig. 2). In the third monkey (754), the highest dose of PCHP evaluated (3 mg/kg) produced nearly 40% ketamine-appropriate responding (upper panels, fig. 2). In this animal, no large differences in the rates of responding were observed at the doses of PCHP evaluated. The effects of higher doses of PCHP could not be observed in this animal because the drug supply was exhausted. In all three animals, a syndrome of PCP-like effects, including ataxia, salivation, and nystagmus, was observed at the conclusion of these experimental sessions.

In each monkey, the monohydroxylated metabolite PPC (open circles) did not produce responses on the ketamine-appropriate lever over doses that ranged from 0.3 to 5.6 mg/kg (upper panels, fig. 2). This compound, however, markedly decreased the rates of responding at the highest doses in each

animal (lower panels, fig. 2). Ataxia, salivation, or nystagmus were not observed in any of the monkeys at the conclusion of these experimental sessions.

Dose-related responding on the ketamine-appropriate lever reached nearly 100% at 3 mg/kg of the monohydroxylated metabolite HPCP (closed circles) in each monkey (upper panels, fig. 2). Over the entire range of doses evaluated, the rates of responding were nearly constant in two of the monkeys (754 and 794, lower panels, fig. 2). Ataxia, salivation, and nystagmus were not observed in any of the animals following these sessions. Higher doses (10.0-17.8 mg/kg) of HPCP, however, elicited these effects when evaluated in subsequent sessions.

4. Discussion

In the present experiment, the smallest doses of ketamine (1.8 mg/kg) and PCP (0.18 mg/kg) that produced ketamine-like discriminative effects (Solomon et al., unpublished observations) were evaluated with respect to the time course of these effects in rhesus monkeys. Ketamine had a slightly more rapid onset and a shorter duration of action than PCP. These results are consistent with the comparative time course of these drugs as discriminative stimuli in rats (e.g., Shannon, 1981) and as anesthetics in man (Domino et al., 1965).

Reports that PCHP and PPC are inactive or that they exert only convulsant activity (McCarthy and Potter, 1963; Domino, 1964) are not supported by the results of the present experiment. Of the three monohydroxylated PCP metabolites, PCHP and HPCP produced ketamine-like discriminative effects in the rhesus monkey and were approximately one-tenth as potent as PCP in this regard. Ketamine-like discriminative effects were not produced by PPC, although the compound was evaluated at doses up to and including those that markedly reduced rates of responding. None of the PCP metabolites produced observable convulsant activity in the present experiment.

In general, the results of the present experiment agree with a report of the PCP-like discriminative effects produced by PCHP and PPC in rats (Shannon, 1981). PCHP produced ketamine-appropriate responding in rhesus monkeys as well as PCP-appropriate responding in rats. It appears, however, that PCHP is slightly less potent relative to PCP in the monkey than in the rat, where only a three-fold potency difference was noted. On the other hand, there was at least a quantitative, and perhaps qualitative, difference between the effects of PPC observed in the present experiment and those reported in the rat. Whereas this compound produced exclusively sham-appropriate responding in the present experiment, almost 65% drug-appropriate responding was observed at the highest dose of PPC tested in the PCP-trained rat (Shannon, 1981). It would be interesting to train a discrimination based on PPC to examine its discriminative effects.

In conclusion, the present results suggest that the behavioral effects of PCP, including the frequently observed long-lasting toxic psychosis (e.g., Luisada, 1978) may not be due to the effects of the three monohydroxylated metabolites evaluated in this study. One of these metabolites (PPC) produced discriminative effects which were distinctly different from those produced by PCP in that response output was reduced by PPC without any significant drug-appropriate responding. Two other monohydroxylated metabolites (HPCP and PCHP) were similar to PCP in that they produced dose-related ketamine-like discriminative stimulus effects, as well as a PCP-like syndrome characterized by ataxia, salivation, and nystagmus. Since these two metabolites were approximately one-tenth as potent as PCP, however, it is unlikely that they would be formed via biotransformation of PCP in amounts large enough to exert PCP-like behavioral effects. The results of the present investigation suggest that PCP is transformed to relatively inactive metabolites. This possibility is supported by the results of a previous report (Kalir et al., 1978) that, following the administration of [^{3}H]PCP, the onset of behavioral effects was consistent with the time course of the distribution of radioactivity to the brain, whereas PCP-like behavioral effects diminished more rapidly than the level of radioactivity in the brain.

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