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Research report

p-Chlorophenylalanine-induced serotonin depletion: reduction in exploratory locomotion but no obvious sensory-motor deficits

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Abstract

Para-chlorophenylalanine (PCPA) depletes central serotonin (5-hydroxytryptamine, 5-HT) by inhibiting tryptophan hydroxylase, an enzyme necessary for the synthesis of 5-HT. The effects of a wide range of PCPA doses (150–1000 mg/kg) on spontaneous exploratory locomotor activity in a novel environment, activity in running wheels and a number of sensory-motor capacities were examined. Administration of 1000 mg/kg PCPA reduced whole brain levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid to 9.4 and 8.2% of control levels, respectively. Treatment with PCPA produced a dose-dependent decrease in exploratory locomotion in an unfamiliar automated open field relative to vehicle-treated animals. Further, all measures of general, horizontal and vertical activity were suppressed by PCPA treatment. In contrast to previous work, hyperactivity of rats chronically housed in cages with running wheel access was not observed. In their home cages, some PCPA-treated rats exhibited hyper-reactivity to cutaneous stimulation. No other sensory-motor deficits were apparent. Previous theories of 5-HT function state that its action may be to inhibit motor activity or promote sleep. The present results challenge this view and suggest that 5-HT, at least in certain environments, may stimulate locomotor activity without directly controlling various sensory-motor capacities in rats.

Key words: Exploratory locomotor activity; *p*-Chlorophenylalanine; Serotonin; Serotonin depletion; Rat

1. Introduction

Serotonergic neurons in the midbrain raphe nuclei project both caudally and rostrally along the entire neuroaxis [1,38]. The extent of serotonin (5-hydroxytryptamine, 5-HT) innervation of the forebrain has led to the assumption that, rather than controlling specific aspects of behavior, 5-HT may exert a more general effect over behavior such as control of activity levels, behavioral inhibition, arousal mechanisms and the sleep-waking cycle [20,34].

The role of 5-HT in the control of locomotor activity has been investigated by depleting 5-HT using *para*-chlorophenylalanine (PCPA), an inhibitor of the 5-HT-synthesizing enzyme tryptophan hydroxylase [21]. Despite extensive investigations, however, there is no consensus regarding the effects of PCPA administration on locomotion. Using various PCPA doses and procedures to assess locomotor activity, both decreases and increases in locomotor activity have been reported. Generally, increases in activity after 150–400 mg/kg PCPA have been reported when locomotion was assessed in a familiar environment (e.g., a home cage with running wheel access) [4,13,19,26]. The enhancement of locomotor activity in familiar environments after PCPA administration is mimicked by lesions of the median raphe [19].

Activity of rats placed in an unfamiliar environment may differ from locomotion in home cages or running wheels in that it includes behaviors such as frequent walking, sniffing, climbing and rearing which have been regarded as 'novelty reactions' and 'exploratory' responses [3,8]. Detailed analyses of such exploratory activity have shown that in an unfamiliar open field, rats establish a home base from which they explore the surrounding environment [10]. For such exploratory locomotor activity in unfamiliar environments, both increases [13,28] and decreases [26,37], as well as no change in locomotor activity [22] have been reported after PCPA treatment.

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Similarly, both reduced [16,23] or unchanged [24] open-field activity has been observed following intraventricular infusions of the 5-HT neurotoxin 5,7-dihydroxytryptamine.

Although studies of the effect of altering brain serotonergic function have not yielded any simple conclusion, other data suggest that serotonin may play a role in the central control of motor activity. A series of mainly pharmacological investigations have indicated that ascending serotonergic pathways exert an activating effect on the neocortex and hippocampal formation that is closely coupled to the performance of certain motor activities [40]. Recordings of the activity of raphe neurons [14] or measurement of 5-HT release [43] are consistent with this in suggesting a correlation between serotonergic function and motor activity. Despite the large amount of data available relating 5-HT transmission to locomotion, however, very conflicting views exist with regard to the precise nature of this serotonergic control over activity and behavior [34].

In the present experiment, we characterize the changes in open field exploratory locomotor activity of rats after PCPA treatment. Using a digitized activity monitor, we measured changes in a variety of movement patterns separately over a 1-h period. Further, we studied the effect of a wider range of doses than was done in previous work and also re-investigated the effect of PCPA on running wheel activity. Finally, we subjected rats to a number of additional behavioral tests to assess the general sensory-motor capacities of rats treated with PCPA. Thus, we hoped to determine whether sensory-motor deficits, especially after high doses, contribute to alterations in locomotor activity after PCPA administration.

2. Materials and methods

2.1. Open-field exploratory activity and sensory-motor tests

2.1.1. Subjects

Forty male Long–Evans rats (260–300 g) were used. The rats were housed individually in wire-mesh cages. Food and water were freely available. In addition to the regular lab chow diet, the rats were provided with a mash consisting of lab chow pellets, water and sucrose. In previous work, we have found that this diet reduces the weight loss that is associated with PCPA treatment at high doses by approximately 50% (unpublished observation). Prior to any behavioral tests, all rats were removed from their home cage, individually handled and placed on a large open-field arena in groups of twelve for approximately 30 min every day for 5 days prior to drug treatments. Thirty-two rats were used for the additional running wheel experiments and twenty-four rats were used for the parallel biochemical analyses.

2.1.2. Drug treatment

PCPA (Sigma Chemical Company) was suspended in gum arabic solution. For the open-field and sensory-motor tests, five groups of rats ($n = 8$) were used, receiving the following injections over 2 consecutive days: (1) 2 × 500 mg/kg PCPA; (2) gum arabic and 500 mg/kg PCPA; (3) gum arabic and 150 mg/kg PCPA; (4) 2 × gum arabic; (5) no injections. Behavioral testing occurred between 08.00 and 16.00 h 3 days following the last injection.

2.1.3. Open-field exploratory locomotor activity

The apparatus consisted of six Digiscan Animal Activity Monitors (Omnitech). Each monitor included a 40 × 40 × 30.5 cm open field, a grid of infrared beams mounted every 2.54 cm horizontally, and one vertical grid 11.5 cm above the floor. Beam interruptions were recorded by means of a microcomputer. The following movement characteristics were measured. (i) General: total distance travelled, average distance travelled per movement, average speed per movement. (ii) Horizontal: number of horizontal movements, time in horizontal movement, time per horizontal movement. (iii) Vertical: number of vertical movements, time in vertical movement, time per vertical movement. This is largely a measure of rearing activity. Rats were individually placed in an activity monitor and the locomotor activity was monitored for 12 consecutive 5-min samples (60 min total).

2.1.4. Sensory-motor tests

Sensory-motor function was evaluated using tests outlined below.

2.1.4.1. Reactivity to stimuli applied to the feet. Using a Q-Tip (a thin wooden stick with one end tightly wrapped in cotton fibers), the feet of rats in their home cage were lightly touched. Responses were recorded manually, including withdrawal of the foot, orienting responses of the head, whole body turns and severity of the response.

2.1.4.2. Hanging duration. A rat was suspended by the forepaws on a horizontal wire 83 cm above a box filled with sawdust. The latency to fall off the wire was determined with a stopwatch. Each rat received three trials with 15-s intervals between trials.

2.1.4.3. Limb strength. A rat was placed on a 16 × 13 cm wire grid which was connected to a spring scale by a 23-cm long wire. Once a rat had a firm grip on the wire grid with all four paws, it was pulled backward by the base of the tail. The spring scale indicated the force of pull a rat tolerated before letting go of the wire grid. Each rat received three successive trials.

2.1.4.4. Platform climb-down test. A rat was placed on an elevated, exposed platform (9 cm diameter, 21 cm above ground) and the time a rat took before climbing down and placing all four paws on the ground was measured with a stopwatch. Each rat received three trials. Any movement abnormalities during climbing were noted by the experimenter.

2.1.4.5. Swim test. The apparatus used was a circular water pool in which two planks were inserted parallel to each other and 30 cm apart to create a straight swim alley (1.5 m length). At one end of the alley, wire mesh suspended on the pool wall provided a rat with a 30 cm high vertical climb out of the pool to a horizontal escape platform attached to the pool wall. A trial consisted of placing a rat in the swim alley opposite to the wire mesh, allowing the rat to swim down the alley and climb out of the pool onto the horizontal platform. The time required to swim from the start point to the alley end was measured with a stopwatch. Further, the experimenter noted whether a rat climbed out of the pool and onto the escape platform. Each rat received a total of ten trials in two blocks of five trials separated by a 20-min interval.

2.2. Running wheel activity

Four groups ($n = 8$) of rats were used. The rats were housed in cages with access to a running wheel. The rats were habituated to the apparatus for 10 days. On day 10 and 11, the groups received the following injection schedule: (1) 500 + 500 mg/kg PCPA; (2) gum arabic + 150 mg/kg PCPA; (3) gum arabic + gum arabic; and (4) no injections. Activity was monitored until day 15, i.e., 4 days after PCPA treatment. Wheel revolutions were displayed by a counter and recorded throughout the entire habituation and test period every day at 15.00 h.

2.3. Biochemical assay

Four groups of rats ($n = 6$) were used. The groups received the following drug treatments over 2 days: (1) 2 × 500 mg/kg PCPA; (2) gum arabic and 150 mg/kg PCPA; (3) 2 × gum arabic; and (4) no injections. Three days after the last injection, rats were decapitated, the brain was rapidly removed, frozen in liquid isopentane kept in frozen carbon dioxide and stored at −70° C. After homogenization in 0.1 N perchloric acid, centrifugation and retention of the supernatant, whole brain biochemical assays were performed using high-pressure liquid chromatography with electrochemical detection as described previously [2].

2.4. Statistics

All data are presented as mean ± S.E.M. Analyses of variance and, where appropriate, Newman–Keuls follow-up tests were performed using the software packages SPSS/PC + and CLR Anova (Version 1.1, Clear Lake Research). A Fisher exact probability test was also used [33].

3. Results

3.1. Biochemical assay

As shown in Fig. 1, 1000 mg/kg PCPA treatment resulted in a profound depletion of whole brain 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), which were reduced to 9.4% and 8.2% of control (no injection) levels, respectively. Even at the 150 mg/kg dose, PCPA still produced a significant reduction in 5-HT and 5-HIAA. Dopamine and noradrenaline levels were affected only slightly at the 1000 mg/kg PCPA dose.

3.2. Open-field exploratory locomotor activity

PCPA treatment at all three doses, but especially at the 500 and 1000 mg/kg doses, resulted in a clear reduction of all measures of locomotor activity (Fig. 2). All general activity measures (total distance travelled, distance and speed per movement) were decreased at a PCPA dose of 1000 mg/kg (Fig. 2a). At lower PCPA doses, total distance

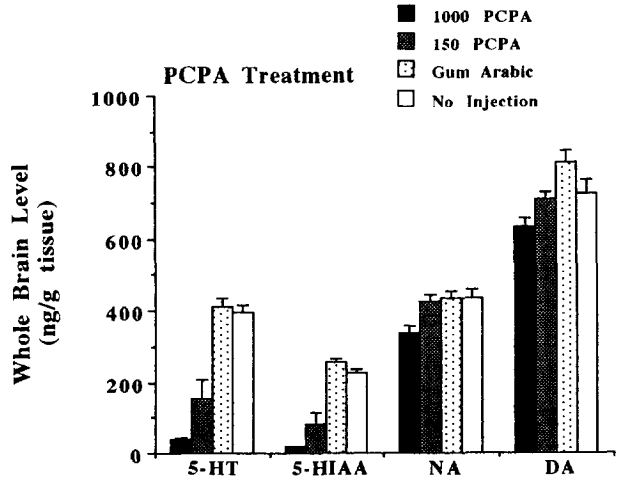
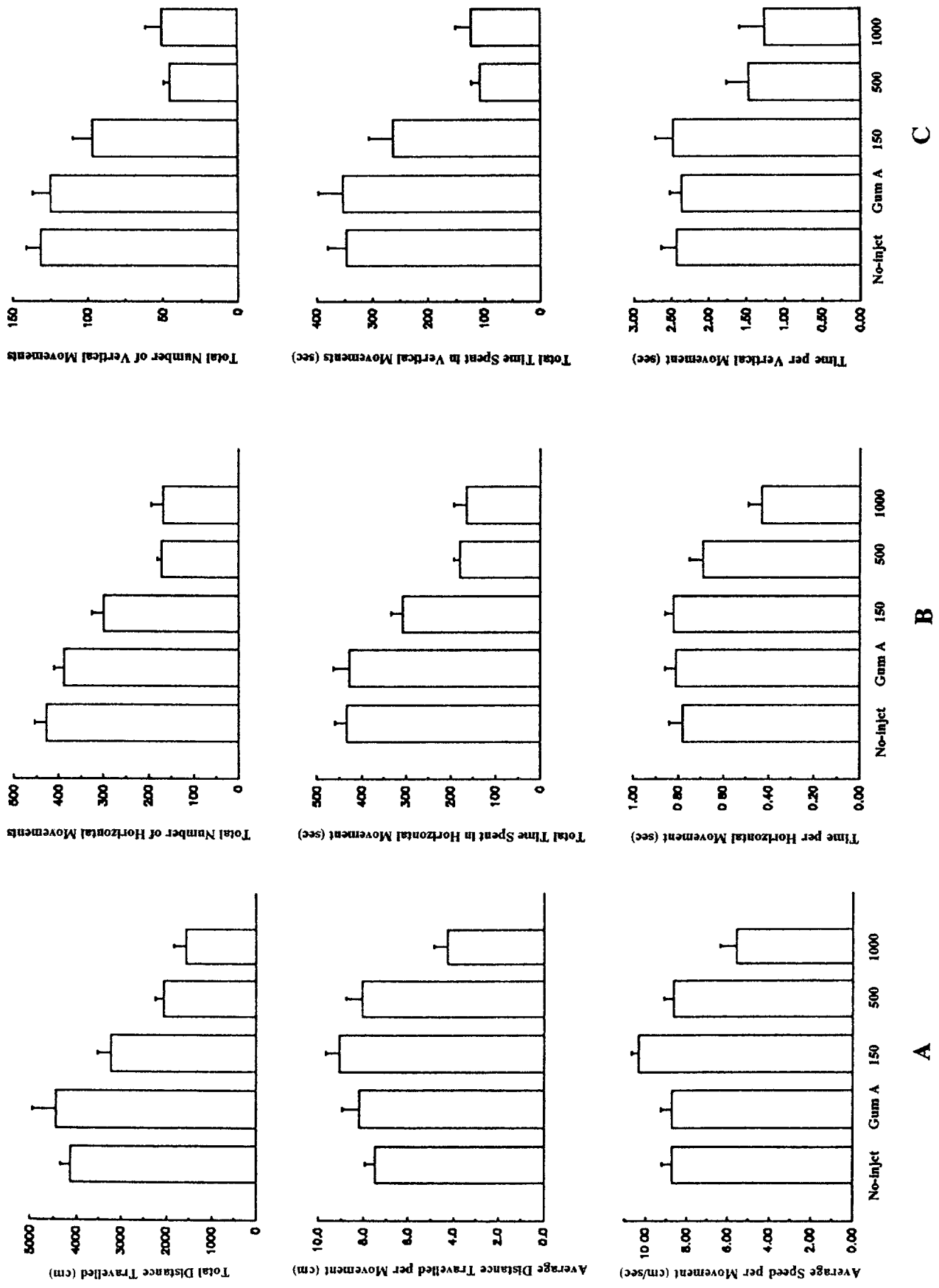


Fig. 1. Effect of PCPA treatment on whole brain levels of 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), noradrenaline (NA) and dopamine (DA) (group size $n = 6$). There were significant effects of drug treatment on all compounds, $P < 0.007$ or better. 5-HT and 5-HIAA were both significantly reduced at both PCPA doses ($P < 0.01$) and the 1000 mg/kg dose reduced both more severely than the 150 mg/kg dose ($P < 0.05$). NA and DA were reduced only after treatment with 1000 mg/kg PCPA ($P < 0.05$).


Average Speed per Movement (cm/sec)
Average Distance Travelled per Movement (cm)
Total Distance Travelled (cm)
Time per Horizontal Movement (sec)
Total Time Spent in Horizontal Movement (sec)
Total Number of Horizontal Movements
Time per Vertical Movement (sec)
Total Time Spent in Vertical Movements (sec)
Total Number of Vertical Movements
No-inject
Gum A
150
500
1000
A
B
C

travelled was decreased, whereas speed and distance per movement were not decreased relative to the control groups. Interestingly, there was a tendency for the 150 mg/kg PCPA group to show increased speed and distance travelled per movement, whereas the 1000 mg/kg PCPA group showed a clear decrease in these activity measures.

All measures of horizontal activity were decreased by PCPA treatment (Fig. 2b). Both the number of horizontal movements and the time spent in horizontal movement were decreased at all three PCPA doses and the decrease was maximal at the 500 and 1000 mg/kg doses. The time per horizontal movement was decreased only after 500 and 1000 mg/kg PCPA.

Administration of PCPA also decreased all measures of vertical activity (Fig. 2c). Again, all three doses reduced the number of vertical movements and the time spent in vertical movement. As in the case of horizontal activity, the effect of PCPA on vertical movements was saturated at a dose of 500 mg/kg. The time per vertical movement was reduced only after 500 and 1000 mg/kg PCPA.

Inspection of activity levels over consecutive 5-min samples for a total of 60 min revealed that the total distance travelled, the number of horizontal and vertical movements (Fig. 3) and the time spent in horizontal and vertical movement were reduced by the two highest PCPA doses already at the onset of the test period. Further, the 500 and 1000 mg/kg PCPA groups tended to remain at reduced activity levels relative to the control groups throughout the entire 60 min test period. The overall increase in the distance and speed per movement after 150 mg/kg PCPA was caused by an increase of these activity measures relative to the control groups during the second 30 min of testing (data not shown).

3.3. Sensory-motor tests

The sensory-motor tests did not reveal any impairments after PCPA treatment and all three PCPA groups performed at control levels in all the tests. There was, however, a tendency for PCPA-treated rats toward hyper-reactivity in their home cage to cutaneous stimulation of the feet. Nine PCPA-treated rats (three in each PCPA group) or 37.5%, displayed hyper-reactivity and frequently these rats would run, jump or even climb upon the food tray or cage wall when their feet were touched. Only one rat or 6%, in the two control groups displayed similar responses. This difference is significant according to a Fisher exact probability test ($P = 0.02$). Interestingly, hyper-reactivity of PCPA-treated rats was never observed in any other test situation.

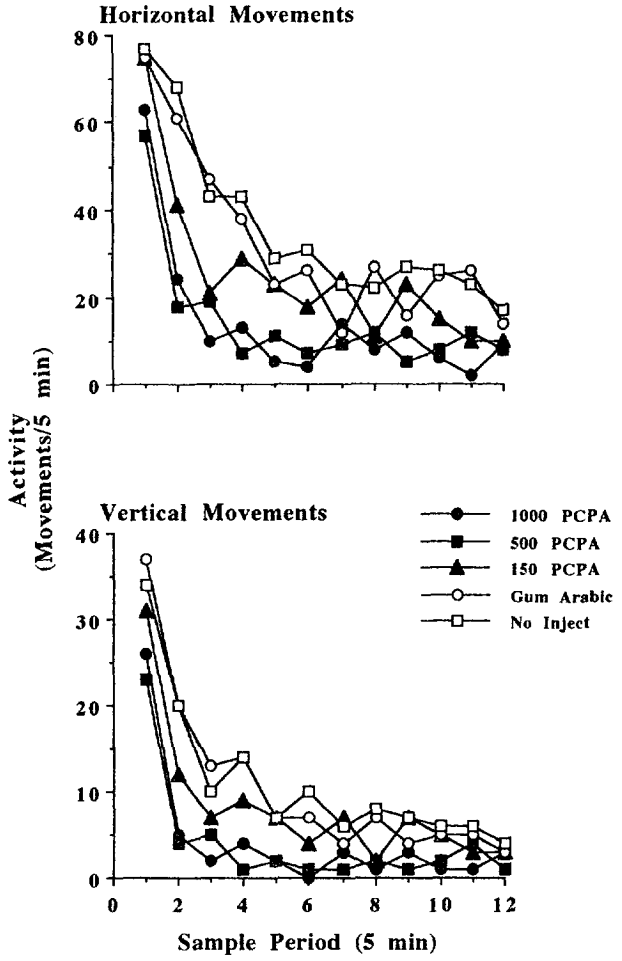


Fig. 3. Spontaneous exploratory locomotor activity in an open field during 12 consecutive 5-min samples for a total of 60 min. Both horizontal ($F_{11,385} = 59.6$, $P < 0.0005$) and vertical ($F_{11,385} = 102.7$, $P < 0.0005$) movements decreased over the test period. There also were significant interactions between drug treatment and sample period ($F_{44,385} = 2.0$, $P < 0.0005$ for horizontal movements; $F_{44,385} = 2.1$, $P < 0.0005$ for vertical movements). Note that relative to the control (gum arabic and no inject) groups, the 500 and 1000 mg/kg PCPA groups displayed reduced activity levels already at the onset of the test period. Students' t-tests comparing the combined activity levels of the two high dose PCPA groups to the combined control group activity levels indicated that during the first 20 min of testing, both horizontal ($P = 0.007$) and vertical ($P = 0.037$) activity were reduced in PCPA-treated rats relative to controls. Thus, immediate exploration of the unfamiliar open field was particularly sensitive to PCPA treatment.

Fig. 2. The effects of treatment with gum arabic or PCPA on spontaneous exploratory locomotor activity during 60 min in a digitized open-field activity monitor ($n = 8$/group; No-inject, no injection; Gum A, gum arabic injections). PCPA treatment in doses of 150, 500 and 1000 mg/kg produced a dose-dependent decrease of general locomotor activity characteristics (A) (omnibus test $F_{44,112} = 7.0$, $P < 0.0005$), horizontal movement characteristics (B) (omnibus test $F_{16,140} = 4.4$, $P < 0.0005$) and vertical movement characteristics (C) (omnibus test $F_{16,140} = 2.6$, $P < 0.001$). Univariate F-tests revealed significant effects of drug administration on every movement characteristic across all groups ($P < 0.001$) and across the three PCPA groups only ($P < 0.013$).

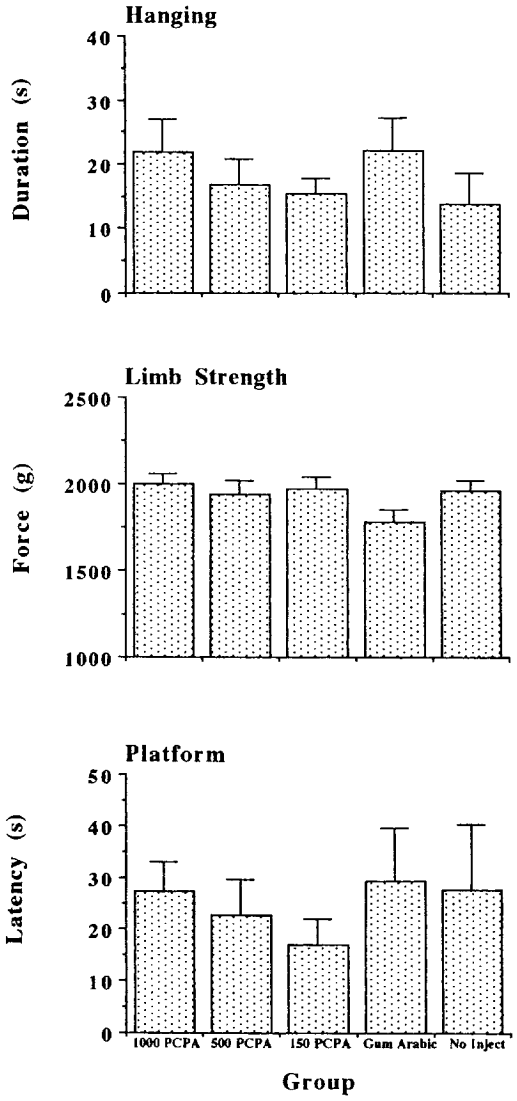


Fig. 4. The effects of PCPA and gum arabic treatment on hanging duration (top), limb strength (middle) and latency to climb down from an elevated platform . There were no effects of drug treatment on the time rats spent hanging by their forepaws before falling ($F_{4,35} = 0.95$, $P = 0.45$), toleration of force applied to the feet ($F_{4,35} = 1.0$, $P = 0.42$) or escape latency from the platform ($F_{4,35} = 0.3$, $P = 0.87$). For each test, the means and S.E.M. are based on three trials/rat, $n = 8$/group.

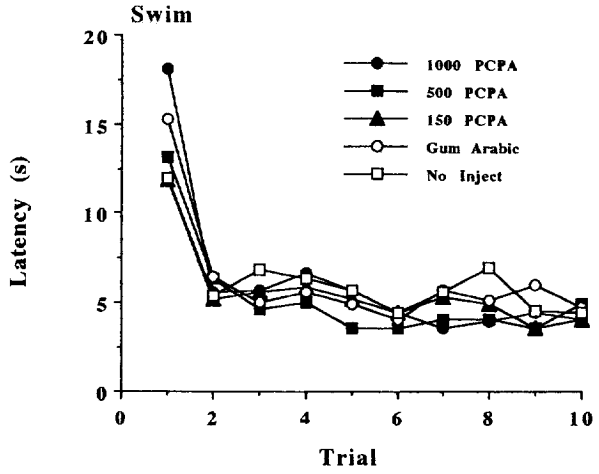


Fig. 5. The effects of PCPA and gum arabic treatment on swim speed ($n = 8$/group). The drug treatments had no effect on the time taken to swim along the alley to the escape climb ($F_{4,35} = 1.9$, $P = 0.14$). There was a significant decrease in the time over trials ($F_{9,315} = 47.0$, $P < 0.0001$) which was equivalent for all groups (group by trial interaction $F_{36,315} = 1.3$, $P = 0.12$).

As shown in Fig. 4 (top), rats in the two control groups had a hanging duration of approximately 15–20 s and PCPA did not significantly affect this duration. Similarly, limb strength was not affected by PCPA treatment (Fig. 4, middle). When control and PCPA-treated rats were placed on a wire grid and pulled backward, they all tolerated a pull of approximately 1800–2000 g before letting go of the grid.

As depicted in Fig. 4 (bottom), control rats remained on the elevated platform for about 30 s. There was a tendency for PCPA-treated rats to remain on the platform for a shorter time and this trend was more pronounced after lower PCPA doses. However, the latencies of PCPA-treated rats did not differ significantly from those of control rats. Also, there were no obvious abnormalities in the motor pattern when rats climbed down from the elevated platform. Generally, rats would position their forelimbs against the side walls of the platform to support their upper body while they slowly lowered themselves in a head-down posture, keeping their hind feet on the platform. When the forelimbs and head were close to the ground, the hind limbs were taken off the platform and rats would perform a small jump to land on the ground.

Fig. 5 displays the latency for rats to swim along the alley to a climb escape on the opposite end of the alley. After a single trial, all rats had acquired the necessary motor pattern to direct themselves toward the opposite end of the alley and swim along the alley when placed in the water. There were no differences in the swimming speed between PCPA and control groups. At the far end of the alley, all rats reliably climbed up the wire grid and escaped to the elevated rest platform.

3.4. Running wheel activity

PCPA treatment using doses of 150 and 1000 mg/kg was without significant effects on activity levels for rats housed in cages with running-wheel access (Fig. 6). There was a decline in activity levels on the days following either 150 or 500 mg/kg injections, but the effect was not significant. On the subsequent day and throughout the remainder of the test period, activity returned to approximately the same levels as those observed prior to drug treatment. The activity levels of both control groups continued to increase slightly after the treatment period.

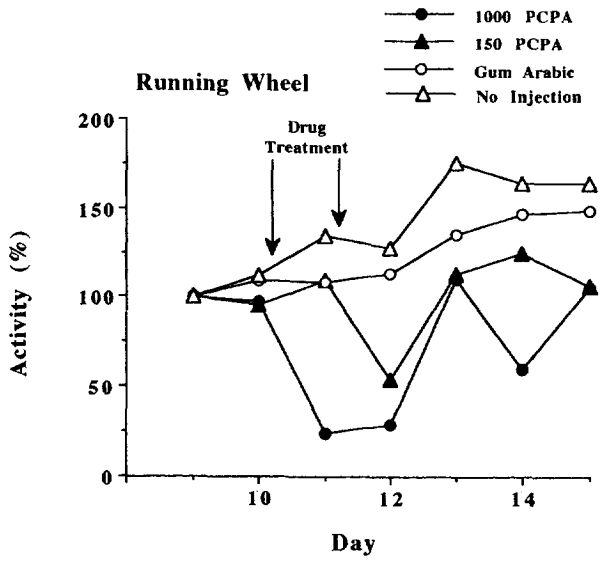


Fig. 6. The effects of PCPA and gum arabic treatment on activity in running wheels ($n = 8$/group). Injections of either 150 or 500 mg/kg PCPA, but not of gum arabic, produced an acute decrease in activity during the subsequent 24 h. However, activity levels returned to pre-treatment levels 2 days after the last PCPA administration. An ANOVA for the data of the last 3 days before drug treatment and days 2–4 after drug treatment did not reveal significant group differences ($F_{3,28} = 0.8$, $P = 0.5$) or pre- and post-treatment by group interaction ($F_{3,28} = 2.0$, $P = 0.13$).

4. Discussion

The fact that there is no consensus regarding the role of 5-HT in the control of behavior is illustrated in a recent review by Soubrie [34] and the subsequent open peer commentary. Even when clearly defined behaviors such as locomotor activity have been under investigation following the manipulation of central serotonergic transmission, the data are inconsistent. Thus, both increases and decreases of various types of locomotor activity have been reported following depletion of brain 5-HT [4,13,23,26]. In order to develop a more coherent understanding of the role of 5-HT in the control of behavior, it is important to develop an understanding why such significant discrepancies exist in the data on behavioral correlates of 5-HT manipulations.

In the present study, we employed a wide range of PCPA doses to deplete 5-HT in order to test whether PCPA may have a biphasic effect on exploratory locomotor activity. However, our results indicate that doses between 150 and 1000 mg/kg all reduce spontaneous exploratory locomotor activity, but some activity measures were affected only at doses larger than 150 mg/kg (average distance per movement, average speed per movement, time per horizontal movement, time per vertical movement). These doses cover and extend the range of those used by other investigators. Thus, the contradictory results regarding the locomotor effects after PCPA treatment may not be due to a simple biphasic relation between PCPA dose and locomotion.

A problem with the interpretation of previous work on the behavioral consequences of 5-HT depletion with PCPA is the fact that most studies have not included biochemical analyses to indicate the level of 5-HT depletion achieved. The present and previous experiments suggest that doses substantially higher than those used in previous studies may be needed to produce sufficiently complete depletions of 5-HT and, consequently, behavioral or electrophysiological consequences of lowered brain 5-HT. In the present study, 1000 mg/kg PCPA produced a significantly higher level of depletion of 5-HT than 150 mg/kg PCPA. Further, as mentioned already, several components (e. g, average speed of movement, time spent in horizontal movement, time per vertical movement) of exploratory locomotion were not suppressed by 150 mg/kg PCPA, whereas higher doses had pronounced effects on all movement characteristics measured. As shown previously, three doses (i.e., 1500 mg/kg) of PCPA, but not one dose of 500 mg/kg, block atropine-resistant hippocampal and neocortical activation [41]. Also, depletions of 76% of cortical 5-HT are without any significant effects on a number of complex behaviors in rats [31]. These data strongly suggest that the use of inadequate doses of PCPA and, consequently, insufficient levels of 5-HT depletions may, in part, account for the fact that some investigators did not observe decreases in activity after doses of up to 300 mg/kg [5,22,37].

A further concern for the interpretation of behavioral effects following partial 5-HT depletion is the possible development of pre- and postsynaptic compensatory changes. Such changes occur after partial dopaminergic denervation [17] and, consequently, significant behavioral abnormalities often are apparent only at very high levels of dopamine depletion [30,35], even though it is possible that more sensitive behavioral measures may detect lower levels of depletion. It may be that similar compensatory mechanisms obscure the effect of reduced brain 5-HT and may potentiate the action of remaining (e.g., after inadequate PCPA treatment) or recovering 5-HT transmission.

It is not obvious whether manipulation of 5-HT transmission has a direct effect on locomotor activity or whether such activity changes are secondary to some peripheral effects or alteration in the sensory-motor capacities of animals. PCPA treatment, especially at high doses, has a number of adverse side effects such as reduced body temperature [4], reduced food and water intake [4,26], fur discoloration and decreased body weight (present study). However, in the present study, rats treated with PCPA did not show deficits in their general sensory-motor capacities.

The only behavioral abnormality we could identify was a tendency of PCPA-treated rats to display hyper-reactivity in their home cage to cutaneous stimuli applied to their feet. In all other behavioral capacities examined, the rats appeared normal. Thus, peripheral effects or deficits in the general sensory-motor capacities cannot directly account for the changes in activity levels associated with PCPA treatment.

It is noteworthy to point out that in the present study, even very high doses of PCPA (1000 mg/kg) produced only marginal alterations of central levels of dopamine and noradrenaline. This is also the case for doses of 500 mg/kg PCPA [41]. A dose of 150 mg/kg PCPA decreased 5-HT levels without affecting dopamine or noradrenaline, but produced decreases in several of the measures of exploratory locomotor activity. Thus, it appears that non-specific effects on brain amines probably do not account for the changes in exploratory locomotion observed in the present study.

Surprisingly, we did not see hyperactivity after PCPA treatment in rats chronically housed in cages with access to a running wheel. If anything, PCPA treatment appeared to produce a reduction of activity. This finding is in definite contrast with those of several other reports of PCPA-induced increases in running wheel activity [13,19]. Dose-differences cannot account for this discrepancy, since our low PCPA dose (150 mg/kg) is approximately equivalent to that used by others investigators who have observed increased running wheel activity. Neither this dose, nor our 1000 mg/kg PCPA dose, produced any indications of hyperactivity. At present, we cannot account for this discrepancy. However, it seems worth pointing out that running wheel activity and other types of locomotion such as exploratory open-field activity or stabilimeter activity appear to have distinct neural substrates that can be dissociated anatomically by means of brain lesions [6,9,25,42]. Thus, it is not surprising that pharmacological manipulations, like brain lesions, may have different effects on different measures of motor activity.

Ideally, laboratory measures of behavior should give results that are applicable to real life situations. Running in a rotating wheel is quite unlike running on a fixed surface, since the momentum of the wheel provides cutaneous and proprioceptive stimulation that is not present in running under more natural conditions. When tested with a Q-tip in the home cage, many PCPA-treated rats reacted to tactile stimulation of the feet with a burst of running and climbing. If a PCPA-treated rat in a running wheel attempts to stop running, the cutaneous stimulation resulting from the inertia of the wheel may trigger further running. Thus, the hyperactivity often seen in running wheels after PCPA treatment may be an artifact of this method of testing. Our results indicate that the true effect of PCPA treatment may be a reduction in spontaneous motor activity, particularly exploratory activity.

Other results also suggest a link between levels of central 5-HT transmission and locomotor activity. Forebrain 5-HT levels are higher in more active relative to less active rats [32]. Electrical stimulation of 5-HT-containing cells groups [27] or pharmacological elevation of central 5-HT levels [29] increase locomotion, as does administration of the direct-acting 5-HT receptor agonist RU 24969 [15]. Further, 5-HT produces activation of the electrocorticogram in conjunction with movement but not with immobility [40]. Serotonergic neurons in the dorsal raphe discharge at higher rates during active waking than quiet waking or sleep [18] and extracellular 5-HT levels are elevated during active behavioral states [43]. This serotonergic control over activity and locomotion may be a phylogenetically old control mechanism, since it is present even in invertebrates [44]. In addition, the present results suggest that not all forms of locomotion are equally dependent on central 5-HT levels or transmission. Exploratory locomotor activity in an unfamiliar environment (see [10]) may be especially sensitive to PCPA-induced depletions of 5-HT.

Central 5-HT transmission has been suggested to play a role in 'anxiety mechanisms' and there is substantial evidence that drugs that act as agonists at 5-HT $_{1A}$ receptors reduce 'anxiety' in humans and animals [7,11,12,36,39]. Whether changes in locomotor or exploratory activity following PCPA treatment are, in some way, related to decreased 'anxiety' levels remains to be established.

It appears that neither dose-differences across studies, nor the presence or absence of sensory-motor deficits following different PCPA doses can satisfactorily account for the inconsistent results of PCPA-induced 5-HT depletions on locomotor activity. In the present study, 5-HT depletions of over 90% reduced all components of exploratory activity in an unfamiliar open field. This reduction in locomotion was apparent for doses between 150–1000 mg/kg. Thus, our results provide strong support for a stimulatory role of 5-HT in the control of, at the least, exploratory locomotor activity. The specific nature of this locomotor facilitation, as well as its interaction with different environments (i.e., familiar and novel) could be the focus of future research.

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