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Facilitation of Avoidance Acquisition in Rats Produced by P-Chlorophenylalanine or P-Chloroamphetamine[1]

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VORHEES, C V *Facilitation of avoidance acquisition in rats produced by p-chlorophenylalanine or p-chloroamphetamine* PHARMAC BIOCHEM BEHAV 10(4) 569–576, 1979 —The effects of reducing brain serotonin using p-chlorophenylalanine (PCPA) were examined as a follow up to our previous report that reducing serotonin with p-chloroamphetamine (PCA) facilitated Y-maze avoidance acquisition and reduced open field activity In the current work, PCPA was also found to facilitate Y-maze avoidance acquisition, while open field activity, although reduced, was not reduced significantly In a second experiment, we re-examined PCA, except that the apparatus was changed in order to test the generality of the effect of PCA on avoidance performance in a task other than the Y-maze Testing was also run at varying shock intensities to determine if this was a significant determinant of the effect PCA reliably facilitated shuttle-box avoidance acquisition and did so at all shock intensities tested Finally, in a third experiment, the time course of the onset of the PCA-induced avoidance facilitation was examined and found to develop 8–10 hours following drug treatment and not at a shorter drug to test interval of 4 hours The present data, in conjunction with our previous data support the concept that lowered brain serotonin content facilitates avoidance acquisition regardless of the specific method used to reduce serotonin or to assess avoidance acquisition

p-Chlorophenylalanine p-Chloroamphetamine Serotonin Y-maze avoidance learning Shuttle-box learning Open field activity

IN a recent publication Kohler and Lorens [8] reported that rats with reduced brain serotonin (5-HT) produced by p-chlorophenylalanine (PCPA) failed to show facilitated two-way shuttlebox avoidance acquisition That a facilitation could have been detected in their test system was demonstrated by the fact that raphe lesioned rats with similar 5-HT reductions were facilitated In apparent contrast to their PCPA finding, we have previously reported data demonstrating that reducing brain 5-HT using a different drug, p-chloroamphetamine (PCA), produced a marked facilitation of Y-maze avoidance acquisition [27] Unfortunately, it has been impossible to conclude whether the discrepancy between these studies was due to differences in the drugs or the apparatus, even though it has been shown that shuttle-box and Y-maze avoidance procedures have some common features [5] As a first step towards reconciling these differences, we sought to test the generality of the effect of 5-HT reduction on avoidance acquisition by testing to see whether PCPA would produce a Y-maze avoidance facilitation similar to that which we had obtained previously with PCA [27]. Open field behavior was also examined since Kohler and Lorens [8] found no change in open field activity with PCPA, whereas we had found hypoactivity with PCA [27].

EXPERIMENT 1

Since the purpose of this experiment was to compare the behavioral effects of PCPA to our previous PCA data we designed this experiment to be identical to our previous study [27] The central question was whether two drugs which act in different ways to reduce 5-HT both produce facilitated Y-maze avoidance acquisition and altered open field activity. As in our earlier experiment the rats were tested at various times after treatment in an open field and/or Y-maze apparatus.

METHOD

Animals

Animals were forty 77 day old male Sprague-Dawley rats

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TABLE 1
PRE- AND POST-TREATMENT BODY WEIGHTS MEAN ± SE*

	Pre-Treatment		Post-Treatment	
	PCPA	Control	PCPA	Control
Period 1	341 2 ± 5 1	345 3 ± 4 9	326 8 ± 4 3†	355 2 ± 6 1
Period 2	340 2 ± 4 0	338 2 ± 4 3	328 5 ± 5 5†	348 7 ± 5 1

*There were 10 animals in each group
Period 1=rats that had begun testing 1–5 days following the last treatment
Period 2=rats that had begun testing 10–15 days following the last treatment
†$p<0$ 02 compared to Control

(Holtzman Co , Madison, WI) housed singly and maintained on ad lib food and water on a 12 hr light-dark cycle.

Apparatus

The open field was 122 cm^2, with sides 30 5 cm in height The floor was painted gray and divided into 16 equal 30 5 cm^2 sections by black lines. Illumination was provided by a 60 W red light and white noise was used for background masking

The Y-maze is an extension of traditional shuttle-box apparatus, except that the addition of the third arm results in two important changes. First, an animal must not only learn when to run, as in a shuttle-box, but also where to run to avoid shock, i e , he must learn a position brightness discrimination Second, because the animal must learn two responses simultaneously, avoidance acquisition is more demanding and hence more gradual than in a shuttle-box [5] Nevertheless, the Y-maze contains the essential element of two-way shuttle-box avoidance tasks, namely, that on subsequent trials the animal must learn to re-enter an area where he was previously shocked The Y-mazes were constructed in triplicate and were automated, each arm was 28×18×15 cm with an 18 cm triangular junction The grid floor was made of 0 6 cm bars spaced 2 0 cm apart The warning stimulus was a 7 W white light at the end of each arm Scrambled foot shock (1 25 mA, 60 Hz AC) was delivered to the floor through a fixed resistance of 270 KΩ

Procedure

Rats were randomly assigned to either the drug or control groups Drug animals received 100 mg/kg of D,L-p-chlorophenylalanine IP in distilled water on 3 consecutive days (PCPA group) Controls received equivalent volumes of distilled water (1 ml/kg) on the same consecutive three days (Control group) Beginning 1 day after the last injection, 5 PCPA and 5 Controls were begun in the open field test and another 5 PCPA and 5 Controls were begun in the Y-mazes Animals tested in the open field on Days 1–5 post-treatment were begun in the Y-mazes on the afternoon of the fifth day This procedure was repeated with separate groups begun in open field or Y-maze testing 10 days following their last treatment The groups tested beginning 1–5 days after their last treatment were termed Period 1 and those tested 10–15 days after treatment were termed Period 2 Thus, 40 animals were used, 20 in Period 1 and 20 in Period 2

Each animal tested in the open field was observed for 3 min/day on 5 consecutive days The number of squares entered and the number of fecal boluses was recorded each day

All animals were tested for 6 consecutive days in a Y-maze brightness discrimination test for 25 trials/day The warning interval was 10 sec and the ITI was 30 sec The test was started by placing the rat in the lighted (safe) compartment On subsequent trials arms were lighted in a random sequence If the rat entered the newly lighted arm within the warning interval an avoidance was recorded, if he did not enter within the warning interval shock came on until an escape response occurred On each trial the rats initial arm choice was recorded as either correct (entry into the lighted arm) or incorrect (entry into the dark arm) Incorrect responses were further separated as incorrect voluntary responses (those preceding shock onset) or incorrect forced responses (those following shock onset) Response latency, intertrial safe arm activity and intertrial crossings (safe arm exits) were also recorded

All data were analyzed by analysis of variance with repeated measures on days or in Experiment 3 on blocks of trials Individual a posteriori comparisons were made using Scheffé tests [17]

RESULTS

The effect of PCPA administration on body weight is shown in Table 1 In Period 1 the PCPA group showed a 4 2% loss in body weight and in Period 2 a 3 4% loss in body weight as a result of the treatment, while their respective controls gained weight during that same interval (2 9% and 3 1%)

The results of open field testing of locomotor activity are shown in Fig 1 The PCPA Period 1 group appeared to be somewhat less active, but the Treatment×Period×Days interaction was not significant, $F(4,64)=2$ 46, $0.05>p<0$ 10 There were no activity differences for Period 2 There were no significant differences in defecation rate for either period (Period 1 PCPA=9 4 ± 2 4, Control=9 2 ± 2 6; Period 2 PCPA=6 4 ± 3 1, Control=5 8 ± 2 6)

The Treatment×Period×Days interaction for avoidances was significant, $F=(5,180)=3.60$, $p<0.01$, whereas the main effect of treatments was not This resulted from the fact that PCPA produced a significant avoidance facilitation among Period 1 animals (overall avoidance rate PCPA=8 8 ± 2 1, Control=4 9 ± 1 6) but not among Period 2 animals (PCPA=4.6 ± 2 1, Control=5 2 ± 1.6) The facilitated avoidance performance of the Period 1 PCPA group may be

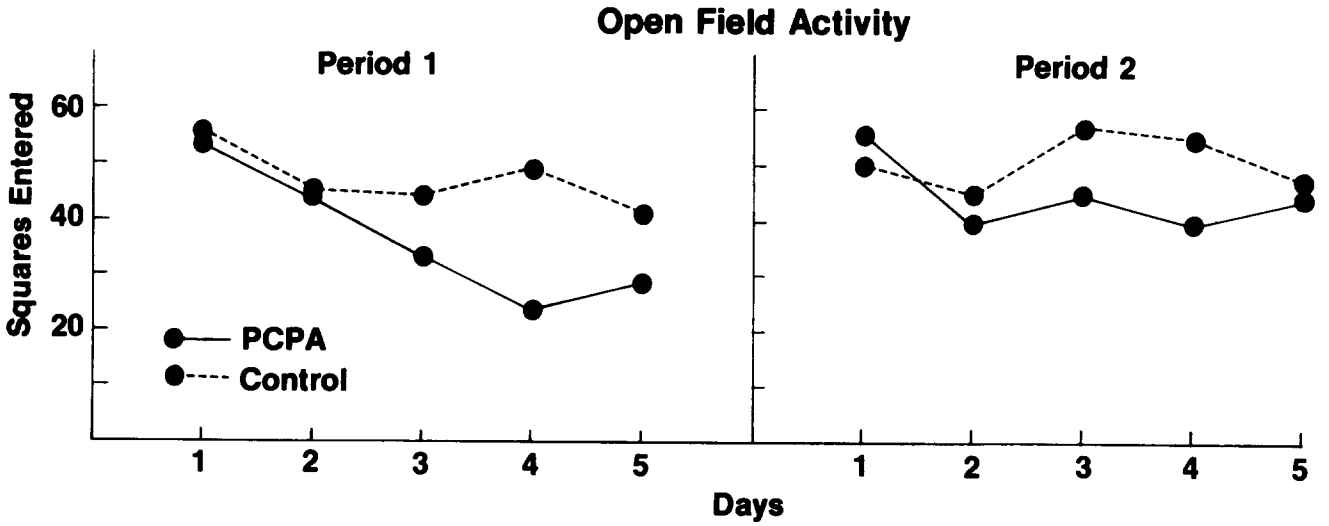

FIG 1 Open field activity in rats treated with 100 mg/kg of PCPA or saline on 3 consecutive days either 1–5 (Period 1) or 10–15 (Period 2) days prior to testing There were no significant differences for either Period 1 or 2 (n=5 per group per Period)

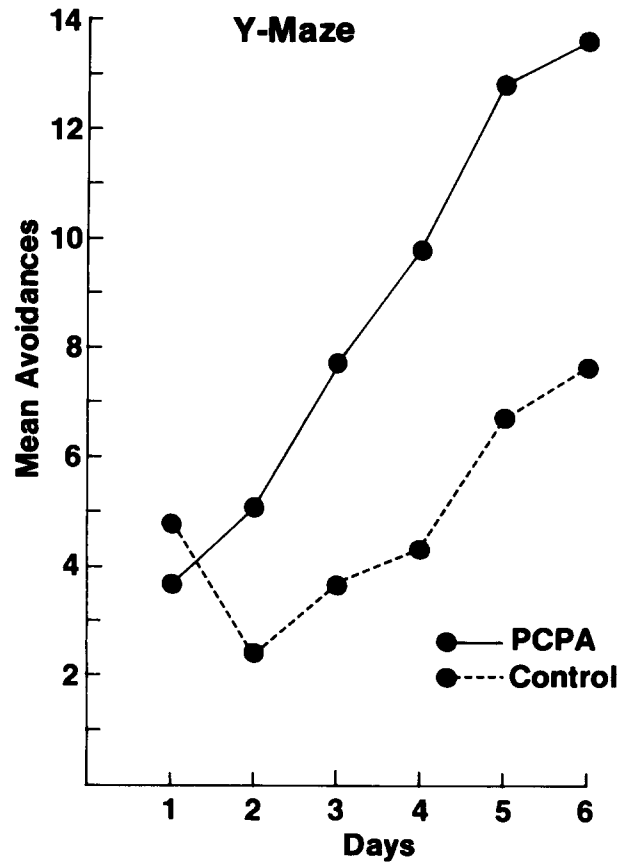

FIG 2 Y-Maze avoidance acquisition for rats in Period 1 There was a significant avoidance facilitation in the PCPA group compared to controls (n=10 per group) There were no differences in Period 2 (not shown)

seen in Fig. 2 Scheffé tests revealed that this facilitation was significant on Days 3–6 of testing

Other response measures recorded during Y-maze testing were consistent with the pattern of avoidance effects seen among the PCPA animals in Period 1, i e., they had shorter response latencies (2356 ± 283 vs 3087 ± 412 sec), increased safe arm activity (292 ± 43 vs 169 ± 23) and more choice errors prior to shock onset (since they were avoiding better) (1.60 ± 0 72 vs 1 40 ± 0.27) than Controls The groups did not differ in the number of safe arm exits between trials

DISCUSSION

A comparison of the Period 1 PCPA induced avoidance facilitation in the present study with that obtained previously in an analogous experiment using PCA [27] shows that the degree of facilitation obtained was virtually identical in the two studies In the previous PCA study, the avoidance facilitation was not limited to Period 1, but extended through Period 2 The failure to find a comparable avoidance facilitation in the Period 2 PCPA group in the present study is not surprising, however, since it has been well established that brain 5-HT levels return to normal within 10–14 days following PCPA treatment [10,12] This is in marked contrast to the effects of PCA which reduces brain 5-HT for at least 4 months [12,13]

Thus, the results of Experiment 1 are at variance with those of Kohler and Lorens [8] with regard to PCPA induced avoidance facilitation but are in agreement with regard to open field effects The reason for the difference in avoidance findings is not clear, but might be related to testing sequence and/or number of trials Whereas Kohler and Lorens [8] used a single massed 50 trial session to assess avoidance acquisition, a distributed procedure of 25 trials/day over 6 consecutive days was used here Accordingly, we found no group separation in the first two days (50 trials), the point comparable to that where Kohler and Lorens ceased testing. It was not until the third day of testing that the enhanced performance of the PCPA group became evident and statistically reliable It is not possible based on our current results

to determine whether the differences we observed were in fact due to the larger number of trials employed (150 vs 50 for Kohler and Lorens) or whether differences in trial distribution, task or some other factor was most critical to the effect

In contrast to avoidance acquisition, distributed trials made no difference in open field performance, a finding in accord with that of Kohler and Lorens [8] It is noteworthy, however, that there was a trend toward departure of the PCPA group from Controls in Period 1 during the last 3 days of testing and the direction of this trend was the same as that which we had previously reported from PCA [27], viz., hypoactivity rather than hyperactivity as has been reported by others using PCPA [6] Note that this effect apparently does not generalize to stabilimeter activity, which has been reported to be increased by PCA treatment [9,25]

EXPERIMENT 2

The results of Experiment 1 and our previous PCA study support the hypothesis that it is the reduction of brain 5-HT that mediates facilitated Y-maze avoidance acquisition, since PCPA and PCA have little in common other than that they both deplete 5-HT. The issue might be resolved except for the data of Kohler and Lorens [8] that PCPA produced no facilitation of shuttle-box avoidance acquisition under their experimental conditions. They interpret their data as indicating that 5-HT reduction per se is not sufficient to produce facilitated avoidance acquisition [8]. Unfortunately, the situation is unclear because PCPA affects 5-HT generally and is not CNS specific In contrast, PCA is a specific depletor of brain and only brain 5-HT [13, 14, 15] Therefore, for purposes of examining the role of 5-HT reduction in facilitating shuttle-box avoidance acquisition PCA represents a cleaner drug than PCPA and was therefore used in this experiment We also examined the influence of shock intensity in this experiment because of the suggestion that the effects of PCPA on avoidance acquisition may be shock intensity specific [26]

METHOD

Animals

Animals were 54 male Sprague-Dawley rats (Zivic-Miller Laboratories, Glenshaw, PA) 69 days of age at the time of treatment Housing, lighting and feeding were the same as in Experiment 1

Apparatus

Six identical shuttle-boxes were used. Each consisted of two identical compartments (23×20×17 cm) with grid floors made of 0.6 cm bars spaced 2.0 cm apart A 7 5 W bulb mounted on each side on the lid served as the warning stimulus

Procedure

Animals were randomly assigned to either drug or control groups. Drug group rats received a single IP injection of 6.0 mg/kg of D,L-p-chloroamphetamine HCl (5.0 mg/kg free base). This dose has been shown to produce a 60% reduction in brain 5-HT within 4 hr that remains at least 40% reduced for 30 days without affecting peripheral 5-HT [13, 14, 15, 16, 25, 27]. Controls received an equivalent dose of physiological saline (1 ml/kg) Each group was then subdivided into 3 subgroups for avoidance testing at one of three shock intensities One-third were tested using 0 50 mA, one-third using 0 75 mA and one-third using 1.50 mA. All rats were tested for 9 consecutive days beginning 1 day following injection Rats were tested for 25 trials/day, the warning interval was 10 sec, the ITI interval 30 sec and testing at each shock level was balanced for time of day. Responses measured were avoidances, response latency, safe side activity and intertrial crossings

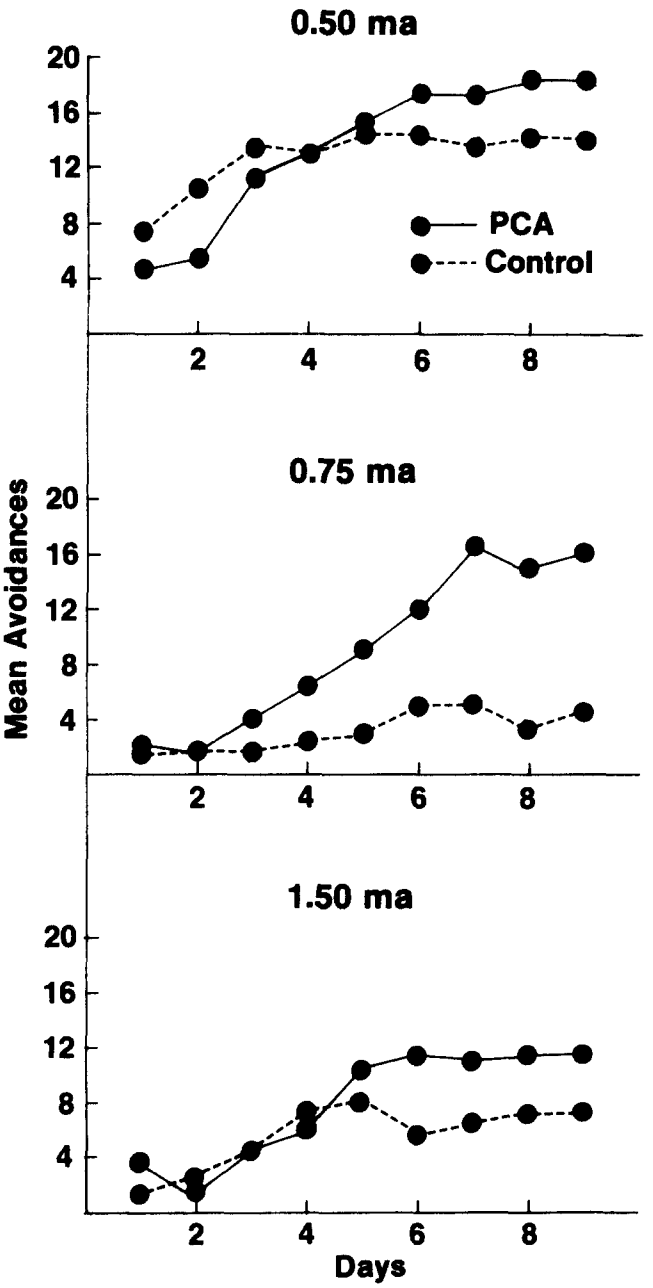

FIG 3 Shuttle-box avoidance acquisition at 3 different shock intensities in rats treated with a single injection of either 6 mg/kg of PCA or saline 24 hr prior to the first day of testing There was a significant avoidance facilitation across all shock intensities (n=9 per group per shock intensity)

RESULTS

The PCA group weighed 360.6 ± 4 2 g and the Controls 368.2 ± 4 1 g prior to treatment. PCA produced a transient weight reduction which was recovered within 72 hours (359.8 ± 3.7) Controls gained weight during this same 72 hr interval (381.0 ± 5.0) and hence were significantly heavier than PCA animals ($p<0.01$).

Avoidance acquisition curves at each foot shock intensity are shown in Fig. 3. The PCA groups avoided significantly better than controls at all shock intensities as indicated by the Treatment×Days interaction, $F(8,374)=9.96$, $p<0.001$ Overall the PCA group performed significantly better on Days 5–9 by Scheffé comparisons. The main effect of shock intensity was also a significant factor, $F(2,47)=5.48$, $p<0$ 01, the higher the shock intensity the poorer the avoidance performance irrespective of drug treatment; however, somewhat surprisingly the Treatment×Shock intensity and the Treatment×Shock intensity×Days interactions were not significant. Thus, although the largest PCA induced avoidance facilitation was produced at the intermediate shock intensity (0.75 mA) this larger departure did not contribute significantly more to the overall effect of PCA than did the PCA groups at the other two shock intensities

The effect of PCA on avoidance was also reflected on the other dependent measures recorded in the shuttle-boxes, viz., response latencies were shorter in PCA groups than Controls (251 ± 8 and 309 ± 31 sec, respectively) and activity (safe arm and intertrial crossings) of PCA groups was greater than for Controls (safe arm activity PCA=36.0 ± 1 4 vs Control=28.4 ± 1.4 and intertrial crossings PCA=3 1 ± 0.4 vs Control 1.4 ± 0.2).

DISCUSSION

The results of Experiment 2 clearly demonstrate the replicability of the PCA induced facilitation of avoidance effect [27] even when using a different avoidance task. These data do not resolve whether or not this facilitation is the result of an altered pain threshold as has been suggested, but these data differ with previous findings that 5-HT depletion with PCPA only facilitates avoidance at low shock intensities [26]. It may be argued that PCA induced 5-HT depletion is different from that produced by PCPA and that such a difference could explain the discrepancy in results, but it seems equally likely that the discrepancy is a function of the interaction between 5-HT depletion induced facilitory effects and the combined influence of the shock intensity and task requirements. It is clear from our data that the more difficult the task the higher the shock level needed to obtain adequate avoidance learning (cf. Y-maze shock level with shuttle-box) Thus, it appears that there must be a compatability of factors before the facilitory effects of 5-HT reduction can be revealed. In our situation a shock intensity of 0.75 mA appeared to be optimal in relation to the difficulty of the task and the amount of drug induced change in behavioral response This conclusion must be tempered by the observation that since the Treatment×Shock level and Treatment×Shock level×Days interactions were not significant, a detailed interpretation of the effect of shock intensity is not possible

EXPERIMENT 3

It has been suggested recently that even though PCPA, PCA and raphe lesions are all capable of facilitating avoidance performance in certain contexts, that these effects may be due to factors unrelated to the 5-HT depleting influence of these treatments. Kohler and Lorens [8] suggest that raphe lesions may damage other structures that mediate the facilitation of avoidance in such lesioned rats. Others have suggested that catecholamine changes are responsible for avoidance facilitations seen shortly after PCA administration [24] If it is true that 5-HT is not involved in the avoidance facilitation produced by PCA, then there should be no satisfactory relationship between the temporal effects of PCA on 5-HT and avoidance acquisition. We sought to test this possibility by comparing the effects of PCA on shuttle-box avoidance acquisition at either 4 or 8 hr following treatment. At 4 hr the effects of PCA on catecholamines are waning [10], while the effects on 5-HT are waxing [25]. At 8 hr, the 5-HT depleting effects are dominant [25]. We anticipated that avoidance facilitation from PCA would be time dependent and that a facilitation would begin to appear at 4 hr and increase by 8 hr.

METHOD

Animals

Animals were 36 male Sprague-Dawley rats (Zivic-Miller Laboratories, Glenshaw, PA) 70 days of age at the time of treatment Housing was the same as in Experiment 1.

Apparatus

The shuttle-boxes were those used in Experiment 2. The shock intensity used was 0 75 mA

Procedure

The rats were divided as in Experiment 2 and received the same IP dose of PCA (6.0 mg/kg) or saline (1 ml/kg). Half of each group began testing 4 hr following treatment and were tested for 3 hr and 20 min, i.e., 10 blocks of 25 trials, each block lasting 20 min (including a 3 min time-out interval to record data at the end of each block). The other half were tested in the same way beginning 8 hr after treatment

RESULTS

As in Experiment 1 the PCA treated groups showed an initial weight loss At 24 hr the weight reduction in the PCA group was 3.4%. The PCA groups initial weight was 373.5 ± 9.9 and the Control groups was 360.7 ± 7.0 and at 24 hr post-treatment they were 360.8 ± 9.8 and 363.7 ± 7 2 g, respectively (neither difference was significant) This is comparable to that reported by others 24 hr after treatment [22], but it should be noted that weight reductions of up to 6% have been reported using this same dose of PCA 3 hr following injection [20,21].

The results of PCA on avoidance acquisition is depicted in Fig. 4. The only significant effect other than blocks was the Treatment×Test interval×Blocks interaction, $F(9,288)=3.48$, $p<0$ 001. Individual Scheffé comparisons revealed that the 8 hr PCA group was avoiding significantly better than Controls from the sixth block of trials onward, i.e., from 2 hr into the test session onward or 10 hr from the time of treatment. The 4 hr PCA group, on the other hand, actually performed slightly worse than Controls, this being significant, however, only on Bocks 5 and 6

DISCUSSION

The results of Experiment 3 demonstrate that the effects

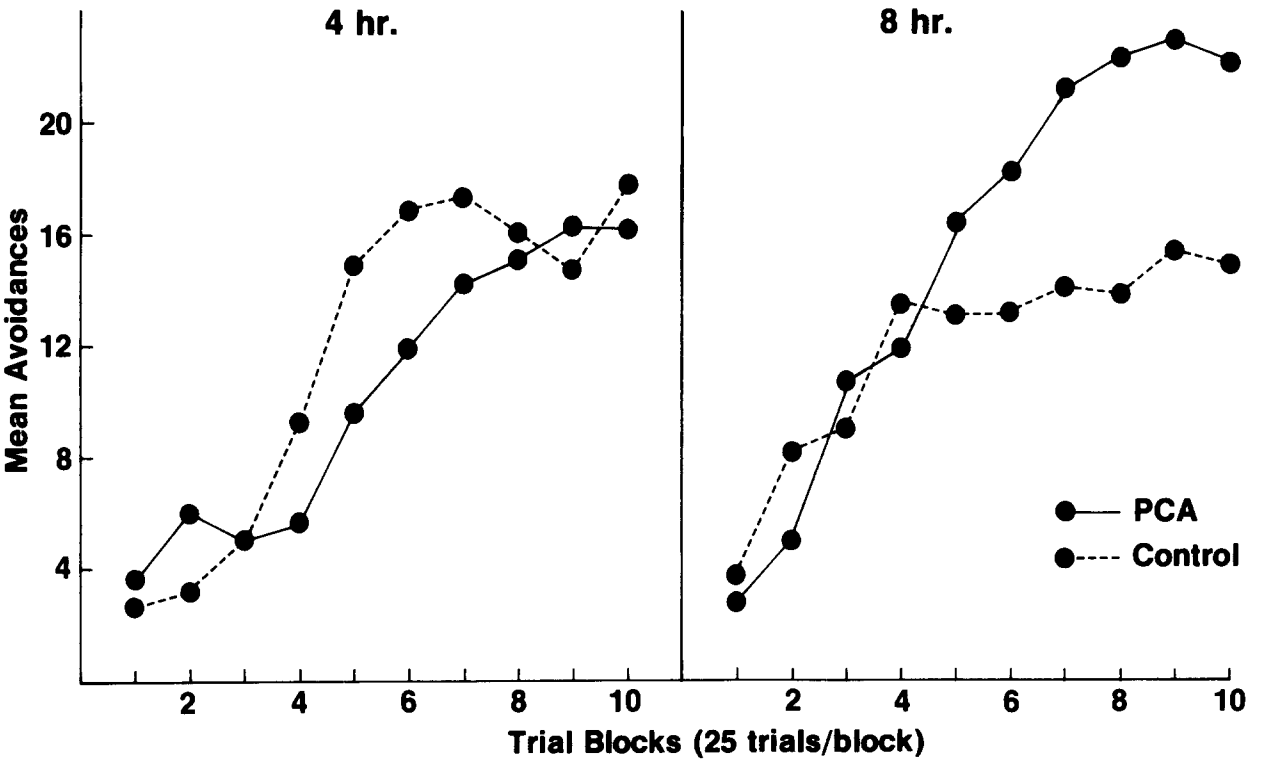

FIG 4 Shuttle-box avoidance acquistion as a function of time since treatment with either 6 mg/kg of PCA or saline Each block of 25 trials lasted 20 min The only significant effect was the facilitated avoidance performance of the 8 hr PCA group (n=9 per group per test interval)

of PCA occur fairly early after treatment, but not quite as early as we had anticipated, i.e , not until 8–10 hr Others have found Sidman avoidance facilitation at shorter intervals, 2–3 hr, that disappeared by 4 hr [24]. These authors provide evidence that this early effect of PCA is adrenergically mediated and the time course of the avoidance facilitation they observe is consistent with that interpretation [24], it is also consistent with other evidence that PCA produces an increase in catecholamines lasting about 4 hr [10]. But there may be a second phase of avoidance effects, with a longer time course that is serotonergically mediated The question that arises is why the previous authors using Sidman avoidance found no facilitation at longer intervals such as we have found in Experiment 3 if there is a second serotonergically mediated avoidance phase? The answer may be related to the fact that the study using Sidman avoidance involved a non-acquisition paradigm The rats were pretrained and were not learning to avoid when the drug was administered. The effects of serotonin depletion may not be evident in non-learning situations, since 5-HT, if it acts by mediating stress induced response suppression, may not be playing a prominent role in an ongoing behavior such as Sidman avoidance in which the animals have already become fairly efficient at avoiding shock In contrast, in an acquisition paradigm the animals initially receive considerable shock and since shock generally tends to suppress active responding, this process slows avoidance acquisition, except in the situation in which 5-HT is depleted In this situation the inhibiting effect of 5-HT is reduced and hence freezing reactions to shock are reduced Since reduced freezing behavior is more compatible with avoidance learning, faster acquisition occurs (see references [1, 2, 3, 5, 23, 27] for fuller discussions of this concept)

GENERAL DISCUSSION

The results of the current experiments suggest that 5-HT reduction produced by PCPA is capable of facilitating avoidance acquisition, but the effect may be limited to instances in which distributed avoidance trials are provided In any event, the facilitory effect of PCPA on avoidance appears to dissipate by about 10–15 days after treatment, a finding consistent with the recovery interval for brain 5-HT [10,12] Finally, the facilitory effect of PCPA on avoidance acquisition does not appear to generalize to hyperactivity in an open field, indeed the trend we observed in open field activity tended to be in the direction of hypoactivity

Regarding the effects of PCA, the present data replicate our previous findings showing a significant facilitation of two-way avoidance acquisition [27]. However, there is a contradictory report in the literature in which PCA was found to produce an impairment in shuttle-box avoidance acquisition rather than a facilitation [11] That study differed from ours in several important respects Rats were pretrained to escape shock prior to drug administration and the test population was selected to eliminate rats that tended to freeze in response to shock during training. If 5-HT mediates a response suppression system, this selection procedure could be critical since rats that may be most disinhibited by the drug would have been eliminated prior to testing

Perhaps of greater relevance to the present findings are the reports that a single dose of PCA facilitates stabilimeter activity for up to 3 days [9] and decreases shock jump thresholds for up to 1 day following treatment [19] It seems probable that these changes, although transitory, initiate more rapid avoidance acquisition during the first few days of learning, days which are crucial in determining the ultimate shape of the learning curve. Moreover, Sheard and Davis [19] also found that shock thresholds were increased 15 min after treatment, which may explain in part why in Experiment 3 of the current study, the 4 hr post-injection group showed no avoidance facilitation, while the 8 hr group did show facilitation Apparently PCA produces a bi-phasic change in pain sensitivity that may substantially contribute to changes in avoidance performance

The PCA data also showed that facilitated avoidance acquisition occurred over a fairly broad range of shock intensities, although as can be seen in Fig 3, the effect was not entirely uniform across all shock intensities tested Thus, it appeared that although avoidance rates in both groups decreased as shock intensity increased, the largest facilitation seen among the PCA groups compared to their respective controls was at the intermediate shock level even though the Treatment×Shock intensity effect was not significant Qualitatively, however, it appeared that there was a larger decrease in avoidance rate among controls than in PCA groups with increasing shock intensity. The major part of this decrease in avoidance rate occurred between the lowest and middle shock levels for controls, whereas for the PCA groups the major decrease in avoidance rate occurred between the middle and highest shock levels. This pattern of effects tends not to support previous data on PCPA that reducing brain 5-HT increases avoidance responding only at low shock intensities [26] or that it increases activity only to high shock intensities [7]

The present data, when viewed in the larger context of other manipulations that reduce brain 5-HT, appear consistent Thus, reducing brain 5-HT using 5,6-dihydroxytryptamine (5,6-DHT) produces facilitated shuttle-box avoidance acquisition [4], reducing 5-HT using PCPA produces facilitated pole climbing [26], platform jumping [18] or Y-maze (present study) avoidance acquisition, reducing 5-HT using PCA produces facilitated Y-maze [16,27] or shuttle-box (present study) avoidance acquisition and reducing 5-HT using raphe lesions produces facilitated Y-maze [23] or shuttle-box [8] avoidance acquisition.

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