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Para-Chlorophenylalanine, Serotonin and Killing Behavior[1]

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MICZEK, K. A., J. L. ALTMAN, J. B. APPEL AND W. O. BOGGAN. *Para-chlorophenylalanine, serotonin and killing behavior.* PHARMAC. BIOCHEM. BEHAV. 3(3) 355–361, 1975. – Both p-chlorophenylalanine (PCPA) and PCPA methyl ester were found to reliably induce mouse-killing in non-killer rats only when unusually large doses were used (three successive daily injections of 300 mg/kg) and brain serotonin (5-HT) concentration was drastically reduced (about 90 percent). Neither three doses of 100 mg/kg of PCPA nor p-chloroamphetamine (3 × 3.5 mg/kg) caused similar effects in spite of the fact that these compounds depleted brain 5-HT by 85 percent and 60 percent, respectively. PCPA-induced mouse killing was reversed by 5-HTP (100 mg/kg) only when this serotonin precursor completely restored levels of 5-HT. The topography of PCPA-induced killing did not resemble normal interspecies aggression and was also directed toward rat pups. These findings suggest that 5-HT depletion might facilitate nonspecific killing reactions, but is not a sufficient condition to induce the species-specific predatory behavior in rats.

Para-chlorophenylalanine (PCPA) Para-chloroamphetamine Serotonin 5-Hydroxytryptophan Mouse-killing Rats

BRAIN serotonin has been proposed to function as a neurotransmitter in a central trophotropic system and may exert an inhibitory role in the mediation of several classes of behavior [3]. Evidence for this hypothesis comes primarily from studies which reduce brain serotonin by pharmacological means or by brain lesions. Sufficiently high doses of para-chlorophenylalanine (PCPA) are reported to deplete brain serotonin (5-HT) in rats to about 10–15 percent of normal concentration (85–90 percent depletion) by inhibiting tryptophan hydroxylase, an enzyme required for the biosynthesis of 5-HT from dietary tryptophan [11,15]. Weissman [33] has reviewed the extensive literature on the behavioral effects of PCPA which include dramatic changes such as insomnia [12,30], increased sexual activity [7, 26, 27, 28], and certain aggressive responses [14, 26, 27, 34], hyperreactivity to painful and aversive stimuli [10, 25, 29], hypersensitivity to drugs such as LSD [2], and increased spontaneous motor activity [29,32].

Several investigators have questioned whether or not certain behavioral changes that are induced by PCPA can be attributed to the action of this compound on 5-HT biosynthesis [4, 5, 25] or are drug-specific. Most of the evidence, however, has been in favor of the notion that 5-HT inhibits in some fashion certain behaviors, one of which is predatory killing in the rat [5, 15, 16, 27] and that the effects of PCPA are produced by the removal of this inhibition. Additional support for this hypothesis comes from a study in which mouse-killing was observed in 9 out of 10 and 8 out of 15 rats following destruction of serotonergic neuronal systems by very large raphe lesions as compared to 3 out of 10 and 2 out of 9 rats following sham operations [9]. On the other hand, extensive studies by Vergnes *et al.* [31] and Sheard [27] found also profound 5-HT depletion after discrete raphe lesions, but little or no evidence for lesion-induced mouse-killing behavior.

The purpose of the present experiments was to further explore the relationship between mouse killing and 5-HT. In addition to treating animals with several dosage regimens of PCPA, para-chloroamphetamine (PCAmp) and the immediate 5-HT precursor, 5-hydroxytryptophan (5-HTP) were used to alter whole brain concentrations of 5-HT (15,24).

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In view of recent reports that serotonin-depleting drugs may lead to bizarre behaviors (e.g., unprovoked rearing, indiscriminate mounting behavior, difficulty of handling) which do not occur normally [16, 33, 36], special attention was given to the topography of the muricidal response.

GENERAL METHOD

Animals

Adult, male, albino rats of the Sprague-Dawley strain (Sprague–Dawley, Madison, Wisconsin), weighing 275–325 g were housed individually in a colony with constant temperature (75°F) and a 12 hr (7:00 a.m. – 7:00 p.m.) light cycle. The animals had ad lib access to food and water throughout all experiments.

Behavioral Procedure

One week after arrival in the colony, each rat was tested to determine whether it was a mouse killer or non-killer by placing an adult mouse into its stainless steel home cage (25 X 18 X 18 cm) for 6 hr per day. If the rat neither attacked nor killed the mouse on 3 successive days, it was labelled a non-killer [11] and retained for further experiments. Rats which killed mice on any of the 3 test days were designated as killers and were removed from the experiment. Non-killer rats were then randomly divided into two major groups, the first of which was subjected to various drug treatments and tested on designated days for muricide; animals in the second group underwent drug treatments identical to those of the first group and were sacrificed, decapitated, and assayed for brain 5-HT concentration by the method of Anden and Magnusson [1]. Recoveries for 5-HT were about 95 percent; no corrections were performed. Control samples were always run with experimental samples. The neurochemical data of the first two experiments are summarized in Table 1.

The test for mouse-killing during and following drug treatment followed a procedure identical to that described for the predrug tests. An adult mouse was introduced into the rat's home cage and remained there for maximally 24 hr. Precise latencies and topography of attack and killing behavior (if present) were recorded for the first three hours after introduction of the mouse; thereafter approximate latency was recorded. Since those PCPA-treated rats which started to kill mice did so almost instantaneously (see below), in almost all instances exact latency measurements and description of topography was possible. Serotonin depletion has been frequently reported to result in bizarre and exaggerated behavioral reactions (e.g., [33]); therefore, we attended closely to the topography of the killing behavior. Predatory killing in rats involves a rather stereotypic sequence of several behavioral components. Being confronted with a mouse the rat initially orients towards the mouse and initiates a well-directed pursuit, which ends in seizing the mouse with the front paws and mouth, and positioning it so that the back and neck region are exposed. A very quick attack jump accompanied by kicking movements with the rear feet follows and, eventually, kill biting, directed toward the neck and/or back region, terminates the sequence. Predatory killing is rarely accompanied by bloodshed and very few signs of autonomic activity are detectable in the rat. The most important elements of predatory killing, including seizing of the mouse, attack jump and kill biting, are described in detail by Woodworth [35]. In addition, the mice that were killed were removed shortly after death and were examined for lacerations and sites of bites.

Pharmacological Procedure

All compounds were injected in volumes of 1.0 ml or less and were administered intraperitoneally (i.p.). Doses are expressed in terms of the free acid or base. p-Chlorophenylalanine (PCPA), p-chlorophenylalanine methyl ester (PCPA-ME), p-chloroamphetamine (PCAmp) and DL-5-hydroxytryptophan (5-HTP) were purchased from the Regis Chemical Company (Chicago, Ill.). The control solutions of sodium chloride were at body pH (7.4) or were adjusted to pH value necessary to dissolve the PCPA (pH = 2.8).

EXPERIMENT 1

The first experiment was designed to replicate the earlier reports of muricide in previously non-killer rats following administration of PCPA [14, 18, 27]. A very large dose (300 mg/kg per day for three days) was administered to ensure maximal behavioral effects and serotonin depletion. The PCPA was given in two forms, the free acid and the methyl ester, in order to test whether the more recently synthesized water soluble PCPA methyl ester was as effective as the less soluble free amino acid in producing behavioral and biochemical changes. The original behavioral and biochemical studies were performed with the free acid form of PCPA [11, 14, 15, 27].

Animals and Procedure

The rats were assigned to 3 groups, each of which received either drug or vehicle for three successive days. Group 1 (n = 15) was given 300 mg/kg PCPA; Group 2 (n = 15) was injected with 300 mg/kg PCPA-ME, and Group 3 (n = 15) received volumetrically equivalent amounts of the NaCl vehicle at the adjusted pH (2.8) that was used to dissolve the PCPA. All rats received no injections on the fourth and fifth day. At the time of peak tryptophan hydroxylase inhibition and serotonin depletion [2, 11, 15], on Day 6, six rats in each group were tested for mouse-killing, and the remaining rats were sacrificed and assayed for concentrations of serotonin in whole brain.

Results and Discussion

Administration of 3 daily injections of either 300 mg/kg PCPA or PCPA-ME depleted significantly (about 90 percent) whole brain 5-HT to 50.44 ng/g and 58.67 ng/g compared with saline controls (pH = 2.8) to 465.88 ng/g (t = 29.51, df = 27, $p<0.001$; t = 33.78, df = 27, $p<0.001$; see Table 1).

The free acid form of PCPA induced mouse-killing in four of the 6 previously non-killer rats which survived long enough to be tested on Day 6 (Group 1) and the methyl ester form induced mouse-killing in all 6 animals (Group 2). In both cases, muricide was almost instantaneous, i.e., within 10 sec after the mouse had been placed in the cage, despite the rather debilitated condition of the rats. In the two PCPA-treated animals which died, post-mortem examination of the stomachs and intestines revealed extensive lesions, probably due to the acidity of the injection solution. The rats which had received only vehicle injections

TABLE 1

EFFECTS OF PARA-CHLOROPHENYLALANINE, PARA-CHLOROAMPHETAMINE, AND 5-HYDROXYTRYPTOPHAN ON BRAIN 5-HYDROXYTRYPTAMINE CONCENTRATIONS

Treatment	DAYS 1	2	3	4	5	6	N	5-HT (ng/g ± S.E.)	Percent Change	p†
NaCl (pH = 2.8)	1 cc	1 cc	1 cc			A*	9	465.88 ± 14.48	–	N.S.
NaCl (pH = 7.4)	1 cc	1 cc	1 cc			A	12	468.83 ± 9.84	–	
PCPA	300 mg/kg	300 mg/kg	300 mg/kg			A	9	58.67 ± 7.99	− 87.4	<0.001
PCPA-ME	300 mg/kg	300 mg/kg	300 mg/kg			A	9	50.44 ± 3.75	− 89.2	<0.001
PCPA-ME	100 mg/kg	100 mg/kg	100 mg/kg			A	9	66.44 ± 4.06	− 85.8	<0.001
PCAmp	3.5 mg/kg	3.5 mg/kg	3.5 mg/kg	A			6	183.40 ± 23.80	− 60.8	<0.001
PCPA-ME +5 HTP	100 mg/kg	100 mg/kg	100 mg/kg			100 mg/kg A	5	317.20 ± 93.69	− 32.2	<0.01
NaCl (pH = 7.4) + 5HTP	1 cc	1 cc	1 cc			100 mg/kg A	5	937.0 ± 44.30	+100.4	<0.001

*A = assay †p = statistical difference from vehicle control as determined by standard analysis of variance

(Group 3), did not display any muricidal behavior on the test day. The absence of any killing behavior in the vehicle-injected rats (Group 3) indicates that the pain caused by the injections at the rather low pH level (pH = 2.8) is not the sole cause for the induction of mouse-killing in Groups 1 and 2, although possibly a contributing factor.

The topography of the killing response which was displayed by the PCPA-treated animals differed clearly from that seen in natural mouse-killer rats. In spite of the obvious incapacitation, a PCPA-treated rats captured the mouse very quickly and bit it indiscriminately in any region of the mouse's body. Post-mortem examinations revealed severe lacerations of the mouse's entire body.

These results replicate and extend Karli's [14] and Sheard's [27] earlier observations of PCPA-induced muricide. However, none of the previous reports note the striking topographical differences between natural and PCPA-induced killing behavior. Of course, the unusually high dose of PCPA in the present experiment could account for the indiscriminate killing reaction which we observed.

EXPERIMENT 2

The purpose of the second experiment was to determine the extent to which depletion of brain serotonin is related to the production of muricide in rats. If the muricide observed in Experiment 1 was due to shifts in the levels of brain serotonin, lower doses of PCPA (e.g., 100 mg/kg) should also produce killer rats though perhaps to a lesser extent. Similarly, other serotonin-depleting agents such as p-chloroamphetamine (PCAmp) should produce muricide. Both PCPA and PCAmp inactivate cerebral tryptophan hydroxylase and thereby cause a depletion of brain serotonin, PCAmp having a more prolonged effect than PCPA

[24]. Furthermore, PCAmp appears to affect exclusively brain serotonin, whereas PCPA also inhibits hepatic hydroxylation [24].

Conversely, restoration of depleted serotonin concentrations by the administration of the serotonin precursor 5-HTP [13] to PCPA-treated animals should at least partially block mouse-killing [15,16].

Experiment 2 was also designed to test the effects of prolonged versus one-time (delayed) exposure of mice to PCPA-treated rats since preliminary observations suggested that prolonged exposure of rats to mice while the rats were being treated with drugs might block the induction of mouse-killing.

Animals and Procedure

Because of the difficulty of dissolving the free acid form of PCPA at acceptable pH levels, and because no differences had been found either biochemically or behaviorally between PCPA and PCPA-ME in Experiment 1, we used only the PCPA methylester dissolved in saline (pH = 7.4) in all further experiments.

All rats were assigned to four groups. Group 1 (n = 30) received 100 mg/kg PCPA-ME for three consecutive days; Group 2 (n = 20) rats were injected with 300 mg/kg PCPA-ME; Group 3 (n = 20) was given saline vehicle injections on the identical schedule, Group 4 (n = 12) rats were administered with 3.5 mg/kg PCAmp for three consecutive days. Biochemical and behavioral examinations for the rats of Groups 1, 2 and 3 were conducted on Day 6, and for the rats of Group 4 on Day 4. As in Experiment 1, biochemical and behavioral tests were performed in parallel groups. Specifically, assays for whole brain concentrations of 5-HT were undertaken in Group 1 (n = 9), Group 3 (n = 12), and Group 4 (n = 6). Serotonin concentrations for the 3 X 300 mg/kg PCPA-ME treatment (Group 2) were determined in Experiment 1.

In addition to the treatment schedule outlined above, 10 rats in Groups 1, 2 and 3 each, were housed with a mouse in their home cages from the day of the first drug injection until either the mouse was killed, or the end of Day 6, whichever came first. The remaining half of the rats in these three groups were presented with the mouse on Day 6 only. On Day 6, the day of peak 5-HT depletion, those rats of Groups 1 and 2 that exhibited muricide at anytime after the start of the drug treatment were (1) presented also with 20-day-old rat pups, and subsequently (2) injected with 100 mg/kg of 5-HTP, i.p., and tested after 30 min for mouse-killing. Kulkarni [18] found this dosage to be effectively inhibiting muricide.

Results and Discussion

Seven of the 20 rats which received three daily injections of 100 mg/kg of PCPA methyl ester killed mice either on or before Day 6 (Group 1). This drug regimen reduced brain serotonin concentration by 85 percent to 66.44 ng/g which is significantly less depletion than that produced by the three injections of 300 mg/kg of PCPA methyl ester (t = 2.59, df = 25, $p<0.02$; see Table 1, Fig. 1). Continued presence of the mouse in the rats' test cage resulted in 50 percent killing (5 out of 10). However, 3 out of the 5 rats which killed, did so by the end of Day 2 – before all of the PCPA was administered and thus before maximal serotonin depletion occurred [13]. If the introduction of the mice to the 100 mg/kg PCPA methyl ester group (Group 1) was delayed until Day 6 only 2 out of the 10 rats killed mice, and these animals displayed latencies of up to 7 hr.

The 9 rats which received the 3 consecutive daily injections of 300 mg/kg PCPA methyl ester and survived (Group 2) became killers (Fig. 1). Every rat in this group killed the mouse introduced on Day 6 almost instantaneously (within 10 sec). All rats which were housed with mice for the period of the three 300 mg/kg injections exhibited muricide by the end of the third day.

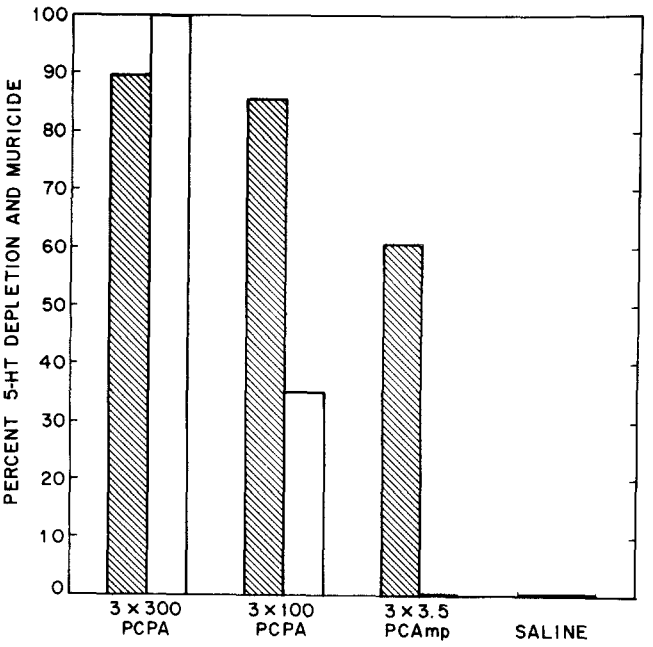

FIG. 1. The effects of three consecutive daily injections of 300 mg/kg PCPA-ME, 100 mg/kg PCPA-ME, 3.5 mg/kg PCAmp, and saline on percent 5-HT depletion (shaded columns) and percent muricide (white columns).

None of the rats that received the 3 saline injections (Group 3) killed mice. Similarly, none of the rats treated with three para-chloroamphetamine injections (Group 4) killed mice despite a statistically significant (65 percent) decrease in brain serotonin concentrations on Day 6 to 183.4 ng/g (t = 14.39, df = 23, $p<0.001$; see Table 1, Fig. 1).

In spite of the high degree of 5-HT depletion with both 3 X 100 mg/kg and 3 X 300 mg/kg of PCPA, surprisingly clear differences in the incidence of mouse-killing were apparent with both treatments. Moreover, most rats which were subjected to either treatment and were housed with a mouse started to kill mice before peak depletion of 5-HT was present. Also, the PCAmp administrations were ineffective in inducing mouse-killing, although this treatment produced a large depletion of 5-HT. These findings suggest a reconsideration of the relationship between the degree of PCPA-induced serotonin depletion and elicitation of mouse-killing.

In the instances were PCPA induced mouse-killing, the topography of the reaction was clearly different from the stereotyped pattern of predatory aggression in killer rats. Indiscriminate and prolonged biting of the mouse's entire body were characteristic of the PCPA-treated killer rat.

TABLE 2

EFFECT OF PCPA-ME AND 5-HTP ON BRAIN 5-HT AND MURICIDE[a]

	Group	N	5-HT (ng/g ± SE)	Killers before final injection	Killers after final injection
1	(3 × SAL + SAL[b])	5	460 ± 14.6	NT[e]	NT[e]
2	(3 × PCPA-ME[c] + SAL)	5	39 ± 4.7[f]	3	3
3	(3 × PCPA-ME + 5-HTP[d])	5	515 ± 31.9	3	0
4	(3 × SAL + 5-HTP)	5	937 ± 44.3[g]	NT[e]	NT[e]

[a]PCPA-ME or saline (SAL) was given on Days 1, 2, and 3. Animals were tested for 30 min on Day 6 for muricide, given SAL or 5-HTP and again tested for muricide 15 min later. The duration of the final test was 15 min. The animals were then sacrificed.

[b]Animals were sacrificed on Day 6, 30 min after last injection.

[c]PCPA-ME dose was 300 mg/kg

[d]5-HTP dose was 100 mg/kg

[e]NT = not tested

[f]Significantly less than Group 1 ($p<0.001$)

[g]Significantly greater than Group 1 ($p<0.001$)

When 20-day-old rat pups, similar in size and appearance to the mice, were presented to PCPA-treated rats on Day 6, all of the 300 mg/kg group killed the pups in less than 2 min. None of the rats which had been injected with the 100 mg/kg (including the rats that had killed mice) attacked the pups.

The administration of 100 mg/kg of 5-HTP on Day 6 did not block the muricidal response in any of the PCPA-induced killers (Groups 1, 2); this may have been due to the fact that 5-HTP did not completely restore normal concentrations of 5-HT (317.2 ng/g after 5-HTP, 468.83 ng/g in normal control; see Table 1).

While serotonin concentrations in animals given 5-HTP as well as PCPA differed significantly from controls (t = 3.23, df = 23, $p<0.01$), they did not differ from animals given PCAmp (Group 4) (t = 1.38, df = 8, $p>0.05$).

EXPERIMENT 3

The results of Experiment 2 suggest that massive depletion (89 percent or higher) of 5-HT by PCPA induces killing behavior in non-killer rats and that depletion to a lesser extent (32–85 percent) does not increase the probability of muricide (as, for example, in PCAmp-treated animals). In contrast to the results of Experiment 2, when 5-HTP failed to block muricide and to replete 5-HT concentrations, the third experiment shows that killing can probably be blocked even in killer rats, if 5-HT concentration is restored to normal levels.

Animals and Procedure

Four groups of rats were utilized in this experiment. Group 1 (n = 5) received saline on Days 1, 2 and 3 and saline on Day 6. Group 2 (n = 5) received PCPA-ME (300 mg/kg) on Days 1, 2 and 3 and saline on Day 6. Group 3 (n = 5) received PCPA-ME (300 mg/kg) on Days 1, 2, and 3 and 5-HTP (100 mg/kg) on Day 6, and Group 4 (n = 5) received saline on Days 1, 2 and 3 and 5-HTP (100 mg/kg) on Day 6. Groups 2 and 3 were tested for muricide for 30 min on Day 6 prior to their final injections. At the end of this 30 min Group 2 was given saline and Group 3 was given 5-HTP (100 mg/kg). Fifteen min later these animals were again exposed to a mouse for 15 min. The incidence and latency of muricide was recorded. At the end of this period the rats of all four groups were sacrificed and their brains assayed for 5-HT [1].

Results and Discussion

Table 2 summarizes the behavioral and biochemical data. On Day 6, in the 30 min test before the final injection, 6 out of 10 rats in Groups 2 and 3, given 3 X 300 mg/kg PCPA-ME killed mice. Of the 3 of these 6 killers that were given 5-HTP (100 mg/kg) no animals killed during the second test period; the 3 killers given NaCl killed a second time. Thus, 5-HTP effectively blocked killing in this experiment. Of the 4 non-killers, neither 5-HTP nor NaCl induced any killing during the second exposure period.

5-HTP effectively increased the concentration of 5-HT in the brains of both normal and PCPA-ME-treated animals (Table 2). Thus, in this experiment animals given 5-HTP, showed at least normal levels of 5-HT (515 ng/g as compared with 460 ng/g in controls). These results confirm the observations by Kulkarni [18,19] who found inhibition of mouse-killing after 5-HTP in natural killer rats, and extend the blocking action of 5-HTP on mouse-killing to PCPA-ME-induced killing.

EXPERIMENT 4

The final experiment was designed to study the time course between serotonin concentration and muricide. Appel *et al.* [2] reported that the increased reactivity to LSD-25 of rats pretreated with PCPA persists until the concentration of 5-HT in brain is restored to normal (by

Day 22 after the initial PCPA injection). If muricide is correlated with brain serotonin concentration, we would expect the muricidal response to persist as long as 5-HT is significantly depleted and to disappear when serotonin concentration returns to normal.

Animals and Procedure

Thirty rats were divided into 4 groups. Groups 1 (n = 7), 2 (n = 8), and 3 (n = 7), received 3 consecutive daily injections of 100 mg/kg PCPA methyl ester and were tested for muricide on Day 6 (Group 1), 13 (Group 2), and 22 (Group 3). Group 4 (n = 9) received saline injections on Days 1, 2, and 3 and was divided into thirds for behavioral testing – 3 rats were tested for muricide on Day 6, 3 more were tested on Day 13, the remaining 3 were tested on Day 22. Brain 5-HT concentrations were not determined in this experiment.

Results and Discussion

Muricide was observed in 4 of the 7 rats tested on Day 6 after 3 injections of 100 mg/kg PCPA methyl ester. No rats tested on Days 13 or 22 exhibited any mouse-killing. Control rats (Group 4) never killed mice. PCPA-induced mouse-killing is apparently only detectable when 5-HT is drastically reduced, but not during the gradual recovery period of 5-HT [15].

This observation suggests further that the role of 5-HT in the mediation of mouse-killing behavior is not of a direct manner. Other behavioral phenomena such as increased reactivity to LSD-25 appear to be much more closely linked to the time course of 5-HT depletion [2].

GENERAL DISCUSSION

The present series of experiments shows that the large doses of PCPA (three successive days of 300 mg/kg) reliably induce muricide in rats which survive the toxic effects of this treatment (Experiments 1, 2, and 3). This behavior is accompanied by massive depletion (about 90 percent) of 5-HT and can be blocked by 5-HTP only if the precursor restores the concentration of 5-HT (Experiments 2 and 3). On the other hand, less drastic depletion of 5-HT either by PCPA (3 daily doses of 100 mg/kg) or by PCAmp (3 X 3.5 mg/kg) does not produce muricide reliably (Experiments 1, 2, and 4).

These findings appear to suggest that the severity of 5-HT depletion determines whether or not PCPA also induces mouse-killing. However, several observations complicate the functional relationship of 5-HT and mouse-killing behavior. A comparison of the presently observed degree of 5-HT depletion and that reported by others shows that our control values as well as depletion values of 5-HT are quite similar, although dissection and assay procedures differed. As a matter of fact, our whole brain values after 3 X 100 mg/kg (50–90 ng/g of 5-HT, representing 85.8 percent depletion from control) or 3 X 300 mg/kg (30–90 ng/g of 5-HT, representing 89.2 percent depletion from control) PCPA are somewhat lower than those reported by others. For example, Sheard [26] found forebrain levels of 5-HT 17–24 hr after 320 mg/kg PCPA HCl ester at 120 ± 32 ng/g (representing 75.3 percent depletion from control), and in another study [27] forebrain levels of 5-HT were measured at 15–18 hr after 400 mg/kg PCPA-ME and amounted to 250 ± 30 ng/g. In both studies, a high incidence of aggressive behavior, including muricide, was reported.

Moreover, when 5-HT depletion is produced by raphe lesions and subsequently mouse-killing is examined also variable results have been reported. Grant *et al.* [9] found about a 70 percent depletion of 5-HT 30 days after extensive lesions in the raphe nuclei and a high incidence of mouse-killing (9 out of 10 and 8 out of 15 killer rats postoperatively). On the other hand, Vergnes *et al.* [31] did not detect any significant correlation between 5-HT depletion and the incidence of mouse-killing in rats after raphe lesions; only 6 out of 20 previously non-killer rats became killers after surgery. Vergnes *et al.* also found no differences in degree of 5-HT depletion between those rats which started to kill mice and those which did not. Also, Sheard [27] did not observe exaggerated aggressive behavior, including muricide, after raphe lesion, although 5-HT was depleted to an extent which was similar to that after PCPA treatment. Of course, a direct comparison of PCPA- and raphe lesion-produced 5-HT depletion is not possible, since there are considerable differences between both procedures in terms of mechanisms of depletion, time course of depletion, reversibility of depletion, central vs. peripheral effect, general incapacitation, etc. [8, 11, 15, 17, 27, 33]. Similarly, the biochemical differences [16,24] in the mechanism as well as degree of 5-HT depletion between PCPA and PCAmp could possibly explain the failure to induce mouse-killing with PCAmp administrations.

A further point of consideration is the topography of the PCPA-induced killing response. When rats did become killers, they often did not only kill on days prior to maximal 5-HT depletion, but in all experiments, the topography of PCPA-induced muricide differed strikingly from that seen in natural mouse-killers (see Behavioral Procedure). A PCPA-treated rat bit indiscriminately at any region of the mouse's body, lacerating the body, and devouring the mouse. The same topography was noted in the killing of the rat pups. The characteristics of the killing response were similar to those observed after septal lesions [22].

Thus, we would argue that although 5-HT may be involved in muricide, its involvement is probably indirect. PCPA-induced 5-HT depletion seems to produce an exaggerated and aberrant killing reaction directed towards mice as well as rat pups. This reaction is clearly different from the natural predatory aggression in rats. The present observations are compatible with Weissman's [33] view that "in the relative absence of 5-HT, animals and man tend to overrespond to social, non-social and possibly internal stimuli, and thereby exhibit varied manifestations of aberrant behavior." Whatever treatments deplete 5-HT probably have effects on brain mechanisms perhaps in the amygdala or septum [14, 20, 22, 23] which might mediate certain aggressive reactions in the rat. The precise relationship of 5-HT to these mechanisms will probably remain unknown until the role 5-HT plays in specific parts of the central nervous system has been delineated.

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