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p-Chlorophenylalanine Effects on Shock-Induced Attack and Pressing Responses in Rats

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SEWELL, R. G., J. A. GALLUS, F. P. GAULT AND J. P. CLEARY. *p-Chlorophenylalanine effects on shock-induced attack and pressing responses in rats.* PHARMAC. BIOCHEM. BEHAV. 17(5) 945–950, 1982.—The literature concerning the effects of d,l-parachlorophenylalanine (PCPA) upon shock-induced aggression (SIA) was examined and found to be inconsistent. PCPA, a known serotonin depletor, has behavioral effects in a variety of other procedures which collectively suggest that PCPA should produce SIA enhancement. The present study analyzed PCPA (300 mg/kg, IP) effects upon SIA in rats restrained spatially close to an inanimate target and panel operandum. The results showed marked increases in both aggressive biting and panel-pressing for several days following each PCPA treatment, for each subject tested. These data were interpreted to indicate that serotonin depletion by PCPA does indeed enhance SIA but that this effect is not selective for aggression. Potential controlling variables are suggested to account for reports of no effect on SIA after PCPA treatment. It is concluded that procedural variables may be the critical determinants of variation in reported PCPA-aggression effects across studies, rather that hypothesized differences in neurochemical mediators.

p-Chlorophenylalanine Shock-induced aggression Pressing responses Serotonin Restraint Rats Monoamines

THREE indirect lines of evidence have collectively suggested that PCPA should enhance shock-induced attack (SIA), yet this relationship has remained controversial. One type of indirect evidence has come from studies of behavioral reactivity, in which PCPA-treated subjects appeared hyperresponsive to environmental stimuli in general, and to aversive stimuli in particular. Various authors have described increased irritability and aggressiveness upon handling PCPA-treated rodents [22,37]. Paxino, Burt, Atrens, and Jackson [28] specifically rated behavior upon handling and concluded that PCPA-treated rats did show a slight enhancement in irritability that was reversed by administration of serotonin's immediate precursor 5-hydroxytryptophan (5-HTP). In addition, treatment with PCPA has increased reactivity to stimuli of other modalities. Reaction to visual [36], gustatory [3], and auditory [8] stimuli have all been magnified, and habituation to repetition of such stimuli has been diminished [4,8].

PCPA has consistently produced decreased pain thresholds in various tests of nocioception [31, 32, 37]. In addition, Fibiger, Mertz and Campbell [14] have shown that PCPA diminishes the behavioral suppression normally observed in situations involving shock. Investigations have demonstrated enhanced avoidance acquisition [31,37] and increased performance of already-learned avoidance responses [3] after PCPA treatment. Such results suggest that serotonin functions to inhibit the behavioral effects of nocioceptive stimuli, and that depletion of serotonin removes this inhibitory process, thus yielding hyperreactivity.

A second indirect line of evidence suggesting that PCPA should enhance SIA has come from studies of another model of aggression, predatory mouse-killing by rats (muricide) [15, 24, 25, 28]. In these experiments rats typically did not consume mice after muricidal aggression, which indicates that PCPA-induced mouse-killing is not related to an enhanced tendency to feed.

A third indirect line of evidence has emerged from experiments of PCPA upon feline rage behavior generated by intracranial brain stimulation (ICBS). Three reports have indicated enhancement of affective aggression in PCPA-treated cats [13, 21, 23], although Zitrin, Beech, Barchas and Dement [41] have reported a lack of effect.

Many studies have demonstrated pain-induced aggression to be a direct function of stimulus intensity over a wide range of values [2, 10, 38]. As PCPA enhances pain sensitivity and behavioral reactivity to nocioceptive and various other stimuli, and as PCPA increases attack produced in the muricide and ICBS models of aggression, it might be inferred that PCPA should enhance attack produced in the shock-induced aggression procedure. The data which directly bear on this issue have remained equivocal, however. Three studies have reported enhancement in shock-induced attack

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[12, 32, 33], whereas three investigations revealed no effect [7, 11, 24] and two studies actually demonstrated decreased SIA after PCPA treatment [1,29].

The source of variation remains obscure, but one possibility suggested by Sheard and Davis [32] is that inter-shock interval (ISI) is a critical determinant of PCPA's effect upon SIA. These authors have reported PCPA-induced enhancement of SIA with an ISI of 15 seconds, but no effect with an ISI of 3 seconds. Using non-drugged subjects, Hutchinson and co-workers [18] demonstrated that a brief ISI yields marked behavioral suppression and rapid response habituation, whereas an extended ISI yields behavioral enhancement and accruing response facilitation. Thus, it is plausible that subjects exposed to an ISI substantially longer than 15 seconds would show marked facilitation of SIA subsequent to PCPA treatment. Such studies have not been performed.

A second potential source of variation in reported PCPA effects upon SIA may lie in the nature of the attack induction procedures. All SIA procedures used in the assessment of PCPA have been social in that two subjects are simultaneously shocked, each then serving as aggressor and target. This technique has proven problematic for the assessment of drug effects on aggression as considerable variability is inherent [9]. Non-social procedures have been developed for analyzing rodent aggression employing single subject attack of inanimate objects. These techniques thus circumvent much of the complexity and variability endemic to social procedures. The advantages and characteristics of the non-social procedures are discussed elsewhere [2,17].

The objective of the present study was thus to analyze the effects of the serotonin depletor PCPA upon shock-induced attack in rats. This study employed a non-social aggression assessment procedure with an ISI considerably longer than those previously reported. It was surmised that use of a non-social procedure and a lengthy (3.5 min) ISI might maximize the effects of this drug.

METHOD

Subjects

Three adult male Wistar rats supplied by Charles River Breeding Laboratories (Wilmington, MA) served. The animals were approximately nine months of age, and were experimentally naive at study onset. Subjects were individually housed in a colony with a 12-hour day/night cycle and access to food and water in home cages.

Apparatus

The instruments used (one for each subject), generally similar to that described by Azrin *et al.* [2] but with several modifications, had four principal features. A restraining tube loosely held the rat so that the tail emerged from the rear of the tube toward two secured, surface electrodes which were laid across the rat's tail. An acrylic "nose-press" panel was positioned with the restraint tube directly in front of the animal. An inanimate bite target was affixed to a digital switch and protruded through the tube's removable cap.

The restraining tube (9.5 cm dia., 28 cm long) was secured by two stockades onto an acrylic baseplate (51 cm long). A slit in the tube ceiling allowed for the "threading" of the animal into the tube. The slit in the tube was then covered with a snap-on acrylic strip. A hole in the tube floor (2.5×2.5 cm) allowed for the passing out of urine and feces. The subject's tail emerged from the tube rear and was taped to an extended acrylic bar with the tape posterior to both electrodes. The tail-restraint bar was connected to the restraint tube by two supports; to the top of each were hinged aluminum electrodes (0.95×0.95×10.0 cm).

Each restraint tube held two response operanda, always available to the subjects. Hinged to the removable tube cap was an acrylic nose-press panel which fit snugly within the internal diameter of the restraint tube. Operation of the manipulandum required a force of 0.14 N and a displacement of 2.5 mm. Protruding from the nose-press panel was an inanimate bite target of laminated nylon-leather strips (LL=30×; Joseph E. Loughhead Co., Kalamazoo, MI) (1.2×7.5×0.7 cm). The target extended 2.5 cm into the restraint tube at a 12° angle from the floor. Biting activity which produced target excursions of 2.0 mm into the tube, via application of 0.10 N of force, yielded switch closure. Mechanical definition of biting attack dictated that only target travel directed back into the tube, toward the subject, would produce switch closure. All other activities such as gnawing, grooming, swatting, and pawing did not result in switch closure, and thus not in bite definition.

Each restraint tube apparatus was enclosed in a force-ventilated, sound-attenuating chamber equipped with masking noise from a running fan and "white noise" (80 dB). Shock was produced by a Grason-Stadler Shock Generator (W. Concord, MA; model #700). Exposure to chamber illumination (a single GE 7.5-watt bulb), ventilation, white noise, and shock, as well as the recording of all responses, was controlled by conventional electromechanical equipment.

Procedure

Subjects were studied daily in behavioral test sessions six times per week. The electrical resistance of each subject's tail was monitored before and after each session. Before each session the subject's tail was cleansed with isopropyl alcohol and then massaged with Electro-Sol EKG Cream (Lumiscope Co., New York, NY). This procedure yielded resistance below 3,000 ohms.

Each 49-minute session yielded 13 shocks to the rat's tail. Shocks were delivered independent of response on a fixed-time, 3.5-minute schedule with 3.5 minutes elapsing before the first and after the final shocks. Tail shocks were 500 msec in duration, unsignalled, and 4.0 mAmp in intensity. All sessions were conducted within a temperature range of 22–28° C. (monitored daily). The entire restraint apparatus was washed with water and soap (Healthco Inc., Boston, MA) after each test session.

Each session a new bite target was affixed to the bite transduction switch. Throughout each session the target remained in front of the subject so that all biting was continuously, automatically and instantaneously recorded on digital counters and displayed upon cumulative records.

Drug Preparation and Administration

Vehicle control solutions consisted of 4.0 ml/kg volumes of physiological saline solution into which was dissolved a wetting agent, Triton X100 (1 ml Triton X100/200 ml saline). Drug treatments were prepared by suspending 75 mg d,l-parachlorophenylalanine hydrochloride (Sigma Chemical Co., St. Louis, MO) in each ml of the vehicle solution; preparations were stored under refrigeration. Drug and control

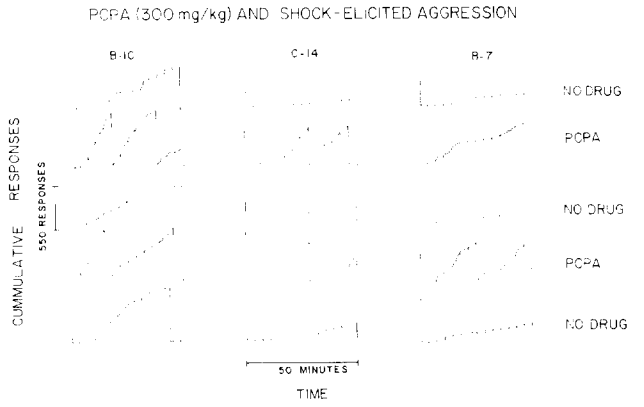

FIG. 1. Actual reproduction of cumulative records displaying biting under drug and no-drug conditions for each subject. The top and middle rows of "no-drug" records were taken from sessions that immediately preceded PCPA treatment. Each PCPA record represents that session of maximal biting enhancement (see text for specific days).

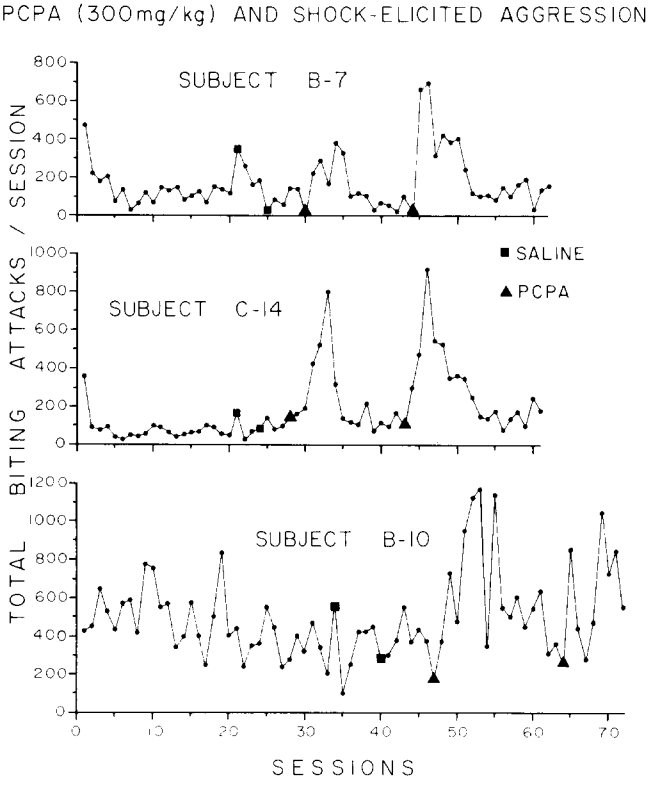

FIG. 2. Total number of bites per session across sessions for each subject. (▲) Represents behavior during sessions initiated 10 minutes after 300 mg/kg PCPA treatment. (■) Represents behavior during sessions initiated 10 minutes after vehicle injections.

solutions were injected intraperitoneally (IP). PCPA (75 mg/ml) was given at dosages of 300 mg/kg. All three subjects received two initial vehicle control injections several days before the first drug treatments (rat C-14: 10 and 6 days; rat B-10: 15 and 8 days; rat B-7: 10 and 6 days); they then received two PCPA treatments spaced at least 2 weeks apart (rat C-14: 15 days; rat B-10: 17 days; and rat B-7: 15 days).

RESULTS

The selected cumulative records from the last day in the no-drug conditions displayed in Fig. 1 indicate biting behavior occurred in the immediate post-shock period, with biting probability highest immediately after shock and rapidly declining thereafter. Cessation of biting during the immediate pre-shock period was characteristic for each animal during most shock-to-shock intervals (see Fig. 1, No-Drug conditions). Visual inspection of subjects indicated that biting activity was greatest in frequency, duration, and force during the immediate post-shock period; and as the time remaining before the next shock lessened, gross-motor behavior virtually ceased.

Once stability was achieved, highly individualized patterns of within-session biting became evident for each subject under the no-drug condition (see Fig. 1). For rat B-7, the number of bites across successive shock deliveries remained approximately constant. For rat B-10, and to a lesser extent rat C-14, an increase in the number of shocks was accompanied by a greater number of bites per shock.

The number of bites per session are presented in Fig. 2 for each of the three subjects. Each subject achieved biting stability within 40 sessions. Calculated over the 20 control sessions that preceded PCPA treatment, both subjects C-14 and B-7 displayed uniformly low mean rates of biting (Mean±S.E) (C-14: 74±8; B-7: 119±14), whereas subject B-10's mean biting rate was higher and more variable (B-10: 353±24).

PCPA markedly enhanced each subject's biting rate for several days after each of the two drug injections. This result is shown in Fig. 2 comparing mean attack levels for the final 20 no-drug sessions with the peak biting rates from the 14-day periods following each of the two PCPA treatments. For rat C-14, biting rose to 803 and 913 compared to the mean no-drug rate of 74±8 bites per session. The attack behavior of rat B-7 increased to 374 and 678 as compared to a mean no-drug rate of 119±14 bites per session. For rat B-10, with a mean no-drug rate of 353±24, attack rose to peak values of 1172 and 1063 bites per session. The maximum aggression-enhancing effect was reached between 2 and 6 days post administration for all drug injections (Mean=4.0 days post drug). Analysis of variance of regression ANOVAR) procedures were used to evaluate changes in individual subjects' rates of biting attack across the nine days which immediately preceded first drug treatments, and the 9-day periods which followed each of the PCPA injections. For each subject, ANOVAR analysis revealed significant changes in rates of biting subsequent to PCPA (C-14: $F(6,26)=8.7527$, $p<0.00009$; B-10: $F(6,26)=3.6154$, $p<0.01361$; B-7: $F(6,26)=3.8574$, $p<0.01017$).

Enhancement of aggression subsequent to PCPA treatment is also indicated in Fig. 3 for each subject where data are stated as percent change from baseline, averaged for each day over the two drug periods. The mean percent increases at peak effect were 208%, 305%, and 973% for rats B-10, B-7, and C-14, respectively. This effect is further indi-

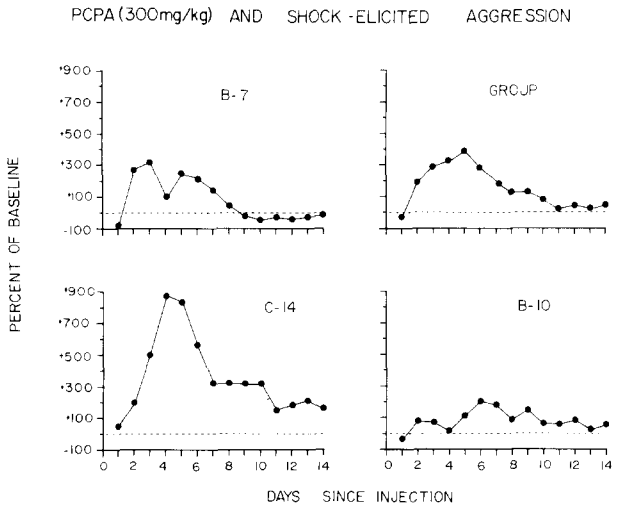

FIG. 3. Effects of 300 mg/kg PCPA upon biting behavior as percent baseline as a function of days since injection. Day 1 entitles those sessions that occurred 10 minutes after PCPA administration. Each point represents the mean percent change, averaged for that day in first and second regimens. The exception to this occurs for B-10 where Days 10–14 represent only the first determination.

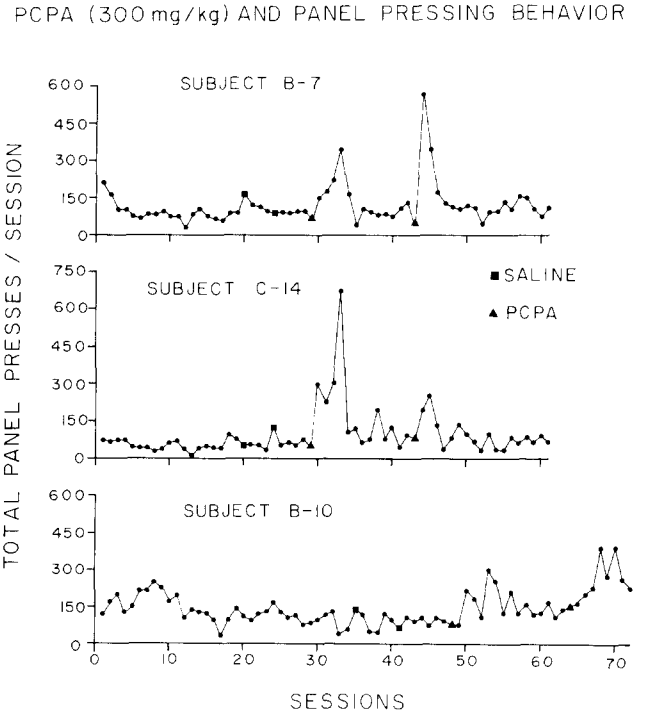

FIG. 4. Total number of panel presses per session across sessions for each subject. (■) Represents behavior during sessions initiated 10 minutes after control injections. (▲) Represents behavior during sessions initiated 10 minutes after 300 mg/kg PCPA treatments.

cated in the percent change from baseline expressed as means for the three subjects, each with two administrations. For the group, the maximum mean percent increase was 380%. Examination of the group plot reveals that maximum enhancement occurred four days after drug treatments. These group data show that biting decreased from this maximum only gradually over the ensuing 5-day period. By Day 10 (post administration), there had occurred a virtual reinstatement of pre-drug attack levels.

In addition to altering overall attack rates, PCPA changed the temporal distribution of biting both within single shock-to-shock intervals and across succeeding shocks during individual sessions. This effect can be noted in Fig. 1 by comparing no-drug records with PCPA records. Typical attack in the no-drug conditions appeared as highly stimulus-bound, occurring immediately after shock delivery. This pattern is exemplified in Fig. 1 for each no-drug record which immediately preceded each of the two treatments for each subject. However, in sessions subsequent to PCPA, attack often continued throughout shock-to-shock intervals with little or none of the baseline pre-shock suppression or immediate post-shock enhancement of biting. Cumulative records taken from the day of peak effect subsequent to each of the two PCPA treatments for each subject illustrate this change in temporal patterning (rat B-10: 1st PCPA, Day 7, 2nd PCPA, Day 6; rat B-7: 1st PCPA, Day 5, 2nd PCPA, Day 3; rat C-14: 1st PCPA, Day 5; 2nd PCPA, Day 4).

Biting attack was not the only response that showed an enhanced rate subsequent to PCPA treatment. PCPA-induced behavioral enhancement was demonstrated for panel-pressing activities. Under no-drug conditions, as shown in Fig. 4, panel-pressing activity developed for all three rats and was considerably lower in both frequency and variability than biting, both within and across sessions. Thus, during the 20-session baseline which immediately preceded first drug treatment, the following panel-press data were obtained (Mean±S.E.): rat C-14: 58±4; rat B-7: 86±6; and rat B-10: 82±6. PCPA treatments enhanced this behavior for each subject subsequent to each treatment (see Fig. 4). After the first and second drug injections the following peak values were obtained for each given subject: rat C-14: 672 and 257; rat B-7: 352 and 563; and rat B-10: 301 and 378. ANOVAR procedures were used to evaluate changes in individual subjects' rates of pressing responses, across the nine days which immediately preceded first drug treatments and the 9-day periods which followed each of the two PCPA injections. ANOVAR analysis revealed significant changes in rates of pressing subsequent to PCPA for both subject C-14, $F(6,26)=3.3181$, $p<0.01966$, and B-10, $F(6,26)=13.0934$, $p<0.00001$, but not for subject B-7, $F(6,26)=1.1882$, $p<0.13388$.

In addition to biting and panel pressing, various other activities appeared augmented throughout several sessions after PCPA administration. Visual inspection revealed that subjects often appeared hyperreactive to touch and handling, urination seemed more copious, and occasional sperm plugs were noted post session. Vocalization became prominent in pre-session preparation periods. On those few post-session instances when subjects made incidental contact with other colony rats, there ensued stereotypical fighting postures similar to those reported by Ulrich and Azrin [38].

DISCUSSION

Individual, stable patterns of post-shock biting were gen-

erated for all three subjects (Fig. 1). These results corroborated those previously obtained in social [38] and non-social procedures with rats [2] as well as with many other species [39]. In addition, stable subject-specific patterns of panel pressing were obtained for each rat in a manner consistent with earlier work [5,6].

PCPA enhanced shock-induced aggression for each subject subsequent to each of two drug administrations (Figs. 1, 2 and 3). This demonstration of increased aggression following treatment by this serotonin depletor is in agreement with Sheard and Davis [32,33] and Ellison and Bresler [12] but is at variance with several other reports [1, 7, 11, 24, 29]. Various lines of indirect evidence have collectively suggested that SIA should increase following PCPA administration. PCPA has increased sensitivity to nocioceptive events [16,37], increased general behavioral reactivity to various stimuli [4, 8, 36], and increased aggression in other procedures including muricide [15,28] and affective attack subsequent to ICBS [13,21]. The present results are in accord with this literature.

The factors which account for the several failures to obtain PCPA-produced enhancements of SIA remain unclear. The suggestion by Sheard and Davis [32] that ISI may be a critical determinant of PCPA effects receives at least partial support in the present results. Sheard and Davis demonstrated increased SIA with an ISI of 15 seconds. The present study employed 3.5-minute ISI's and also produced aggression enhancements.

A second possibility is that short sessions employed in previous studies either precluded observation of, or contributed to an excessive variation in, the effect across investigations. All previous studies have used sessions of 5 minutes duration or less (4.5 min [7]; 5.0 min [24]; 3.0 min [29], for examples). Examination of Fig. 1 in the present study reveals that, even during sessions of peak effect, substantial increases in SIA were often not in evidence until 7–15 minutes following test initiation. This interpretation is confounded however, since differences exist in shock densities employed for this report and those used in studies previously cited.

In addition to biting attack, PCPA treatment increased shock-associated panel pressing for each subject after each of the two drug injections (Fig. 4). This result indicates that PCPA-induced increases in behavioral reactivity are not specific to aggression. Rather, panel-pressing enhancements suggest that PCPA may increase general reactivity to aversive stimuli; thus placing the present results in consonance with other reported PCPA effects in noxious circumstances [14, 31, 32, 37]. As indicated in the results, our incidental observations suggested that several other topographies may have been potentiated by the drug, including reactivity to tactile stimulation, urination, vocalization, and ejaculation of sperm plugs during sessions.

It appears likely that serotonin depletion is functionally related to the enhancement of aggressive and manipulative activities subsequent to PCPA treatment, reported here and elsewhere. Although in this study a single subject design precluded direct assessment of CNS monoamine levels, several previous investigators have demonstrated a time course of PCPA-induced serotonin depletion similar to the time course of our biting and panel-pressing enhancements. Koe and Weissman [22] found CNS 5-HT levels to be maximally depleted for more than 8 days after single 316 mg/kg PCPA treatments. Serotonin did not return to control values until approximately 2 weeks later. Miller, Cox, Snodgrass, and Maickel [26] reported that 400 mg/kg PCPA injections produced 68% maximum depletion, with 5-HT significantly lowered for 12 days. Sheard and Davis [32] produced maximal 5-HT depletion (85–90%) in brain at 3–4 days following single IP injections of 300 mg/kg PCPA. Various authors have shown severe 5-HT depletion at 24 hours post PCPA and recovery requiring up to 14 days [19,30]. In the present study, PCPA-induced biting enhancement reached a maximum at approximately 80 hours. For the group, biting activity was reinstated to baseline about 10 days after drug injection (Figs. 2 and 3).

Various evidence intimates that serotonin may mediate the behavioral suppression generated in situations involving aversive stimuli [14, 34, 35, 40]. Thus, lesions of raphe nuclei, areas known to be dense in serotonergic cell bodies, yield enhanced avoidance acquisition [35]. PCPA treatment reduces the suppressive effects of punishment in the "conflict" procedure [34]. Further, Fibiger *et al.* [14] have demonstrated that PCPA attenuates the decrease in motor activity typically noted in situations involving shock. The present results show that under no-drug conditions, subjects typically attacked less as time preceding next shock decreased (see Fig. 1). Other workers also have noted a general absence of gross-motor behaviors during immediate pre-shock periods [17]. Under PCPA conditions however, the present results indicate a virtual absence of response cessation throughout many shock-to-shock intervals, for all three subjects (Fig. 1). This relative lack of pre-shock suppression under drug conditions appeared to develop gradually within and across sessions through the day of maximum bite frequency. Subsequently, this pattern decayed only gradually through the ensuing week. It is plausible that PCPA enhanced biting attack, normally absent during pre-shock periods, by attenuating behavioral arrest reactions (see [17], for a discussion of these reactions). If so, these results would be in keeping with the notion espoused elsewhere [34] that serotonin is a mediator of behavioral inhibition. Noteworthy in this regard are results [18] that demonstrate accruing facilitation of SIA by simply lengthening ISI's. It may be that serotonergic agents can selectively modulate such facilitation.

In analyzing biogenic amine-attack relations, numerous investigators have discussed Moyer's [27] typology of aggression (e.g., [7, 20, 24]). Moyer [27] has suggested the existence of at least seven distinct forms or types of aggressive behaviors. SIA is subsumed under the "irritable aggression" rubric whereas muricide falls within the "predatory aggression" concept. The variations in reported drug effects across aggression assays have been explained by assertion that different aggression types, and therefore different neurochemical mechanisms, are being manipulated. This explanation has been used to account for discrepancies in PCPA-aggression effects; the enhancement of muricide, versus SIA, which often shows a lack of effect or an actual decrease [1, 7, 11, 24, 29]. The results of this report and others [12, 32, 33] demonstrate increased SIA after PCPA. Such enhancements suggest that failure to obtain PCPA-produced increases in SIA may be a function of the parameter values selected, and not differential manipulation of physiological substrates.

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