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Effects of Phencyclidine on Shock-Induced Aggression in Rats

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CLEARY, J., J. HERAKOVIC AND A. POLING. *Effects of phencyclidine on shock-induced aggression in rats.* PHARMAC. BIOCHEM. BEHAV. 15(5) 813–818, 1981.—The effects of phencyclidine were assessed under two distinctive paradigms. In a traditional laboratory assay where pairs of rats received intermittent foot shocks, phencyclidine at doses of 0.5 to 2.0 mg/kg decreased the number of shock-elicited fighting bouts in dose-dependent fashion. Similar dose-dependent decreases in biting were also observed under a procedure where single restrained rats received intermittent tail shocks, which evoked biting of an inanimate target.

Shock-induced aggression Phencyclidine Biting Rats

ORIGINALLY used as an anesthetic agent in veterinary medicine, phencyclidine 1-(1 phencyclohexy) piperidine (PCP) has shown considerable abuse potential in humans [2,10]. Neurochemical investigations have revealed a broad spectrum of action for PCP in the central nervous system, including interaction with adrenergic [11], cholinergic [9], and serotonergic [26] systems. Specific receptors for PCP have also been identified in rat brain [34].

When gross, unlearned behaviors are considered, the differential effects of PCP across species have been well documented [3,7]. In rodents, sympathomimetic effects have most often been reported [6], while general calming effects have been reported for some nonhuman primates [3]. However, considerable interspecies consistency has been found in the effects of PCP on schedule-controlled behavior, where the drug produces rate-dependent effects similar to those of amphetamines [13, 20, 31, 32].

In humans, PCP has been repeatedly linked to violent, assaultive, combative, and hostile behaviors [16, 17, 24, 25]. Although anecdotal accounts of PCP's contribution to aggressive behavior are numerous, there have been few attempts to experimentally assess PCP's effects on violence and aggression in humans or nonhumans. Rewerski, Kostowski, Piechocki, and Rylski [23] reported that low doses (1.0 mg/kg) decreased isolation-induced aggression in mice, while higher doses (5.0 mg/kg) increased aggression, although this latter effect was dependent upon the length of isolation. Muricide by rats was unaffected by PCP. In a more recent study, Burkhalter and Balster [4] found that PCP increased isolation-induced aggression in mice at 1.0 mg/kg but had no effect at 3.0 mg/kg.

The present studies examined the effects of PCP on shock-induced aggression in rats. In one procedure, fighting by pairs of male rats was measured, while in the second, biting of an inanimate target by single restrained rats was the dependent measure.

EXPERIMENT 1

Aversive stimuli, in the form of electric shocks delivered through a grid floor, have been shown to reliably produce fighting in pairs of rats (e.g., [27, 28, 29, 33]). This traditional approach to the laboratory study of aggression was used as an initial technique to assess the effects of PCP on aggression in a situation where animals can interact.

METHOD

Subjects

Twelve experimentally-naive adult male (340–360 g body weight) Sprague-Dawley rats served as subjects. One week prior to and throughout the study (approximately 5 months), they were individually housed with free access to food and water in a constantly-illuminated colony room maintained at 24°C.

Apparatus

Subjects were tested in a clear plastic chamber 30 cm high wide, and deep. The floor of the chamber consisted of 0.2 cm diameter metal grids spaced 0.9 cm apart. Scrambled electrical shocks of specified duration and intensity could be delivered to the grids at will. Delivery of shocks was controlled by electromechanical equipment located in an adjacent room. A 15-W white houselight located in the chamber's ceiling supplied constant illumination during experimental sessions, while a 7-W red light located below the chamber (and out of sight of the subjects) flashed each time a shock was delivered. This light served as a cue for observers (below).

Procedure

Throughout the study, rats were tested in pairs at

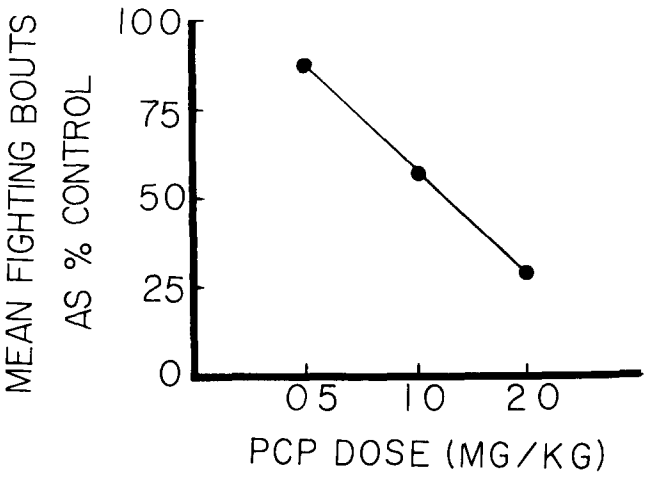

FIG. 1. Group data showing the effects of PCP on paired fighting by six pairs of rats. Mean number of fighting bouts per session at each drug dose (2 administrations per pair) is expressed as percent of the mean number of fighting bouts per session during the three control sessions immediately preceding drug administration (SEM=4.01%). Fighting was elicited by electric shocks delivered under a FT 4-sec schedule; each session terminated after 450 deliveries.

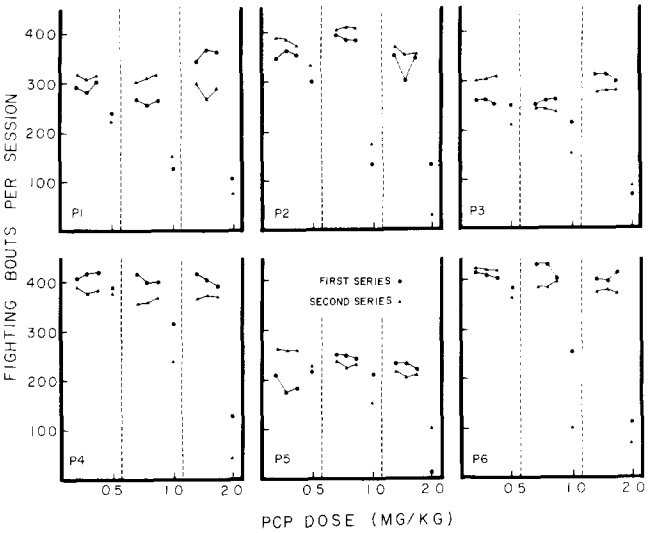

FIG. 2. Data showing the effects of PCP on fighting by individual pairs of rats. Number of fighting bouts are presented for the three sessions preceding each drug administration, and for each drug administration. Each dose was given to each pair on two occasions; circles represent the first administration, triangles the second. Fighting was elicited by electric shocks delivered under a FT 4-sec schedule; each session terminated after 450 shock deliveries.

12:00–2:00 p.m., with the same two rats always tested together. Prior to each session, a pair of rats was placed in the darkened chamber. Five min later, the chamber was illuminated and the 30-min session began. During the session, 0.5-sec, 1.5 mA (measured at the grid) electric shocks were delivered at 4-sec intervals irrespective of the subject's behavior; this constitutes a fixed-time 4-sec (FT 4-sec) schedule of shock delivery. Following each shock delivery, an observer unaware of experimental conditions recorded whether fighting occurred. Each shock was rated as either evoking or failing to evoke a fighting bout. Fighting was defined according to criteria advanced by Ulrich and Azrin [28]. At minimum, a fighting bout involved each animal standing on its hindpaws and mutual "boxing" (striking with the forepaws) or biting. During every third session, on the average, a second observer unaware of experimental conditions independently scored performance along with the primary observer. Comparing her ratings with those of the primary observer allowed interobserver agreement to be calculated. Across all sessions scored by the two observers, mean interobserver agreement was 93% when calculated according to the formula (shock deliveries where the two ratings agreed/shock deliveries where the two ratings agreed + shock deliveries where the two ratings disagreed) × 100, with a range across sessions of 86 to 98%. These values indicate that fighting could be scored reliably.

Isotonic saline (1.0 ml/kg) was injected intraperitoneally 30 min before each control session. Phencyclidine hydrochloride, dissolved in isotonic saline and injected at a volume of 1.0 ml/kg, was administered whenever the number of fighting bouts was stable across three consecutive sessions. Stability was defined as the mean number of fighting bouts during sessions N and N+1 being within 10% of the mean number of fighting bouts during sessions N+1 and N+2. Three doses of PCP, in terms of the total salt, were evaluated: 0.5, 1.0, and 2.0 mg/kg. Each pair of rats received each dose on two occasions, in an irregular sequence that differed across pairs. Whenever drug was given, each member of a pair received the same dose.

RESULTS

Figure 1 shows group data depicting the effects of PCP on paired fighting. In this figure, number of fighting bouts during drug sessions are expressed as percent of the number of fighting bouts observed in the three preceding baseline (non-drug) sessions. For the group of rats, across all baseline sessions the mean number of fighting bouts per pair was 328 out of 450 possible opportunities (15 bouts per min × 30 min). For the group, mean number of fighting bouts was reduced to 88% (293 bouts, SEM=9.3%), 57% (186 bouts, SEM=6.1%), and 25% (83 bouts, SEM=1.6%) of control values at PCP doses of 0.5, 1.0, and 2.0 mg/kg, respectively. This reduction was significant across all doses (repeated measures analysis of variance $F(5,25)=41.4$, $p<0.001$), and planned-comparisons tests (t_{LSD}) indicated that, except for the lowest dose of PCP ($p=0.08$), significantly less fighting occurred during each drug condition than during the preceding control sessions ($p<0.001$).

Figure 2 shows the actual number of fighting bouts for each pair of subjects during each session in which drug was administered, and during the three preceding control sessions. In general, the group data presented in Fig. 1 are indicative of the performance of individual pairs. With the exception of pair P5 at the lowest dose of PCP, all doses reduced fighting frequency relative to the pre-drug baseline. The degree of reduction in number of fighting bouts for individual pairs was directly related to dose, and the magnitude of the effect produced by a particular dose did not vary systematically across the first and second administrations.

DISCUSSION

As noted above, the inter-species effects of PCP vary widely. The drug reportedly produces depressant effects in some nonhuman primates (e.g., rhesus monkeys), and sympathomimetic effects in rodents (e.g., [3]). Althought the reduction in fighting seen in the present study does not suggest the increased arousal characteristically produced by sympathomimetics in rodents, it does parallel the effects on aggression most often reported for amphetamines, which are potent sympathomimetics ([19], pp. 119–124). However, since no independent measure of general activity was taken, it is possible that the decrements in fighting associated with PCP may have been the result of some nonspecific depressant action of the drug. This possibility was evaluated in Experiment 2.

The adequacy of the paired-fighting model as a measure of aggression has been questioned on several counts. Chance [5] has suggested that the mutual upright posture typically seen with this paradigm may not be functionally related to aggression, but rather is defensive in nature. Further, paired fighting involves an interaction between animals that is not subject to experimental control (see [14,19]). Drug effects on paired fighting reflect its interactive nature, and may differ depending on whether one or both members of a pair are drugged, and if one, whether it is the more dominant or submissive animal. Finally, scoring paired fighting usually involves the use of human observers. This is less than ideal both practically and methodologically (see [21]), although trained observers unaware of experimental conditions can consistently score fighting bouts, as they did in the present study.

Despite these problems, pain-elicited paired fighting has endured as one of the most popular laboratory assays of aggression, and drug effects thereon. Procedures for studying pain-elicited attacks of inanimate objects have also been developed and used to good advantage in studying primate aggression (for review see [12]), but despite an early report of biting in partially restrained rats [1], rat assays of aggression have largely utilized procedures where two or more animals interact. Experiment 2 examined the effects of PCP using a procedure for studying aggression directed toward an inanimate target by individual rats.

EXPERIMENT 2

Experiment 2 examined the effects of PCP on one component of aggression, biting, in single rats exposed to intermittent shocks. This procedure eliminates several of the problems associated with interactive assays of aggression, discussed above, while retaining the advantages of the pain-elicited aggression paradigm.

METHOD

Subjects

Three experimentally-naive adult male Wistar rats served as subjects. They were individually housed from the start of the experiment until its completion (approximately 4 months). Subjects were housed with free access to food and water in a colony room maintained at 23°C under a 12-hr light/dark cycle, and were tested in the middle of the light cycle.

Apparatus

Three restraint tubes patterned after those used by Azrin, Rubin and Hutchinson [1], and described in detail elsewhere [8], were used. They consisted of three separate parts: a restraint tube, a removable cap, and a baseplate to which was affixed an inanimate bite target.

The targets were cut from commercially available conveyor belt material (LL-30X, Joseph E. Laughead Co., Kalamazoo, MI) and were 6.0 cm long, 1.0 cm wide, and 0.7 cm thick. Targets consisted of a nylon core, covered top and bottom with leather. Although this material proved durable enough to allow high rates of biting throughout the session, some damage usually occurred. Therefore new targets were used each session.

The target was attached to the baseplate such that it was positioned directly in front of the rat's nose. Movements of the target directly toward the subject (induced by biting or tearing with the teeth) closed a microswitch and counted as a biting response. Other kinds of contact with the target (e.g., pawing) did not close the switch and were not counted.

The restraint tube was of 0.5 cm clear plastic stock, 23 cm long and 10 cm in diameter. A longitudinal slit 2.5 cm wide ran the entire length of the tube's dorsal surface to allow for threading of the animal's tail. The subject's tail extended out the posterior end of the tube where it could be secured to a plastic bar by clothbacked surgical tape.

A second manipulandum, which consisted of a 0.5 cm thick clear plastic panel, was hinged to the cap at the level of the restraint tube floor. The panel was 8.0 cm in diameter and closely fit the interior of the tube. The animal's nose could displace the panel, closing a microswitch (a force of 0.03 newton was required for closure) and counting as a panel press response.

Experimental sessions were conducted in force-ventilated chambers into which the restraint tubes were placed. Each chamber was equipped with a 40-W houselight. White noise and a ventilating fan combined to produce approximately 80 dB of masking noise within the chamber.

Procedure

Experimental sessions were conducted six days each week. Shocks (4 mA) were delivered under a FT 2-min schedule such that each animal received 0.5 sec of shock every two min regardless of its behavior. There were thirteen shocks each session and the session terminated without shock at the completion of the fourteenth interval.

In order to prevent skin damage, Electro-Sol EKG Cream (Scientific Instruments, Rochester, NY) was applied where the shock electrode made contact with the tail. Electrical resistance through the subject's tail was kept between 15,000 and 20,000 Ω by repeated application of the cream as necessary.

Biting responses and panel press responses were recorded. Neither of these responses had any scheduled consequences. Although the biting attack response was the crucial dependent variable in the experiment, the panel press responses proved useful as a measure of general activity within the restraint tube.

The effects of four doses of phencyclidine hydrochloride (0.25, 0.5, 1.0 and 2.0 mg/kg) were evaluated. Each dose was given once in an irregular order; doses refer to the hydrochloride salt. PCP was given when the frequency of biting appeared stable, with no obvious trend, for three consecutive sessions. Control injections of isotonic saline were given prior to all other sessions. All injections were given subcutaneously 30 min before the experimental session. Both PCP and control injections were given at a volume of 0.2 ml.

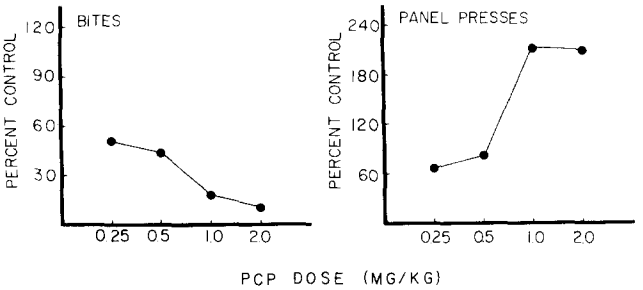

FIG. 3. Group data showing the effects of PCP on biting and panel pressing. Mean number of bites and panel presses per session at each drug dose is expressed as percent of the mean number of bites and panel presses per session during the three preceding control sessions (SEM bites=6.2%, SEM panel presses=7.7%). Bites and panel presses were elicited by electric shocks delivered under a FT 2-min schedule; each session terminated after 13 shock deliveries.

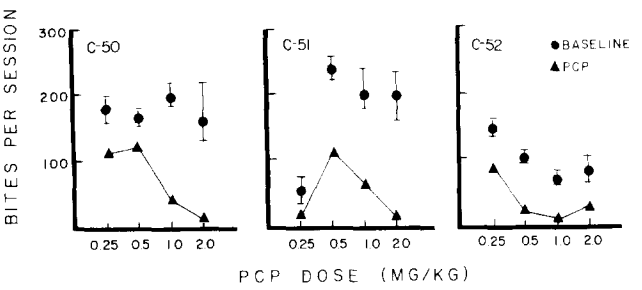

FIG. 4. Individual data showing the effects of PCP on biting. Triangles represent data obtained during sessions in which drug was given. Circles represent the mean number of bites per session during the three control sessions immediately prior to drug administration; vertical lines depict the range across these sessions. Biting was elicited by electric shocks delivered under a FT 2-min schedule; each session terminated after 13 shock deliveries.

RESULTS

The effects of PCP on both biting and panel pressing for the rats considered as a group are shown in Fig. 3, which expresses rate of biting and panel pressing as mean percent of control rate across doses of PCP. At doses of 0.25, 0.5, 1.0, and 2.0 mg/kg, PCP decreased mean group biting to 51% (range across animals 30–62%), 44% (range 11–73%), 17% (range 4–30%), and 10% (range 0.6–29%) of control levels, respectively. The baseline rate of biting was not increased for any subject at any dose. Overall drug effects on biting were statistically significant (repeated measures analysis of variance $F(7,14)=3.8$, $p<0.05$); planned-comparisons tests (t_{LSD}) indicated that the two highest doses significantly reduced responding ($p<0.05$) relative to control values.

Like biting, panel pressing was decreased by the two lower doses of PCP. However, at higher doses, panel pressing was enhanced. At doses of 0.25, 0.5, 1.0, and 2.0 mg/kg, mean group rate of panel pressing was 57% (range across animals 51–63%), 80% (range 24–117%), 215% (range 40–467%), and 208% (range 57–312%) of control values, respectively. For one subject, C-51, panel pressing was reduced at all doses of PCP, while panel pressing was increased for the other subjects at all but the lowest dose.

Figure 4 shows absolute rates of biting for individual rats during drug and control sessions. The bite-decreasing effect of PCP can clearly be seen in each individual subject, even when both the baseline rate and the dose of PCP were low (e.g., C-51 at 0.25 mg/kg). Across subjects, the mean baseline rate of biting was 146 bites per session, or 5.2 bites per min. The mean baseline rate of panel pressing was 181 presses per session, or 6.5 presses per min.

DISCUSSION

Using individual rats in partial restraint, PCP was shown to have aggression-reducing effects that parallel those obtained with the interactive procedure used in Experiment 1. Thus, the effect of the drug on a single component of aggression, biting, was similar to its effect on the more complex aggregation of behaviors manifested in the interactive aggression assay. That these reductions were observed at low doses in the biting paradigm suggests that this procedure is at least as sensitive to drug effects as its interactive counterpart.

The increase in panel pressing seen at the higher doses of PCP is consistent with the enhanced activity often reported in rodents given PCP [3,4], although it is possible that PCP-induced stereotypies (e.g., head bobbing) contributed to the increased panel pressing. However, such stereotypies typically appear at doses higher than those used in the present study (e.g., [3]), and were not appearant in nonsystematic observations of our subjects. Thus it appears that PCP specifically reduced pain-elicited attack without depressing the animal's ability to respond or its general behavioral activity. Consequently, explanations that imply sedation or ataxia as a cause of the reduced biting may be eliminated.

GENERAL DISCUSSION

Previous research has shown that PCP often produces behavioral changes similar to those produced by amphetamines [20,32]. When schedule-controlled operant responding is considered, both drugs have been reported to produce rate-dependent (e.g., [31]) and biphasic effects (e.g., [20]). Similar biphasic effects—low doses increase responding while high doses decrease it—have been reported for both drugs with respect to aggressive behavior [4,30], although amphetamines have most often been found to reduce aggresssion (see [18]). In the present experiments, PCP at all doses decreased both fighting and biting, although biphasic effects were seen in panel pressing in Experiment 2.

Comparison of the present studies and the two previous reports of PCP's effects on rodent aggression yields little consistency. In accordance with the increased panel pressing seen in Experiment 2, Burkhalter and Balster [4] reported increased locomotor activity in mice subjected to social isolation, then given PCP. However, those authors also reported increases in isolation-induced fighting at low doses of PCP. In findings consistent with the present studies, Rewerski *et al.* [23] reported decreases in isolation-induced fighting in mice given low doses of PCP. They also found that PCP did not affect mouse-killing by rats.

Given the inter-species differences often seen under PCP, it is not surprising to find that aggression assays with rats yield results quite different from those assays employing mice. Such species differences, as well as the witnin-paradigm differences in findings noted above, suggest interpretive caution when discussing the effects of PCP on ag-

gression: The drug effects observed under the two assays used in the present studies may relate only to pain-elicited aggression in rats. This decrease in aggression was robust at least to the extent that it was observed under both procedures and was not obscured by minor procedural differences (i.e., route of administraton, ambient light cycle). Nonetheless, further research using a variety of procedures would be required to clarify PCP's effects on attack in rodents and on aggression in general.

Beyond evaluating the effects of PCP on shock-elicited attack, the present research demonstrated the procedure employing biting of an inanimate target to be a tenable assay of aggression in rats. When drug was not given, tail shocks evoked consistent biting by the restrained rats; this reponse was at least as sensitive to drug effects as paired fighting. Yet, despite some obvious advantages, the procedure used in Experiment 2 is not without shortcomings. Clearly, biting attack is only one of an incredibly wide range of behaviors considered under the rubric of "aggression". As others have discussed in detail (e.g., [14, 15, 19]), these diverse behaviors are controlled by many and widely different environmental events, and may not be similarly affected by a given experimental manipulation, including drug administration. Although biting is undeniably a prominent aspect of fighting in rats [19], and can be readily measured by the technique used in Experiment 2, the relation of this assay to other laboratory assays of aggression, and to field studies, must be determined empirically.

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