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# Reduction of Nicotine-Induced Hyperactivity by pCPA[1]

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FITZGERALD, R. E., R. OETTINGER AND K. BÄTTIG. *Reduction of nicotine-induced hyperactivity by pCPA*. PHARMACOL BIOCHEM BEHAV 23(2) 279–284, 1985.–Spontaneous locomotion of female Wistar rats was measured in six to ten minute sessions in an automated tunnel maze consisting of a central arena and six radially symmetrical angled arms. Nicotine (0.2 mg/kg subcutaneous, 20–30 minutes pretest) increased total arm visit frequency, but intrasession habituation and number of repetitive arm visits in the first six choices were not affected. pCPA (300 mg/kg IP three days pretest) reduced arm-visit frequency in nicotine-, but not in saline-treated rats; it had no effect on intrasession habituation or number of repetitions in either treatment group. 5-HTP (50 mg/kg IP 90 minutes pretest) reduced arm entry frequency in saline-, nicotine-, and pCPA-treated groups. Possible reasons for this discrepancy are discussed.

Nicotine pCPA 5-HT 5-HTP Maze Exploration Locomotion Habituation Rat

LOW doses of nicotine in laboratory rodents stimulate locomotor activity [2, 3, 7, 12, 17, 19]. Previous work has found that this hyperactivity is not accompanied by changes in exploratory efficiency in complex asymmetrical mazes [19]. In the first experiment of the present study we used a radially symmetrical tunnel maze configuration to measure nicotine's effects on locomotor activity and exploration.

The rationale for the second experiment was based on reports that repeated daily nicotine administration reduces L-tryptophan uptake and serotonin (5-hydroxytryptamine, 5-HT) synthesis in rat hippocampal synaptosomes [4]. 5-HT depletion itself can induce hyperactivity in the rat, and this is apparently mediated by the hippocampus [13]. This suggests the hypothesis that reduction of forebrain serotonin by nicotine is causally related to nicotine-induced hyperactivity. We therefore examined the effects of depleting 5-HT after nicotine treatment, by administering para-chlorophenylalanine (pCPA), which blocks 5-HT synthesis [14]. The third experiment was designed to test the specificity of pCPA's effects for 5-HT, by administering the serotonin precursor 5-hydroxytryptophan after pCPA treatment.

## GENERAL METHOD

### *Subjects*

A total of 37 experimentally naive adult (approximately three months old) female Wistar rats (KFM Fullinsdorf) were used in Experiments 1 and 2. They were individually housed in transparent plastic cages (37×21×15 (height) cm). We used females because they are behaviourally more sensitive to nicotine [3,12], and to enable comparison with previous results [2, 3, 12, 19]. Food (NAFAG Nr. 890 food blocks) and tap water were provided ad lib throughout the experiment. Animals were handled daily for weighing. The living quarters were maintained at 23°C, with a 12/12 hour light/dark cycle (on at 0600). All testing was done during the light phase, between 0800 and 1300 hr.

### *Apparatus*

Testing was conducted in an undisturbed room adjacent to the animals' living quarters. The apparatus was a Plexiglas tunnel maze, 150 cm in diameter, each alley being 8 cm wide by 15 cm high, with opaque Plexiglas walls and a transparent Plexiglas top which enables observation of the animals. The walls and top form a unit which is hinged to the wall and which is raised to remove the animal after testing. Different maze configurations are produced by inserting barriers in the maze (cf. [2, 3, 19]). The configuration used here was a six-arm radial maze with angled arms (Fig. 1). The sensors used to record the animals' activity are electromagnetic field sensors distributed under the floor of the maze. Sensor activation data are collected and timed in a buffer and transferred to a PDP 11/34 minicomputer. From there, after software reconstruction of the animal's movements, the data are shipped to a CDC Cyber 170–720 mainframe computer for detailed description and statistics [9]. The level of significance adopted throughout was $p<0.05$.

## EXPERIMENT 1

In this experiment the effects of nicotine on locomotor activity and exploration were quantified.

### *Procedure*

Each animal was tested once daily for 10 minutes in the maze on five consecutive days. One group of randomly

[1]These data have been reported in abstract/poster form at the 1984 Meeting of the European Brain and Behaviour Society in Strasbourg.

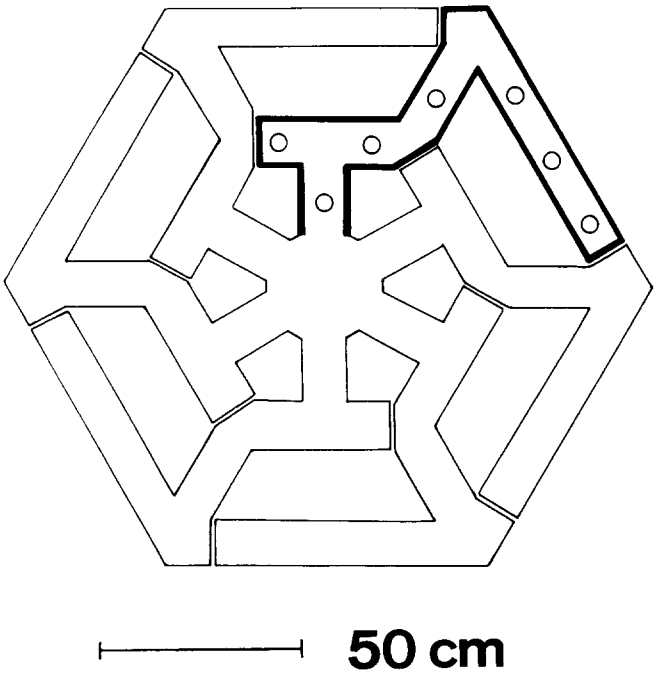


FIG. 1. Ground plan of the six arm radial maze used in the study. The circles represent the positions of the underfloor activity sensors.

selected animals (n=19) was injected subcutaneously in the scapular region (scruff of the neck) 30 minutes before testing with 0.2 mg nicotine base (from nicotine hydrogen tartrate, BDH England)/ml saline/kg. This is a low-level dose which has been found to be activity-stimulating in earlier studies [2, 3, 12, 19]. The other group (n=18) was saline injected. The order of testing was counterbalanced across groups and remained the same throughout the experiment.

## RESULTS

Mean number of arm entries per session was higher in the nicotine-treated group than in the saline-treated group over all five test days, group $F(1,35)=13.28$, $p<0.001$. However, the number of visits made to the arm ends was not significantly higher in the nicotine-treated group, group $F(1,35)=1.93$. It appeared that the nicotine-treated animals were hyperactive because they were making more arm entries than saline controls, but were turning around and leaving the arm before reaching the end. For this reason, we analysed separately 'complete' visits to the ends of the arms, and 'incomplete' visits, in which the animal turned around and left the arm before reaching the end. The results are shown in Fig. 2. For complete visits, there was a significant day effect, $F(4,140)=4.10$, $p<0.01$, but no nicotine effect, group $F(1,35)=1.93$, or day by group interaction, $F(4,140)=0.24$. For incomplete visits, there was a significant day effect, $F(4,140)=16.11$, $p<0.001$, and a group effect, $F(1,35)=16.82$, $p<0.001$, and a day by group interaction, $F(4,140)=2.99$, $p<0.05$. Individual comparisons on each day (Bonferroni multiple-comparison-corrected $t$-tests [9]), revealed no significant saline-nicotine differences in complete visit frequency on any day, but significantly higher incomplete visit frequency in the nicotine group on all five days ($t(35)=2.29$, 2.79, 2.63, 3.50 and 3.70 for days 1 to 5 respectively, all $p$'s$<0.05$, see Fig. 2). Figure 2 suggests that both saline and nicotine groups increased their incomplete visit frequency over days, and that the increase was greater in the nicotine group. This impression was confirmed by trend analysis [22]. There were significant linear trends for both the day factor, $F(1,35)=32.96$, $p<0.001$, and for the day by group interaction, $F(1,35)=6.07$, $p<0.05$. There were no significant higher order trends for either the group factor or the group by day interaction.

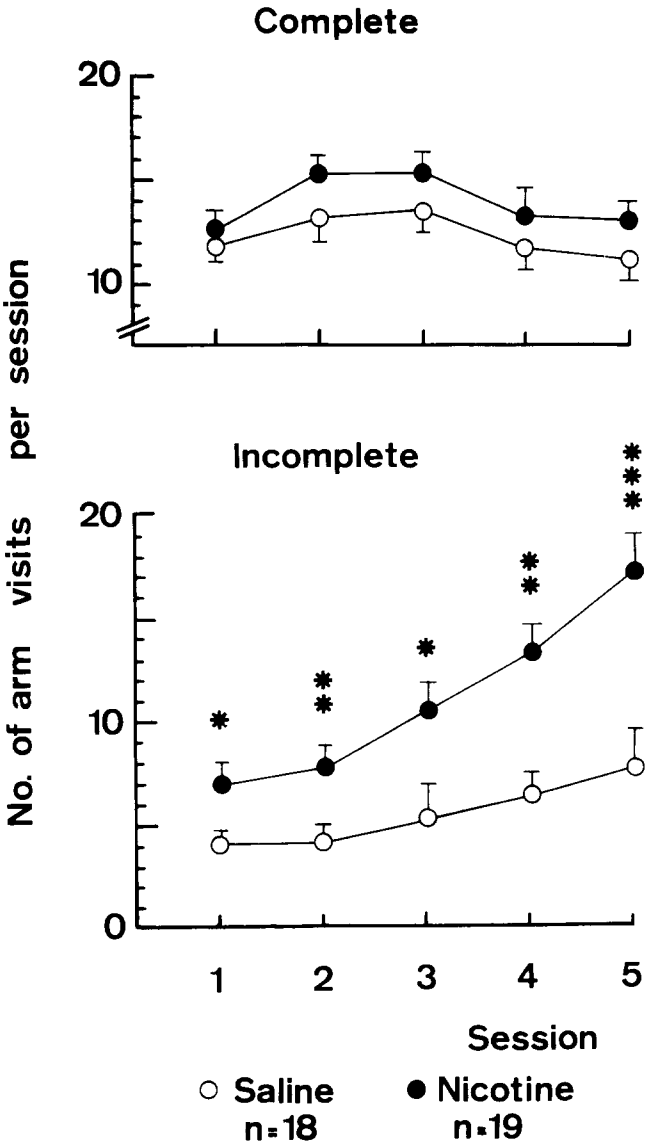


FIG. 2. Mean number of complete visits (to ends of arms) and incomplete visits (leaving arm before reaching the end) in saline- and nicotine- (0.2 mg/kg SC) treated groups on five consecutive test days. *saline-nicotine difference, Bonferroni $t$-test, $p<0.05$; **$p<0.01$; ***$p<0.001$.

To measure within-trial habituation of locomotion, trials were divided into four 2.5 minute subtrials. Repeated measures ANOVA's revealed significant subtrial effects for frequency of complete visits, $F(3,105)=27.80$, $p<0.001$, and frequency of incomplete visits, $F(3,105)=7.48$, $p<0.001$. Trend analysis showed that the number of incomplete visits

decreased linearly over the four subtrial periods, $F(1,35)=17.37$, $p<0.001$; the quadratic and cubic components were not significant, $F(1,35)=0.22$ and 0.66 respectively, NS. The within-trial changes in complete visit frequency were more complex; here the linear, quadratic and cubic components were all significant, $F(1,35)=13.48$, 106.92 and 13.31 respectively, all $p$'s$<0.001$. Most important in the present context, there were no nicotine interactions with these subtrial effects (for complete visits—subtrial by group, $F(3,105)=0.69$, subtrial by group by day, $F(12,420)=1.58$; for incomplete visits—subtrial by group, $F(3,105)=0.31$, subtrial by group by day, $F(12,420)=1.06$.

We measured the efficiency of exploration on day five by counting the number of repetitive arm visits made during the first six choices (perfect performance=0). (One of the animals from the saline group could not be included in the analysis because it did not make six choices.) Considering only visits to arm ends, both saline and nicotine groups made an average of 1.0 (±0.2 SEM) repetitive visits during the first six (complete) visits. When all visits were considered (i.e., repetition of arm entries, thus including incomplete as well as complete visits) the nicotine group made more repetitions than the saline group (mean 1.1 vs. 0.7±0.1) but this difference was not significant ($t(34)=1.87$, $p=0.07$). We also analysed the animals' behaviour at the choice points just after arm entry, where there was a short blind alley to the left, and the main arm to the right. The total number of blind alley entries was not significantly higher on day five in the nicotine group (10.3±1.1 vs. 7.7±0.8 in the saline group, $p=0.07$); in terms of blind alley entries per arm entry, i.e., probability of entering the blind alley when at the left/right choice point, there was no difference between the two groups (saline 0.35±0.04, nicotine 0.30±0.03, NS).

## DISCUSSION

The hyperactivity produced by nicotine in this test apparatus consisted of an increase in the number of radial arm visits in which the animal left the arm before reaching the end. Within-session habituation and efficiency of arm patrolling were not significantly affected by nicotine treatment. These results are in agreement with those found for RHA/Verh rats tested in complex asymmetrical mazes, where nicotine stimulated locomotor activity but did not alter exploratory efficiency [19].

## EXPERIMENT 2

pCPA was administered to half the animals after the completion of Experiment 1, and after an interval of three days, the animals were tested again, receiving saline or nicotine injection as before.

### *Procedure*

At the end of day five of the previous experiment (17–1800 hours), both the saline and nicotine groups were divided into two subgroups, balanced for total arm entry frequency on day five. One group received pCPA (300 mg parachlorophenylalanine) (Sigma)/5 ml 2% Tween 80 (Sigma) in distilled water/kg intraperitoneally (IP), the other group vehicle only. On the third day after injection (62 to 65 hours later, when 5-HT depletion should be maximal and specific [14,15]), the groups were retested at the same time of day, and in the same order as in Experiment 1, 30 minutes after saline or nicotine injection. The data obtained on day five of Experiment 1 were then compared with those obtained three days later after pCPA or vehicle treatment. The entire procedure (Experiments 1 and 2) was run in two consecutive blocks two weeks apart, with approximately equal numbers of subjects in each of the four groups per block; data from the two blocks were combined for analysis.

## RESULTS

Mean body weight in the pCPA-treated groups dropped 6 g, while the vehicle-treated groups showed a mean increase of 3 g, 62 to 65 hours after administration, pCPA by pre-post treatment, $F(1,33)=52.67$, $p<0.001$. Other investigators employing exactly the same treatment as here have reported comparable weight loss 72 hours after pCPA, and greater than 90% depletion of forebrain 5-HT [15].

Total number of arm entries (complete and incomplete visits combined) did not change significantly pre- to post-treatment in the saline+vehicle treated group, mean 21.0–20.1, related $t(8)=0.16$, or in the saline+pCPA treated group, mean 17.1–19.4, $t(8)=1.0$, but increased in the nicotine+vehicle treated group, mean 30.9–33.4, $t(8)=3.64$, $p<0.01$, and decreased in the nicotine+pCPA treated group, mean 29.7–23.8, $t(9)=3.05$, $p<0.05$.

The results in terms of the two subtypes of arm visit, complete and incomplete, are shown in Fig. 3. pCPA had no significant effect on the frequency of complete visits in either saline- or nicotine-treated groups. Incomplete visit frequency was reduced in the nicotine+pCPA group ($t(9)=2.44$, $p<0.05$), but did not change significantly in the other three groups (saline+vehicle, $t(7)=0.81$; saline+pCPA, $t(8)=2.02$; nicotine+vehicle, $t(8)=1.27$).

Intrasession habituation of total arm entry frequency, assessed by repeated ANOVA over the four 2.5 minute subtrials, changed from pre- to post-treatment, pre-post treatment by subtrial, $F(3,99)=6.04$, $p<0.001$, but this occurred without nicotine, pCPA or nicotine by pCPA interaction effects, $F(3,99)=0.69$, 0.19 and 1.49 respectively.

For patrolling efficiency, in terms of the number of repetitive arm entries occurring in the first six choices, related $t$-tests revealed no within-group changes in any group (for the saline+vehicle group, mean number of repetitions in the first six arm entries pre-post treatment was 0.8–0.6, $t(7)=0.55$; for the saline+pCPA group, 0.7–1.0, $t(8)=1.15$; for the nicotine+vehicle group 1.2–0.7, $t(8)=1.89$; and for the nicotine+pCPA group 0.9–1.0, $t(9)=0.43$; standard error of mean for all means=0.2). (One saline+vehicle treated subject failed to make six choices on the pre-treatment day, so it could not be included in this repetitive visit analysis.)

In summary, pCPA reduced arm entry frequency in the nicotine group, by reducing the number of incomplete visits, but did not affect arm entry frequency in the saline group; it had no effects on intrasession habituation or exploratory efficiency in either group.

## EXPERIMENT 3

The purpose of this experiment was to test whether the pCPA effect seen in Experiment 2 was specific to serotonin depletion, by administering the serotonin precursor 5-hydroxytryptophan (5-HTP). If the behavioural effects of pCPA are due to serotonin depletion, then 5-HTP should reverse them.

### *Procedure*

A total of 64 adult female Wistar rats, obtained and housed as in Experiments 1 and 2, were used. Test session

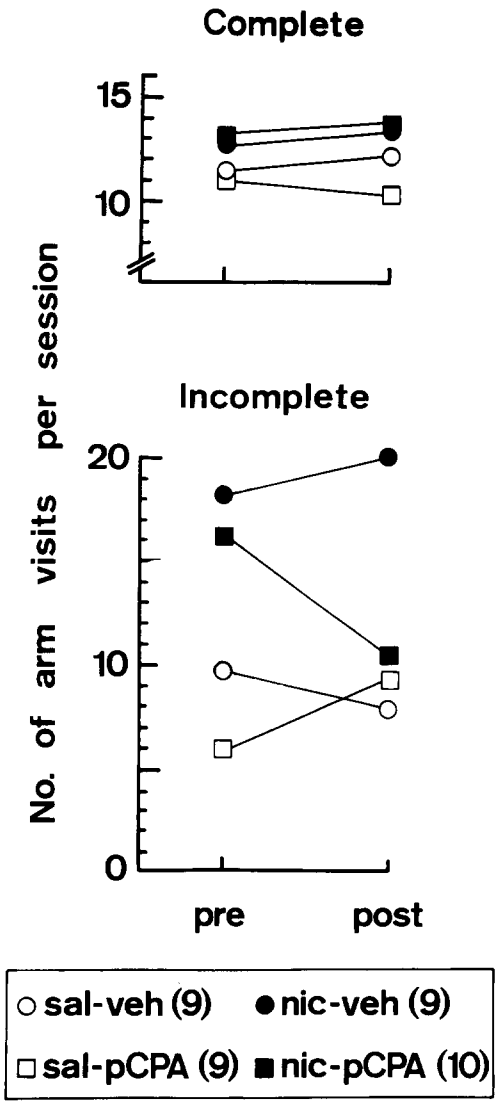


FIG. 3. Number of complete visits (to ends of arms), and number of incomplete visits (leaving arm before reaching end) in saline- and nicotine-treated groups before and three days after pCPA (300 mg/kg IP) or vehicle administration.

duration in this experiment was six minutes instead of 10, and the animals were injected 20 minutes pre-test instead of 30 minutes. The nicotine hydrogen tartrate was dissolved in 0.15 M phosphate buffer (pH 7.0) instead of in saline. These changes were introduced to streamline testing, and to prevent discomfort due to injection of unbuffered nicotine tartrate. The design used was a fully crossed 2×2×2 (nicotine, pCPA and 5-HTP treatment, with repeated measures on nicotine), n=8 per group. Animals were given three six minute test sessions at two day intervals, after saline or nicotine (0.2 mg base/ml buffer/kg SC, 20 minutes pretest). After a further two day interval, they were administered saline or pCPA (300 mg pCPA methyl ester (Sigma)/5 ml saline/kg IP), and were retested (one and) three days later under saline or nicotine. Before this last test session, animals were administered 5-HTP (50 mg 5-hydroxytryptophan (Sigma)/2 ml 2% Tween 80 in distilled water/kg IP, 90 minutes pretest), or vehicle. The dose of 5-HTP used is reported to produce a significant elevation of brain 5-HT 90 minutes after injection with minimal effects on brain dopamine and noradrenaline [8]. Behaviour of the eight groups (saline control, saline+pCPA, saline+5-HTP, saline+pCPA+5-HTP, nicotine control, nicotine+pCPA, nicotine+5-HTP and nicotine+pCPA+5-HTP) was then compared before and after pCPA/5-HTP or control treatment (test three versus test five).

## RESULTS

On the third test day (baseline), the nicotine-treated rats made more arm entries than the saline-treated, mean 23.3 vs. 16.4, respectively, group $F(1,62)=24.89$, $p<0.001$. As in Experiment 1, the number of complete visits was not significantly different, nicotine 10.3 vs. saline 9.8, group $F(1,62)=0.33$, but incomplete visit frequency was increased, nicotine 12.9 vs. saline 6.6, group $F(1,62)=19.56$, $p<0.001$. On the fifth test day, after pCPA or saline treatment, total number of arm entries (both complete and incomplete visits) was not significantly altered in the saline control group, day three vs. day five mean 18.9–16.5, related $t(7)=1.74$, or in the saline+pCPA treated group, mean 15.6–12.8, $t(7)=1.58$, or in the nicotine control group, mean 26.0–23.3, $t(7)=1.03$, but decreased in the nicotine+pCPA treated group, mean 25.1–17.1, $t(7)=2.93$, $p<0.05$. The effects of pCPA on arm entry frequency in both saline and nicotine treated groups were therefore similar to those in Experiment 2.

Both the saline and the nicotine groups treated with 5-HTP made fewer arm entries after than before treatment (saline+5-HTP treated group, mean 15.3–11.1, $t(7)=4.83$, $p<0.01$; nicotine+5-HTP treated group, mean 19.8–14.5, $t(7)=2.78$, $p<0.05$). The nicotine by pre-post 5-HTP treatment interaction was not significant, $F(1,28)=0.04$.

The groups treated with both pCPA and 5-HTP also made fewer arm entries after treatment than before (saline+pCPA+5-HTP, mean 16.0–7.5, $t(7)=4.16$, $p<0.001$; nicotine+pCPA+5-HTP, mean 22.1–13.6, $t(7)=4.25$, $p<0.01$). There was no evidence for non-additivity of the effects of pCPA and 5-HTP. Separate ANOVA's for arm entry frequency in the saline and nicotine groups revealed no significant pCPA-5-HTP interaction; for the saline groups, pCPA by 5-HTP by pre-post treatment interaction, $F(1,28)=1.49$, for the nicotine groups, $F(1,28)=0.18$. Furthermore, there was no overall interaction effect between nicotine, pCPA and 5-HTP pre-post treatment, $F(1,56)=1.07$.

The results in terms of complete and incomplete visits are shown in Table 1. In contrast to Experiment 2, the nicotine+pCPA group did not change their frequency of either complete or incomplete visits significantly after treatment. We had expected a reduction in incomplete visit frequency in this group, as in Experiment 2; in fact, seven of these eight nicotine-treated rats did reduce incomplete visit frequency by seven to ten after pCPA treatment, but one animal increased incomplete visit frequency by 11. This animal lost 10 g body weight in the three days after pCPA treatment, suggesting that the treatment was effective: we could therefore see no reason for rejecting this animal from the analysis. Another discrepancy between Experiments 2 and 3 was the behaviour of the control groups. In contrast to Experiment 2 (Fig. 3), there was in Experiment 3 no increase in incomplete visit frequency in the nicotine control group, and a decrease in incomplete visit frequency in the saline

TABLE 1

EFFECTS OF pCPA AND 5-HTP TREATMENT ON COMPLETE AND INCOMPLETE VISIT FREQUENCY IN SALINE AND NICOTINE GROUPS

| Group | Treatment | N | Complete visit frequency | | Incomplete visit frequency | |
|---|---|---|---|---|---|---|
| | | | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| Saline | control | 8 | 9.8 ± 1.5 | 11.8 ± 1.9 | 9.1 ± 1.7 | 4.8 ± 1.7† |
| | pCPA | 8 | 10.4 ± 1.0 | 7.3 ± 0.9* | 5.3 ± 0.7 | 5.5 ± 1.1 |
| | 5HTP | 8 | 9.4 ± 1.4 | 6.8 ± 1.0* | 5.9 ± 1.4 | 4.4 ± 1.2† |
| | pCPA+5HTP | 8 | 9.8 ± 1.2 | 3.9 ± 0.9† | 6.3 ± 1.4 | 3.6 ± 1.1 |
| Nicotine | control | 8 | 9.4 ± 1.1 | 8.4 ± 1.2 | 16.6 ± 1.9 | 14.9 ± 2.8 |
| | pCPA | 8 | 10.1 ± 1.4 | 6.8 ± 1.6 | 15.0 ± 2.8 | 10.4 ± 3.2 |
| | 5HTP | 8 | 10.9 ± 0.7 | 9.0 ± 1.5 | 8.9 ± 2.2 | 5.5 ± 1.4 |
| | pCPA+5HTP | 8 | 10.9 ± 1.6 | 4.9 ± 0.7* | 11.3 ± 2.4 | 8.8 ± 1.5 |

*$p<0.05$ pre- to post-treatment by related $t$-test.
†$p<0.01$.
Means ± S.E.M. are presented. Numbers of animals per group (N).

control group (Table 1). The most obvious procedural differences between the two experiments were the baseline saline/nicotine treatments (five consecutive daily tests in Experiment 1 versus three tests at two day intervals in Experiment 3), and the additional test session between the baseline and three day post-pCPA tests in Experiment 3. It must also be noted that the baseline values for incomplete visit frequency were rather poorly balanced across groups in this experiment (Table 1, Pre-treatment column).

The saline+5-HTP treated group made fewer complete and incomplete visits after treatment (Table 1), but the nicotine+5-HTP treated group did not. Although from the mean values presented in Table 1, 5-HTP only had a depressant effect on activity in the saline group, interactions between nicotine and 5-HTP treatment were not significant for either complete or incomplete visits; nicotine by 5-HTP by pre-post treatment interaction, $F(1,28)=3.35$ for complete visits, 1.93 for incomplete visits. As was the case in the total visit frequency analysis, there were no interaction effects between 5-HTP and pCPA treatment, for either complete visit frequency, 5-HTP by pCPA by pre-post treatment interaction, $F(1,56)=0.00$, or for incomplete visit frequency, $F(1,56)=0.18$, nor were there significant nicotine by pCPA by 5-HTP by pre-post treatment interaction effects for either complete visit frequency, $F(1,56)=0.92$, or for incomplete visit frequency, $F(1,56)=3.97$.

## GENERAL DISCUSSION

Nicotine-treated animals made more arm visits than saline-treated, due to an increased number of incomplete visits, and this difference increased linearly during the five days of testing (Experiment 1); we have previously found a comparable increase in nicotine-induced hyperactivity with repeated testing in RHA/Verh rats [2, 3, 19]. Nicotine did not alter the efficiency of exploration in this apparatus, either in terms of repetitive arm entries or in terms of blind alley entries, nor did it affect within-session habituation, in agreement with previous studies measuring spontaneous activity [2, 3, 7 (Fig. 3), 17, 19]. In humans, there is evidence that nicotine reduces the decline in stimulus sensitivity which occurs over time in vigilance-like tasks [21]. In rats too, chronic nicotine treatment enhances performance in a visual vigilance task [16], and in aversively motivated water-maze learning [1]. We are at present unable to determine the significance of the increased frequency of 'incomplete' arm visits in nicotine-treated rats in the radial tunnel maze in terms of possible changes in cognitive processes, but since the number of repetitive arm entries, blind alley entries, and intrasession habituation were all unaffected by nicotine, we conclude that nicotine stimulates locomotor activity without affecting the efficiency of exploration.

The role of serotonin in spontaneous locomotor activity is controversial: although some authors report hyperactivity after serotonin depletion [13], others find no change in activity [15], as was the case for frequency of arm entries in the present study. The evidence implicating serotonin in nicotine's locomotor effects is mainly indirect. Correlations have been reported between sex and strain differences in brain serotonin turnover and the locomotor response to nicotine. Female rats have higher brain 5-HT concentrations, and faster turnover, than males [18], and they are more sensitive to the locomotor stimulant effect of nicotine [3,17]. RHA/Verh rats are more hyperactive in response to nicotine than RLA/Verh rats [3,19], and have higher concentrations of cortical 5-HT, and higher mid-brain levels of 5-hydroxyindoleacetate, a metabolite of 5-HT, indicating higher activity of the midbrain cells innervating the forebrain with 5-HT [10]. Repeated daily administration of nicotine (0.4 mg/kg) increases locomotor activity and reduces diencephalic serotonin turnover in high active female rats [17], and the same daily dose reduces tryptophan uptake and serotonin biosynthesis in hippocampal synaptosomes [4]. The hypothesis which we proposed at the outset of this work was that reduction of hippocampal serotonin by repeated nicotine administration is causal to the behavioural hyperactivity: a further reduction in brain serotonin by pCPA should then have enhanced the hyperactivity. This seemed a reasonable hypothesis by analogy to amphetamine, another psychostimulant which reduces forebrain serotonin [20], and whose locomotor stimulant effect is enhanced by serotonin depletion using pCPA [5]. The result which we obtained from application of pCPA, however, was in the opposite direction to that predicted by this hypothesis—pCPA reduced nicotine-induced hyperactivity. This suggests a different hypothesis—that a functional serotonin system is necessary

for nicotine to produce locomotor hyperactivity. It is also possible that these two hypotheses are both correct, but for different levels of serotonin depletion, since the reduced serotonin biosynthesis in hippocampus produced by chronic nicotine [4] may have quite different behavioural effects to the reduced synthesis produced by pCPA, which produces a more global and profound depletion of serotonin [14,15].

The selective decrease in incomplete visit frequency in the nicotine group after pCPA treatment in Experiment 2 was not observed in all animals in Experiment 3. What determines the relative frequency of these two types of arm visit in the undrugged animal is not clear, nor is the reason for the differences in control behaviour between Experiments 2 and 3. Further work will be necessary to determine how far the distinction between complete and incomplete visits is a useful one.

Unexpectedly, the effects of 5-HTP treatment were in the same direction as those of pCPA treatment, and there were no significant interactions between these drug treatments. At the dose levels and test intervals employed here, all published evidence indicates that pCPA should specifically decrease, and 5-HTP specifically increase, serotonin levels [8, 14, 15]. Like pCPA, 5-HTP has been reported to either decrease or increase spontaneous activity [6]. It has been reported that when peripheral metabolism of 5-HTP to 5-HT is blocked by decarboxylase inhibitors which do not cross the blood-brain barrier, 5-HTP produces hyperactivity instead of hypoactivity, and no longer induces a taste aversion, indicating that its activity depressive and aversive effects are peripherally mediated [6,11]. Based on these reports and the present results, it would seem advisable to employ peripheral decarboxylase blockade in conjunction with 5-HTP treatment.

In conclusion, the results presented here show that nicotine stimulates spontaneous locomotor activity without affecting exploratory efficiency. Serotonergic systems appear to participate in this stimulant effect, but their location and function remain to be determined.

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