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Time-Dependent Effects of PCPA on Social Aggression in Chicks

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BUCHANAN, C. P., E. M. SHRIER AND W. L. HILL. *Time-dependent effects of PCPA on social aggression in chicks.* PHARMACOL BIOCHEM BEHAV **49**(3) 483–488, 1994.—We investigated the effects of para-chlorophenylalanine (PCPA), a serotonin (5-HT) antagonist, on social aggression and brain neurochemistry in young domestic chickens (*Gallus domesticus*). In Experiment 1, the effects of four different doses of PCPA (0, 100, 200, and 400 mg/kg) were examined for 3 days after injection. Immediately after PCPA injection, aggressive pecking was low and then increased over the 3-day test period. PCPA significantly decreased 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), and 5-HT turnover. In addition, the frequency of aggression was negatively correlated with levels of 5-HIAA. In Experiment 2, the time-dependent effects of a single 400-mg/kg dose of PCPA were examined for 5 and 7 days after drug exposure. PCPA-treated chicks observed for 5 days after injection had significantly greater frequencies of aggression 4 days following drug exposure and significantly reduced 5-HT levels when measured on the next day. Similarly, chicks observed for 7 days exibited significantly elevated aggression 5 days after injection, after which their pecking decreased to control levels on days 6 and 7. Coinciding with this behavioral pattern, 5-HT levels from these PCPA-treated chicks when assessed 7 days after drug exposure were the same as those for control birds. We concluded that PCPA increased social aggression in birds, an effect that diminished as brain 5-HT levels recovered over a 1-week period.

Aggression Domestic chicks *p*-Chlorophenylalanine (PCPA) Serotonin

THE NEUROCHEMICAL mechanisms underlying aggression are beginning to be understood. Although multiple neurotransmitter systems are likely to be involved, there is increasing evidence that serotonin (5-HT) plays a primary role in mediating aggressive behavior (10,11,19,21,28,29). Research suggests that a decrease in 5-HT turnover leads to a shift from inhibition of aggression to disinhibition (26). Furthermore, through the use of various animal models, functional reduction of 5-HT activity is associated with increases in aggression, whereas augmentation of 5-HT is related to decreases in aggression (e.g., 24,25,29,33,34).

The effect of the 5-HT antagonist, para-chlorophenylalanine (PCPA), has been especially useful in exploring the neural underpinnings of aggression. PCPA is a potent inhibitor of tryptophan-hydroxylase (18) and, as a result, 5-HT synthesis is severely reduced. Coinciding with its serotonergic actions, Vergnes et al. (33) found that male rats given PCPA showed increased offensive aggression, but that PCPA had no effect on defensive aggression. Other studies have shown that PCPA potentiates brain-stimulated affective attack, isolation-induced aggression, shock-elicited aggression, spontaneous aggression, and predatory aggression in mammals (5,7,8, 23,29,31,32).

Although a number of studies on the effects of PCPA have been conducted, they have been confined to an examination of aggression in mammals; the generality of PCPA's action over aggression in birds has been neglected. Indeed, few studies investigating the effects of PCPA on the behavior and physiology of birds have been published (4,12,13,27). Therefore, the purpose of the present research was to examine the effects of PCPA on social aggression in domestic chicks; social aggression can be defined as unprovoked aggression directed at a conspecific for the purpose of establishing, altering, or maintaining a social hierarchy (1,2).

EXPERIMENT 1

Domestic fowl form dominance hierarchies, or pecking orders, and aggression is a crucial component in establishing the rank order among birds (15,28). In this experiment, we sought to determine the role of 5-HT on pecking aggression in young domestic chicks by examining the time-dependent effects of PCPA. Previously, Koe and Weissman (18) found that 3 days

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after a single dose of PCPA, 5-HT levels in rats were <20% of control levels. Consequently, in the first experiment we examined the effects of PCPA for 3 days after injection.

METHOD

Subjects

Forty White Leghorn domestic chickens (*Gallus domesticus*) of unknown sex were purchased on the day of hatch from a local supplier (Avian Services, Frenchtown, NJ). Chicks were divided randomly into four groups, with 10 chicks in each condition: a control group that received saline (0.9%) and three PCPA (Sigma Chemical Co.) groups based on dose (100, 200, or 400 mg/kg). These doses were chosen to correspond to the range of doses used by previous researchers (18,32). Commercial chick starter (Agway) and water were available ad lib. Subjects were housed by group in standard brood units, which were temperature regulated at 30°C. Lights were maintained on a 12-h photoperiod.

Procedure

Pecking observations. Upon the day of arrival, chicks were marked individually with differently colored permanent ink on the top of the head or breast. This facilitated individual recognition during later behavioral observations (see subsequent description). Preliminary observations revealed that this color coding did not affect pecking frequencies. In addition, individually numbered plastic leg bands were placed on the tarsus of each subject. Chicks were then put into the appropriate brood unit. On this day, and on the next day, no observations were made to allow the chicks to habituate to their new environment.

Observations began on the 3rd day after arrival, and the chicks were observed every day for the next 7 days. The daily observations were categorized as baseline (days B1–B3) and test (days 0–3). During behavioral testing each group was observed for 30 min in the midafternoon, and observations were counterbalanced across groups. During observations, the food and water troughs were removed to prevent the chicks from engaging in feeding or drinking during the test period. We defined aggression as a peck to any part of chick's body by another chick, seemingly provoked by a wide range of stimuli, and often unprovoked; offensive and defensive pecks were not differentiated. Aggressive pecks were usually delivered to the head or breast areas of conspecifics, and rarely to the feet. Any pecks obviously aimed at food that might be clinging to a chick's body were not included because they were considered to be part of a feeding response.

Pecking frequencies were recorded using the behavioral-change focal-group sampling technique (3). Observations were made by an experienced observer who stated into a tape recorder the occurrence of pecks made by each chick toward another during the 30-min period. The observer sat or stood, so that the brood unit was at eye level and an auxiliary lamp provided additional lighting inside the housing unit to aid in subject identification. These data were later transcribed as the total number of pecks per individual chick, for each day of observation.

Forty-five minutes before observations on test day 0, subjects received intraperitoneal injections of either saline or PCPA, according to group assignment. Behavioral observations continued from test day 0 (day of injection) through test day 3.

Neurochemical analyses. After the behavioral observations on test day 3, all subjects were decapitated. Brain dissection over ice was conducted, and the hyperstriatum ventrale (14) was extracted and quickly transferred to liquid nitrogen, where it was stored until neurochemical analyses were performed. Levels of 5-HT, dopamine (DA), and their metabolites (5-hydroxyindoleacetic acid [5-HIAA] and homovanillic acid [HVA], respectively) were determined by high-performance liquid chromatography techniques (20,34).

RESULTS

Pecking Frequency

The pecking data from the baseline observations (days B1–B3) and test observations (days 0–3) were analyzed separately. Pecking frequencies during baseline were entered into a 4 (group) by 3 (day) analysis of variance (ANOVA), with repeated measures over day. Pecking frequencies (Fig. 1) did not differ among groups during baseline, although the main effect of day was significant [$F(2, 72) = 5.08, p < 0.01$]. Aggression on day B1 was significantly greater than on day B2 or day B3 (Tukey's test, $p < 0.05$). There was no significant group by day interaction.

Two of the birds in the high-dose PCPA condition died. One chick died on the afternoon after drug injection and the other on test day 2. The number of subjects in the high-dose group was therefore reduced to eight on test day 3. Data from the test period were entered into a 4 (group) by 4 (day) ANOVA, with repeated measures over day. There was a significant main effect of group [$F(3, 36) = 3.17, p < 0.05$] and day [$F(3, 108) = 9.34, p < .01$]. The interaction of group by day was also significant [$F(9, 108) = 2.77, p < 0.01$]. To examine the interaction, one-way ANOVAs were performed on data from each day and comparisons were conducted with Tukey's follow-up tests. Groups differed on test day 0 [$F(3, 36) = 6.58, p < .001$], test day 1 [$F(3, 36) = 3.18, p < 0.05$], and test day 2 [$F(3, 36) = 3.17, p < 0.05$]; on all 3 days, chicks from the saline group pecked significantly more than the three PCPA groups (Fig. 1). There was no significant difference among groups on test day 3, although the pecking frequency for the high-dose group was now almost twice that of the control group.

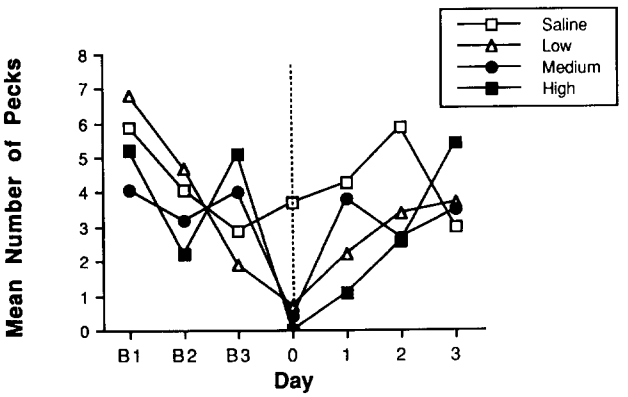

FIG. 1. Mean number of pecks during baseline (days B1–B3) and testing (days 0–3) as a function of PCPA dose. Dashed line (---) represents day on which drug injections were given.

TABLE 1

DOSE-RESPONSE EFFECTS OF PCPA ON BRAIN NEUROCHEMISTRY (MICROGRAMS PER GRAM) 3 DAYS AFTER DRUG INJECTION

	Dose of PCPA (mg/kg)			
Parameter	0 (N = 10)	100 (N = 10)	200 (N = 10)	400 (N = 8)
5-HT	0.895 ± 0.11	0.877 ± 0.09	0.645 ± 0.08	0.582 ± 0.04
5-HIAA	0.385[a] ± 0.03	0.139[b] ± 0.02	0.254[c] ± 0.02	0.062[b] ± 0.01
5-HIAA/5-HT	0.4700[a] ± 0.04	0.1598[b] ± 0.01	0.4436[c] ± 0.06	0.1081[b] ± 0.01
DA	0.9065 ± 0.13	2.0890[a] ± 0.26	1.2341 ± 0.16	2.1327[a] ± 0.09
HVA	0.4201 ± 0.04	0.2099[a] ± 0.04	0.5600 ± 0.06	0.2116[a] ± 0.02
HVA/DA	0.6373 ± 0.16	0.1005[a] ± 0.01	0.4923 ± 0.07	0.0998[a] ± 0.01

Values represent group means ± SE.
[a]Neurochemical levels for groups with different superscripts differed at $p < 0.05$.

Neurochemistry

Neurochemical levels of the hyperstriatum ventrale were analyzed by one-way ANOVAs across PCPA dose. Serotonin levels differed significantly among groups [$F(3, 34) = 2.96, p < 0.05$]. Saline and the low-dose PCPA groups appeared to have the highest levels (Table 1), but Tukey's follow-up test showed this difference was not specific to any group comparisons at the 0.05 level. The serotonin metabolite, 5-HIAA, differed significantly among groups [$F(3, 34) = 40.3, p < 0.01$]: the saline-treated group had a significantly higher level than all three of the PCPA doses, and the medium PCPA dose differed from both the high and the low doses. The ratio of 5-HIAA level to 5-HT level was calculated and used as a measure of 5-HT turnover. Turnover levels differed significantly among groups ($F(3, 34) = 21.0, p < 0.01$). The high- and low-dose groups had significantly less 5-HT turnover than did the saline group and the medium dose group.

Dopamine [$F(3, 36) = 11.3, p < 0.001$], HVA [$F(3, 36) = 10.7, p < 0.001$], and DA turnover [$F(3, 36) = 9.2, p < 0.001$] differed significantly among groups. For all three measures (Table 1), the low- and high-dose groups differed significantly from both the saline and medium-dose groups (Tukey's, $p < 0.05$). For DA, the low- and high-dose groups had significantly elevated levels, whereas HVA levels were significantly lower. Consequently, dopamine turnover (HVA/DA) was significantly lower for the low- and high-dose groups.

Pearson r correlations were performed to determine the relation between aggression on test day 3 and neurotransmitter levels on this day. There was no significant correlation between aggression on test day 3 and serotonin levels or 5-HT turnover. However, there was a significant negative correlation between 5-HIAA levels and aggressive frequency on test day 3 ($r = -0.44, df = 37, p < 0.05$); chicks with low levels of 5-HIAA had generally high rates of pecking. Similarly, HVA levels were significantly correlated with aggression on test day 3 ($r = -0.37, df = 37, p < 0.05$).

DISCUSSION

Contrary to our predictions, the short-term effect of PCPA was a significant reduction in the aggressive pecking of domestic chicks. There was a dramatic decrease in the total number of pecks made by the PCPA-treated subjects on the day the drug was administered (test day 0), possibly because of peripheral effects of PCPA. This decrease appeared to be the result of a drug-induced lethargy; especially in the high-dose group, many of the chicks were sleeping throughout the 30-min of observation. In contrast, when cats are given PCPA there is no alteration in the sleep or EEG patterns during the first 18–24 h after exposure (16,17). This short-term effect of PCPA in chicks should be kept in mind when examining the time-dependent effect of PCPA during the test days.

Exposure to PCPA significantly decreased 5-HT, 5-HIAA, and 5-HT turnover. Although the decline in 5-HIAA and 5-HT turnover was similar to decrements found in rats 3 days after exposure to PCPA (18), 5-HT levels only declined 35% for the high-dose PCPA-treated chicks, whereas serotonin was reduced 80% for rats given a comparable dose. Nevertheless, there was a significant correlation between 5-HIAA levels and aggression, even though pecking did not differ among groups on test day 3. Pecking frequency appeared to increase steadily across the 3 days after PCPA administration, especially for the high-dose group. This continuing rise in aggressive behavior suggests that the subjects may need to be observed for a longer period to determine the complete time-dependent effects of PCPA.

EXPERIMENT 2

According to Koe and Weissman (18), brain 5-HT levels fully recover 15 days after a single dose (312 mg/kg) of PCPA in Sprague–Dawley rats. Similarly, Vallezelli et al. (32) demonstrated low 5-HT levels 1, 5, and 10 days after a 150-mg oral dose of PCPA in Wistar rats. Hence, the full ramifications of exposure to PCPA may not have been apparent in Experiment 1 given the specific time frame used. A longer period of testing was therefore employed in Experiment 2, in which we examined the behavioral and neurochemical effects of a single high dose of PCPA for 5 and 7 days after injection.

METHOD

Subjects

Forty White Leghorn chicks were obtained on the day of hatch and randomly assigned into two PCPA-treated groups and two control groups. One PCPA-treated group was examined for 5 days after drug administration (5-days group), whereas the other was observed for 7 days (7-days group).

Each experimental group had its respective control group. The subjects were banded and housed as in Experiment 1.

Procedure

Baseline behavioral observations began on the 3rd day after arrival, and the same obervation procedures were used as in Experiment 1. On the 4th day of observation (test day 0), PCPA groups were administered 400 mg/kg of the drug, IP, whereas the control groups received saline (0.9%) injections. The groups were sacrificed after behavioral observations 5 and 7 days after injection, according to group assignment. Neurochemical content of hyperstriatum ventrale samples were obtained as described in Experiment 1; however, an additional dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), was also measured.

RESULTS

Pecking

There were no significant differences between PCPA- and saline-treated groups during baseline phases for either the 5-days or the 7-days groups. Five chicks from the two PCPA-treatment groups died during the study: four died on the day of injection whereas one died during baseline. One subject from each of the two saline groups also died during the baseline period.

Pecking data from the 5-days groups during the test phase were entered into a 2 (group) × 6 (day) ANOVA, with repeated measures over day. There was a significant day effect [$F(5, 75) = 3.22$, $p < 0.05$] and a significant group by day interaction [$F(5, 75) = 4.07$, $p < 0.01$]. Comparing the control and experimental groups on each day by one-way ANOVAS yielded a significant difference between groups on test day 0 [$F(1, 17) = 14.76$, $p < 0.001$]. As shown in Fig. 2, the PCPA group exhibited significantly reduced pecking on this day as compared with the saline group. There was a trend toward greater pecking in the PCPA-treated group on test day 4 [$F(1, 15) = 3.09$, $p = 0.09$], when experimental subjects pecked at nearly twice the frequency of that for control subjects.

For the 7-days groups, pecking data during the test phase were entered into a 2 (group) × 8 (day) ANOVA with repeated measures over day. There was a significant day effect [$F(7, 98) = 2.46$, $p < 0.05$] and a significant group by day

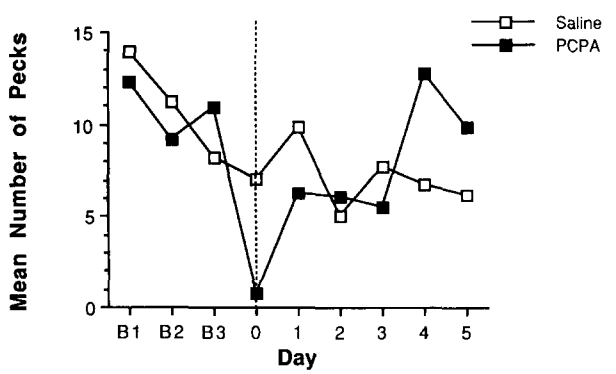

FIG. 2. Mean number of pecks during baseline (days B1–B3) and testing (days 0–5) as a function of saline or PCPA (400 mg/kg). Dashed line (---) represents day on which drug injections were given.

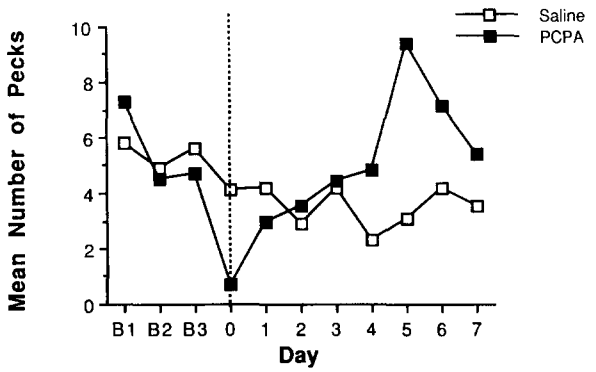

FIG. 3. Mean number of pecks during baseline (days B1–B3) and testing (days 0–7) as a function of saline or PCPA (400 mg/kg). Dashed line (---) represents day on which drug injections were given.

interaction [$F(7, 98) = 3.21$, $p < 0.01$]. Pecking frequency differed significantly between groups on test day 0 [$F(1, 16) = 6.02$, $p < 0.05$]; similar to results from the 5-days group and Experiment 1, the PCPA-treated group showed significantly reduced pecking on the day PCPA was administered (Fig. 3). However, on test day 5 the PCPA-treated birds pecked significantly more than control subjects [$F(1, 15) = 7.68$, $p < 0.05$].

Neurochemistry

Birds exposed to PCPA for 5 days showed a significant depletion of both 5-HT [$F(1, 15) = 26.38$, $p < 0.001$] and 5-HIAA [$F(1, 15) = 109.2$, $p < 0.0001$], as compared with control birds (Table 2). PCPA-treated chicks also showed reduced 5-HT turnover [$F(1, 15) = 27.19$, $p < 0.001$] and significantly lower levels of DOPAC [$F(1, 15) = 5.07$, $p < 0.05$].

Regressing neurotransmitter or metabolite levels on pecking frequency from test day 5 yielded a significant negative correlation between pecking and dopamine turnover (DOPAC/DA: $r = -0.564$, $df = 16$ $p < 0.05$).

No significant differences in 5-HT neurochemistry were found between the two 7-days groups. There was, however, a significant difference between PCPA- and saline-treated birds for DA levels [$F(1, 14) = 7.31$, $p = 0.02$], with experimentals higher than controls (see Table 2). The PCPA-treated birds also showed a trend toward higher HVA levels than controls [$F(1, 14) = 4.57$, $p = 0.0507$].

DISCUSSION

Similar to Experiment 1, chicks administered PCPA exhibited little pecking behavior or general activity on the day of drug injection (test day 0). Aggression, however, increased over days. PCPA-treated chicks observed for 5 days after injection had greater frequencies of aggression 4 days after drug exposure, and their 5-HT levels were significantly reduced when measured 1 day later. Similarly, chicks observed for 7 days exibited significantly elevated aggression 5 days after injection, after which their pecking decreased to control levels. Coinciding with this behavioral pattern, 5-HT levels from these PCPA-treated chicks, when measured 7 days after drug exposure, corresponded with those of control birds.

TABLE 2

EFFECTS OF PCPA (400 MG/KG) OR SALINE ON BRAIN NEUROCHEMISTRY (MICROGRAMS PER GRAM) 5 AND 7 DAYS AFTER DRUG INJECTION

	5 Days Postinjection		7 Days Postinjection	
Parameter	Saline (N = 9)	PCPA (N = 10)	Saline (N = 9)	PCPA (N = 7)
5-HT	0.9626 ± 0.05	0.6544 ± 0.06*	1.0257 ± 0.05	0.8983 ± 0.14
5-HIAA	0.1376 ± 0.005	0.0466 ± 0.007*	0.1492 ± 0.015	0.2126 ± 0.099
5-HIAA/5-HT	0.1456 ± 0.008	0.0724 ± 0.018*	0.1452 ± 0.012	0.3036 ± 0.14
DA	1.9172 ± 0.24	1.3956 ± 0.16	2.2606 ± 0.218	3.1390 ± 0.239*
DOPAC	0.1067 ± 0.014	0.0701 ± 0.007*	0.2219 ± 0.101	0.1571 ± 0.013
DOPAC/DA	0.0565 ± 0.003	0.0508 ± 0.002	0.1034 ± 0.048	0.0505 ± 0.002
HVA	0.2234 ± 0.033	0.1655 ± 0.018	0.1599 ± 0.016	0.2143 ± 0.021
HVA/DA	2.0837 ± 0.101	2.3916 ± 0.127	1.2361 ± 0.165	1.3533 ± 0.052

Values represent group means ± SE. *Significance at $p < 0.05$.

This contrasts with the temporal pattern of PCPA found for rats, for which 5-HT and 5-HIAA levels do not recover until more than 2 weeks after PCPA administration (18,32). The underlying mechanisms that account for the briefer effects of PCPA in domestic chicks remain to be determined. However, given that chicks have been selected for very rapid growth (30), the attendant increase in their basal metabolism might reduce the effective exposure period for PCPA, as compared with the time course found for rats.

GENERAL DISCUSSION

Social aggression in chicks was influenced by PCPA exposure. PCPA affected the levels of 5-HIAA, which were negatively correlated with the frequency of aggression. In addition, the time-dependent decreases in 5-HT and 5-HIAA in Experiment 2 generally coincided with increases in aggression. Nevertheless, the effects of PCPA on the domestic chick contrast with those documented in rats. In Experiment 1, 3 days after a high dose of PCPA, 5-HT levels were 65% that of controls. Koe and Weissman (18) showed that after a similar dose, PCPA-treated rats had 5-HT levels only 20% of controls. Similarly, the time-dependent effects of PCPA are longer in rats than in chicks: alterations in serotonin neurochemistry had returned to control levels after 1 week for PCPA-treated chicks, whereas rats need more than 2 weeks before baseline levels are restored.

Although PCPA is characterized as a specific 5-HT-depleting drug, it also influenced DA neurochemistry in our study. This might be due to an activation of the DA system as a general consequence of the 5-HT imbalance. Or, as noted by Osborne (22), high doses of PCPA could affect the uptake and use of amino acids required for the synthesis of other neurotransmitters, such as dopamine. The effects of PCPA on DA system, however, were not entirely consistent throughout the time frame used in our study. When the effects of a high dose of PCPA are examined across Experiments 1 and 2, DA levels were significantly elevated at 3 and 7 days after injection, but were at control levels 5 days after injection. HVA, which was measured in both studies, was significantly depressed at 3 days after PCPA administration, reached control levels at 5 days after injection, and was significantly elevated by 7 days.

High doses of PCPA, as were used in this study, were toxic to some animals, as shown by subject mortality on the day of injection. This is commonly cited as a disadvantage of PCPA in that high doses are required before behavioral effects become apparent (22). An additional drawback to the use of PCPA is that it reduced growth in our subjects: we observed that PCPA-treated birds did not gain weight at the same rate as did control subjects. This is surprising given that 5-HT has been shown to depress ingestive behavior in chicks (6,9) and hence one would predict that PCPA would increase feeding. Nevertheless, the increases in aggression were not the result of nutritional deficiencies; otherwise, PCPA-treated subjects in the 7-days group would have continued to show high levels of aggression, and yet their pecking decreased during days 6 and 7, coinciding with the time period during which serotonin neurochemistry was returning to baseline levels.

In conclusion, PCPA increased social aggression in birds in a time-dependent fashion, an effect that diminished as brain 5-HT levels recovered over a 7-day period. Domestic chicks recovered more quickly than do rats from a single dose of PCPA and, consequently, the behavioral effects of PCPA were shorter-lived.

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