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Discriminative Stimulus Properties and Brain Distribution of Phencyclidine in Rats Following Administration by Injection and Smoke Inhalation[1]

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WESSINGER, W. D., B. R. MARTIN AND R. L. BALSTER. *Discriminative stimulus properties and brain distribution of phencyclidine in rats following administration by injection and smoke inhalation.* PHARMACOL BIOCHEM BEHAV 23(4) 607–612, 1985.—Four male Sprague-Dawley rats were trained to discriminate IP injections of 3.0 mg/kg phencyclidine (PCP) from saline under a 2-lever fixed-ratio 32 schedule of food presentation. After reliable discriminative control of lever choice was established, other doses of injected PCP were tested resulting in dose-dependent increases in PCP-lever selection and dose-dependent decreases in rates of responding. When doses of PCP were administered by exposure to smoke from cigarettes containing PCP, a dose-dependent increase in PCP-lever responding was also observed. Δ^9-Tetrahydrocannabinol administered via smoke exposure, up to doses which markedly suppressed response rates, did not result in PCP-appropriate responding, demonstrating the specificity of the PCP stimulus by the inhalation route. Brain levels and distribution of ^{3}H-PCP were determined in rats administered doses calculated to result in 50% generalization by the IP injection or smoke inhalation routes. By both routes of administration roughly equivalent brain levels were attained and the distribution was relatively even across the seven brain areas analyzed. These results demonstrate the validity of using the injection route of administration when studying PCP experimentally, in spite of the fact that PCP is abused primarily by smoking.

Phencyclidine Tetrahydrocannabinol Smoking Drug discrimination Biodisposition Rats

AMONG the factors which have contributed to the increase in popularity of phencyclidine (1-[1-phenylcyclohexyl]piperidine; PCP) as a drug of abuse since the early 1970's is the change in the preferred route of administration from oral to inhalation via smoking. Presently, PCP is usually self-administered by smoking cigarettes made from plant materials, such as parsley or marijuana, which have been injected or sprinkled with PCP. Smoking may allow more effective titration of dosage, thus decreasing the chance of consuming dangerous or unpleasant dosages [14,18]. Despite the popularity of the smoking route of administration, few laboratory studies have utilized this route. Since numerous studies have demonstrated the unique discriminative stimulus properties of PCP [3, 11, 15, 17, 20, 23], the first study was conducted to determine whether PCP administered by smoke exposure would generalize in rats trained to discriminate intraperitoneal (IP) injections of PCP from saline. The specificity of stimulus control generated by PCP exposure via smoke was evaluated by testing Δ^9-tetrahydrocannabinol (THC) for generalization in these subjects using the smoking route. An additional study was carried out to study the relationship between the behavioral activity of PCP and brain levels following administration by IP injection or smoke exposure.

EXPERIMENT 1—DRUG DISCRIMINATION

METHOD

Animals

The subjects for the drug discrimination experiments were four experimentally naive, male Sprague-Dawley rats (Dominion Labs, Dublin, VA) maintained at 275–290 g for the duration of the experiment by adjusted post-session feeding (Rodent Laboratory Chow No. 5001, Ralston Purina Co., St. Louis, MO). The animals were individually housed

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in stainless steel mesh cages (18 × 19 × 25 cm) where tap water was continuously available. The animal facility was maintained on a normal phase, 14 hr light, 10 hr dark photoperiod. For operant sessions the animals were transported to an adjacent experimental area.

Apparatus

Standard two-lever operant chambers (Model E10-10, Coulbourn Instruments, Inc., Lehigh Valley, PA) housed inside light and sound attenuating cubicles (Model E10-20, Coulbourn Instruments, Inc.) were used. The levers were arranged 7 cm from the grid floor and 12 cm apart with a food trough located between them. An automatic food pellet dispenser (Model D1, Gerbrands Co., Arlington, MA) delivered a 45-mg food pellet (Formula A, P. J. Noyes Co., Lancaster, NH) to the trough when experimental contingencies were met. A single houselight was located 25 cm above the trough and remained lit during experimental sessions. Solid state programming equipment which controlled the contingencies and recorded behavior was located in an adjacent room.

For smoke exposure, a device was used similar to that described by Freeman and Martin [5,6] for mice. Briefly, rats were restrained in plastic tubes which could be inserted into a manifold, which accommodated four tubes, such that only their noses protruded into the manifold. One end of the manifold was attached via tygon tubing to a cigarette holder and the other end was attached to a vacuum source (water aspirator). When a cigarette was placed in the holder and lit, smoke was drawn through the manifold and thus inhaled by the rats. The vacuum source was switched on and off every 5.8 sec to simulate puffing. The vacuum source was regulated so that it took 8–10 min for an entire cigarette to be burned.

Discrimination Training

The rats were trained to respond on both levers under a fixed-ratio 1 (FR-1) schedule for food reinforcement. Following acquisition of this response, the fixed-ratio was increased in a stepwise fashion across sessions to FR-32, and only responding on one of the levers was reinforced. The correct lever for reinforcement depended on the IP injection which preceded the session. For two of the rats, the right-lever was randomly assigned as correct following PCP and the left lever correct after saline, while the opposite conditions held for the others. Responses on the incorrect lever reset the response requirements on the other lever.

Training sessions were usually conducted 6 days a week. The training conditions altered between PCP (3.0 mg/kg) or saline (1.0 ml/kg) in a double alternation sequence. Following an IP injection, the animal was placed into the operant chamber and 10 min later the houselight was lit to signal that the schedule contingencies were in effect for the 30-min session.

Training continued until the rats responded reliably under the FR-32 schedule, then probes were introduced every third session to assess the degree of stimulus control. Those probes consisted of a 2-min extinction period and were followed by the normal training session. When a subject responded with at least 85% of the responses on the correct lever on four consecutive probes, the testing phase of the experiment was begun.

Generalization Testing

Test sessions following IP injections consisted of a 2-min extinction period occurring 10 min after injection, after which the rats were returned to the home cage. Test sessions were interspersed with training sessions and occurred every third session if the first ratio completed on the previous training day was on the correct lever. If this criterion was not met, training continued until the animal met the criterion for two consecutive training days before testing resumed.

Using this procedure, a range of doses of PCP (0.3, 1.0, 3.0, 10.0 mg/kg) and saline were tested. Doses were administered in an ascending and then a descending order with saline tested as the last treatment of each series. Training with saline and PCP alternated between test days and each test dose was tested once following a saline and once following a PCP training condition.

After a dose-effect curve for PCP by the IP injection route was established, the animals were adapted to the smoking apparatus and procedures. This was done by exposing the rats to smoke from a placebo cigarette followed by either an IP injection of PCP (3.0 mg/kg) or saline and a normal (reinforced) training session. Since all testing following smoke exposure to drugs was conducted under extinction conditions, the rats were occasionally retrained between tests using the above adaptation procedure.

Smoke exposures and generalization testing proceeded as follows: after the rats were restrained and the tubes placed into the manifold ports, the vacuum was applied and the cigarette lit. The entire cigarette was consumed within 8–10 min and then the rats were removed and transported to the operant chambers. Ten minutes after smoke exposure the test session began. As before, a test session consisted of a 2-min extinction trial. However, following smoke exposure, if a rat failed to emit at least 32 total responses during the 2-min trial, the test session was extended in 2-min increments until this criterion was met or until 15 consecutive extinction trials were presented. This repeated testing was done because the smoke-exposure procedure occasionally disrupted responding completely.

Phencyclidine and THC were administered in smoke by treating placebo marijuana cigarettes with a range of concentrations of drug as described below and doses were expressed as mg/cigarette. Doses of PCP (1.5, 3.0, 6.0, 10.0 mg/cigarette) and THC (1.5, 3.0, 6.0, 12.0 mg/cigarette) and vehicle (untreated cigarette) were tested for the ability to occasion PCP-appropriate responding. Testing with PCP preceded THC testing. Each dose was tested twice and doses were administered in a mixed order. Test sessions were conducted every third day using the same criterion as before except that all four rats had to make criterion together so they could be exposed to the smoke as a group, thus occupying the same number of manifold ports.

For controls, the rats were exposed to placebo smoke, then injected (IP) with either the training dose of PCP (3.0 mg/kg) or saline before testing using the same procedure used for testing drugs by smoke administration. As with all the test doses, each control treatment was tested twice, once after a saline training day and once after a PCP training day.

Near the end of the experiment, the lowest dose of PCP in smoke (1.5 mg/cigarette) was again tested, twice as before, because of unusual results initially obtained at this dose. Several "retraining" sessions (as described for adaptation to the apparatus) intervened before this dose was retested. All results obtained are reported.

Data Analysis

The data presented are averages (± S.E.) of the two determinations of each treatment in each of the four subjects. Following drug injections, the number of responses occurring on the PCP lever during the test trials were expressed as a percentage of the total responses; however, data were not included in the average when the response rate was less than 0.05 responses/sec. Response rates were based on the total number of responses which occurred on both levers during the 2-min extinction test period.

Following smoke exposures, the percent PCP-lever responding represented the distribution of responses between the two levers during the last trial, in which at least 32 total responses were made. If this minimum response output was not met within 15 trials, the data were not used in calculating the mean percent PCP-lever responding. Response rates were based on the total number of responses occurring on both levers across all trials until the 32 response criteria was met or 15 trials were presented. Doses estimated to produce 50% PCP-lever responding (with 95% confidence limits) were obtained by least squares linear regression of the linear portions (0.3–3.0 mg/kg IP and 1.5–12.0 mg/cigarette by smoke) of the dose-effect curves.

Drugs

Phencyclidine hydrochloride (PCP) was prepared for administration by IP injection by diluting a stock solution (Sernylan, Bio-Ceutic Laboratories, St. Joseph, MO) with physiological saline to an injection volume of 1.0 ml/kg. For smoke administration, placebo (THC removed by alcohol extractions) marijuana cigarettes (National Institute on Drug Abuse, Bethesda, MD) were used without further treatment or were impregnated with methanolic solutions (100 μl) of phencyclidine hydrochloride (NIDA) or THC (NIDA). The cigarettes were injected axially and evenly into the middle two-thirds with the drug solutions and allowed to dry overnight. Doses of PCP refer to the salt. Doses administered by smoke are expressed as mg/cigarette.

RESULTS

The distribution of responses and overall rates of responding following injections of saline or four different doses of PCP are shown in Fig. 1. Saline and low doses of PCP did not occasion PCP-lever responding. At the training dose of PCP (3.0 mg/kg) approximately 75% of the responses were made on the PCP-appropriate lever. The injected dose (with 95% confidence limits) of PCP which would be expected to result in 50% PCP-lever responding (ED_{50}) was 1.8 (1.2–2.9) mg/kg. For both determinations of the effects of saline injection alone, all 4 rats emitted greater than 32 responses in the single 2-min extinction trial employed for this portion of the study. Rates of responding on both levers following injections of PCP decreased in a relatively dose-dependent fashion. Only the highest dose of PCP (10.0 mg/kg) resulted in marked response rate suppression, so much so that on only two out of eight occasions were response rates greater than 0.05 responses/sec.

When an injection of 3.0 mg/kg PCP followed placebo smoke exposure, nearly all the responses occurred on the PCP-appropriate lever and the mean response rate decreased to about 0.4 responses/sec (Fig. 2). In contrast, when placebo smoke exposure was followed by a control injection of saline, a mean of less than 10% of the responses occurred on the

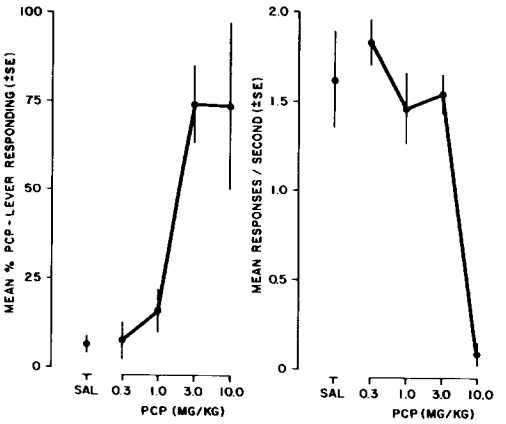

FIG. 1. Dose-effect curves for PCP administered by IP injection. The mean percent PCP-lever responding and mean response rate are on the ordinates with PCP dose in mg/kg (log scale) on the abscissae. The vertical bars indicate the standard errors. The points over SAL are control data for vehicle (saline) injections. Each point represents the mean (± SE) of 8 values (2 determinations in each of 4 rats) except at 10 mg/kg where data from all but 2 tests were excluded from the mean percent PCP-lever responding calculation since the response rate during the test sessions were less than 0.05 responses/sec.

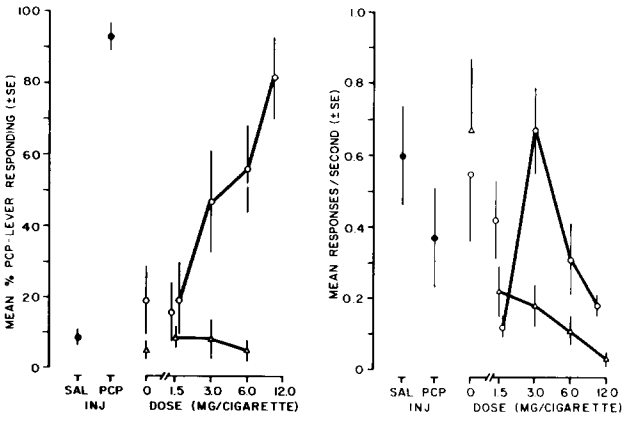

FIG. 2. Dose-effect curves for PCP (○) and THC (△) administered via exposure to smoke. The mean percent PCP-lever responding and mean response rate are on the ordinates with drug dose expressed as mg/cigarette (log scale) on the abscissae. The vertical bars indicate the standard errors. The solid points above SAL and PCP are the effects of IP injections of saline and 3.0 mg/kg PCP which followed exposure to placebo smoke. The points above the 0 mg/cigarette dose are the effects of placebo smoke exposure determined as part of the PCP (○) and THC (△) dose-effect determinations. The unconnected open point above the 1.5 mg/cigarette dose is a redetermination of the effects of that dose of PCP. Each point for percent PCP-lever responding is the mean of 5–8 values. Data were not included in the mean percent PCP-lever responding calculation if the rats failed to emit at least 32 responses within the 15 possible 2-min test trials. Mean response rates are all based on 8 values (2 determinations in 4 rats).

PCP lever and the mean response rate was 0.6 responses/sec. Most of the rats completed the 32-response criterion within the first trial under these conditions; however, one rat required 8 trials on one occasion before meeting the criterion. Nevertheless, even if that determination was excluded from the average, the response rate following smoke exposure plus saline injection was still much less than the response rate following saline injection alone (0.68 compared to 1.6 responses/sec, respectively), evidence for the disruptive effects of smoke exposure. Because of this, when the rats were exposed to smoke, repeated 2-min extinction tests were conducted until the 32-response criterion was met. Note that the injection of saline had no additional effects on response rate, for the response rates following the "0 mg/cigarette doses" (i.e., placebo cigarette alone) were very close to the response rate for placebo smoke plus saline injection (Fig. 2).

The discriminative stimulus properties of IP PCP were generalized to PCP administered in smoke since a dose-dependent increase in the mean percent PCP-lever responding was obtained (Fig. 2). The ED_{50} (with 95% confidence limits) for PCP-lever selection following smoke administration of PCP was 4.0 (2.9–6.0) mg/cigarette. The dose-effect curve for response rate was in the shape of an inverted-U (Fig. 2). Due to the unexpected response rate suppression which occurred with PCP at 1.5 mg/cigarette, this dose level was retested (unconnected open circles in Fig. 2) and no response rate suppression relative to vehicle control was observed on retesting.

Figure 2 also shows the results with THC administered in smoke. Systemic PCP did not generalize to THC by this route since no dose of THC resulted in greater than a mean of 10% PCP-lever responding. This failure to generalize occurred with THC doses that produced clear dose-dependent decreases in rates of responding (Fig. 2, right panel).

EXPERIMENT 2—PCP BIODISPOSITION

In general we have found a good correlation between brain levels and behavioral effects of orally- and systemically-administered PCP [7, 13, 16, 25]. The results of Experiment 1 provided potency estimates for PCP by both IP and smoking routes of administration for discriminative stimulus effects, giving us an opportunity to compare brain levels of PCP following administration of equipotent doses by both routes. If behavioral effects reflect brain tissue concentrations of PCP, then route of administration should not matter except insofar as different doses may be required to achieve comparable concentrations at brain sites essential for PCP action. Thus, in Experiment 2 tissue concentrations in various brain areas of rats were determined following administration of equipotent doses of PCP by IP and smoking routes.

METHOD

The four rats which were used in Experiment 1 were exposed to smoke from cigarettes containing ^{3}H-PCP (25 μCi, NIDA) equivalent to that which was calculated to result in 50% PCP-lever responding following smoke exposure, 4.0 mg/cigarette, as described in the previous experiment. Ten minutes after smoke exposure the rats were decapitated. Eight additional rats with a similar PCP drug discrimination history were divided into equal groups and received an IP injection of either 1.8 (equivalent to that calculated to result in 50% PCP-lever responding following IP injection) or 4.0 mg/kg ^{3}H-PCP (50 μCi/kg). These rats were also decapitated 10 min after the injection. Brains from all animals were removed and dissected into seven anatomical areas (cerebellum, medulla, hypothalamus, midbrain, striatum, hippocampus and cortex) according to the description of Glowinski and Iverson [8]. The resulting brain areas were homogenized with a polytron (Brinkman Instruments, Westbury, NY) in 2 ml of 0.5 N hydrochloric acid containing 0.5 mg PCP HCl/ml. ^{3}H-PCP levels were measured in these brain area homogenates using a method previously described [5]. A hexane extraction scheme was used to selectively separate ^{3}H-PCP from metabolites and pyrolysis products. Thin-layer chromatography was used to verify the selectivity of the extraction [5]. The hexane extracts were counted by liquid scintillation spectrometry for quantification of ^{3}H-PCP.

RESULTS

Levels of PCP (pg/mg tissue) in the seven brain areas are presented in Table 1. A relatively even distribution of ^{3}H-PCP in the seven brain areas was observed following IP injection and to a lesser extent following smoke exposure. Equivalent doses that corresponded to the ED_{50}'s for generalization following smoke exposure or IP injection (4.0 mg/cigarette and 1.8 mg/kg) resulted in brain area concentrations of ^{3}H-PCP that were roughly comparable in most areas regardless of the route of administration, although there was some tendency for higher levels to be found following inhalation exposure than IP injection, especially in the hypothalamus, hippocampus, and cortex. The higher dose of injected ^{3}H-PCP (4.0 mg/kg), which would be expected to produce almost complete generalization, resulted in brain levels that were generally about three times those obtained following injection of 1.8 mg/kg PCP and which were also roughly equal in the various brain areas.

GENERAL DISCUSSION

In rats trained to discriminate IP injections of PCP from saline injections, dose-dependent increases in PCP-lever responding and decreases in response rate were observed when various doses of PCP were tested using the IP route of administration. These findings confirm those of others who have demonstrated that PCP can serve as a discriminative stimulus in rats using an electrified T-maze [11,17] and in rats [3, 9, 20, 23], pigeons [15], squirrel monkeys [2] and rhesus monkeys [24] using operant procedures.

A number of studies have demonstrated that the route of administration of discriminable psychoactive compounds is qualitatively unimportant [1, 12, 21]. In humans, abuse of PCP occurs by a number of routes of administration including oral ingestion, insuflation, intravenous injection and smoking [14]. The effects by these various routes are reportedly similar, differing primarily in onset and duration [19]. Phencyclidine is most frequently self-administered by injecting or sprinkling it on plant material which is smoked as a cigarette. The current popularity of PCP abuse has been attributed to the development of the smoking route because smoking allows more effective titration of dosage, thus decreasing the chances of overdosage [14, 18, 19]. The present study demonstrates similar discriminative stimulus properties of PCP by the injection route and the smoke exposure route. This correlation supports the validity of using injection routes for experimental studies of drugs, such as PCP, which are primarily taken in the human abuse situation by smoking.

TABLE 1

CONCENTRATION OF ^{3}H-PCP IN BRAIN AREAS AFTER IP INJECTION AND SMOKE EXPOSURE

Route	Dose	pg PCP/mg Tissue*						
		Cerebellum	Medulla	Hypothalamus	Midbrain	Striatum	Hippocampus	Cortex
Inhalation	4 mg/cigarette	232 ± 28	234 ± 41	343 ± 25	258 ± 37	358 ± 59	429 ± 53	331 ± 51
IP	1.8 mg/kg	199 ± 21	179 ± 27	238 ± 20	195 ± 20	231 ± 29	245 ± 38	220 ± 20
IP	4 mg/kg	967 ± 170	739 ± 126	997 ± 179	889 ± 185	1021 ± 185	1056 ± 234	1170 ± 240

* Means ± S.E.M., N = 4.

The smoke exposure route of administration has rarely been employed in animal behavioral experiments. This is likely due to the technical difficulties of administering drugs via smoke to animals and in determining the actual amount of drug absorbed. In Experiment 1, this latter problem was circumvented by expressing the smoke exposure doses as the amount of drug contained in the cigarette (mg/cigarette) used to expose four rats. In Experiment 2, similar brain levels and distribution were observed following equivalent doses for generalization by the IP injection route and smoke exposure route; thus some estimate of the smoke exposure dose was obtained.

The active constituent of marihuana, THC, is another compound which is commonly abused by the smoking route. In the present study, THC, delivered in smoke to rats trained to discriminate PCP from saline, was not generalized from injections of PCP up to doses which markedly suppressed response rates. One of the characteristics of the drug discrimination paradigm is that drugs which are pharmacologically dissimilar to the training drug usually fail to be generalized. Drug discrimination experiments with PCP have demonstrated that the arylcyclohexylamines are a unique class of drugs which do not share discriminative stimuli with a wide variety of other psychoactive drug classes [23] with the exception of the psychotomimetic benzomorphan opioids, specifically those with sigma-opiate activity [3, 9, 23]. In this regard, other investigators have reported a lack of cross-generalization between PCP and THC using rats trained to discriminate PCP from saline [11,23] and in rats trained to discriminate THC from vehicle [4,10]. Our results are consistent with these reports. In related studies it was found that rats trained to discriminate THC by the injection route generalized to hashish administered by smoke and vice versa [10,12].

Concentrations of ^{3}H-PCP were somewhat higher in all brain areas after smoke inhalation of 4 mg/cigarette than after IP administration of an equipotent dose of 1.8 mg/kg. This ranged from 17% higher in the cerebellum to 75% higher in the hippocampus. Given the variability of the brain level determinations and the confidence limits for the ED_{50} potency estimates of 2.9–6.0 mg/cigarette and 1.2–2.9 mg/kg, these relatively small differences between brain levels with each route would appear to be within experimental error. We conclude that equipotent doses by both routes produce roughly comparable brain levels. It had been hypothesized that if specific brain areas were importantly involved in the discriminative stimulus effects of PCP, then PCP levels in these areas should be comparable after equipotent doses by any route of administration, whereas areas less involved could be quite different. Since ^{3}H-PCP levels were roughly comparable in all areas, no areas could be excluded as being involved in PCP's actions based on these data.

When testing was done following smoke exposure, a multiple 2-min extinction test procedure was employed due to the disruptive effects of the smoke exposure. Even though we adapted the subjects to the smoke inhalation procedure prior to testing, the procedure remained disruptive of responding in sessions conducted 10 min after removal from the chamber. This finding illustrates one of the difficulties which must be considered when using sensitive operant procedures to assess the behavioral effects of forced smoke exposure to drugs.

Following IP administration, ^{3}H-PCP was rather evenly distributed throughout the rat brain areas studied. This pattern of distribution was consistent with that previously found in brain areas from mice treated SC with ^{3}H-PCP [13]. On the other hand, ^{3}H-PCP was distributed somewhat less evenly in rat brain areas following smoke exposure. The concentration in hippocampus was almost twice that in cerebellum and midbrain with intermediate levels in hypothalamus, striatum and cortex. There is no immediately apparent explanation for these differences in distribution following the two routes of administration. Factors to be considered include the rate at which PCP penetrates the central nervous system after different routes as well as possible interference with PCP disposition by other substances in smoke. It is also possible that the differences are unreliable.

In summary, rats trained to discriminate IP PCP from saline in a two-lever operant procedure generalize the PCP stimulus to PCP delivered in smoke. Since drug discrimination can be considered a model of acute subjective effects of drugs [22], these results provide evidence that the acute subjective effects of PCP in human users are qualitatively similar when smoked or taken systemically. Thus, the current popularity of the smoking route is likely due to a better ability to titrate the intoxication. These results also confirm the validity of studies of the discriminative stimulus properties of PCP using injection routes of administration as a model of PCP effects commonly achieved by smoking.

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