Pharmacology Biochemistry & Behavior, Vol. 35, pp. 847–853. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Effects of *p*-Chlorophenylalanine and Scopolamine on Retention of Habits in Rats

C. H. VANDERWOLF,* C. T. DICKSON* AND G. B. BAKER†

**Department of Psychology, University of Western Ontario, London, Ontario, Canada, N6A 5C2*
†Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G3

Received 10 August 1989

VANDERWOLF, C. H., C. T. DICKSON AND G. B. BAKER. *Effects of* p*-chlorophenylalanine and scopolamine on retention of habits in rats*. PHARMACOL BIOCHEM BEHAV **35**(4) 847–853, 1990.—Rats were trained on a conventional maze test or on a swim-to-platform test. Retention of swim-to-platform performance 7 days later was severely impaired by posttraining treatment with a combination of *p*-chlorophenylalanine (PCPA) and scopolamine although neither drug alone had any effect. Retention of the maze habit was moderately impaired by scopolamine alone and severely impaired by a combination of scopolamine and PCPA, but was unaffected by PCPA alone. Polygraphic recordings confirmed previous reports that a combination of PCPA and scopolamine can abolish neocortical low voltage fast activity and hippocampal rhythmical slow activity. Combined blockade of central cholinergic and serotonergic neurotransmission in rats may provide a useful animal model of Alzheimer's disease.

Behavior Hippocampus Neocortex *p*-Chlorophenylalanine Scopolamine

FOR several decades it has been apparent that the brain contains ascending systems that exert a generalized control over the electrical activity of the cerebral hemispheres. Although the influence of these systems encompasses unit activity and evoked potentials as well as the spontaneous electrocorticogram, their best-known effects are the production of low voltage fast activity (LVFA) in the neocortex and rhythmical slow activity (RSA) in the hippocampal formation. Early research suggested that this cortical activation, as it is often called, is mediated via a reticulothalamocortical pathway, affecting the neocortex (15) and a reticuloseptohippocampal pathway, affecting the hippocampal formation (7). More recent work (23) has revealed that ascending control of cortical activation is mediated by: a) cholinergic projections from the basal forebrain, and b) serotonergic projections from the midbrain, to both the neocortex and hippocampal formation. The activation patterns produced by these systems, especially the serotonin-dependent system, are closely correlated with concurrent motor activity, possibly suggesting a role in the moment-to-moment regulation of waking behavior. This suggestion is supported by evidence that combined blockade of central cholinergic and serotonergic neurotransmission produces a profound disorganization of behavior. It appears that loss of cerebral activation is associated with a dementia-like condition rather than sleep or coma as would have been expected on the basis of classical concepts (22).

The experiments reported in this paper extend our knowledge of the behavioral effects of cholinergic and serotonergic blockade by exploring the effect of treatment with scopolamine (a cholinergic muscarinic antagonist) and *p*-chlorophenylalanine (PCPA, an inhibitor of the synthesis of serotonin) on retention of previously established learned behaviors. In previous work in this area (22) training was begun only after the administration of PCPA. Data on the effects of these drugs on cortical electrical activity and on the effect of PCPA on some aspects of brain chemistry are also presented.

METHOD

Subjects and Surgical Procedures

Experiments were performed in 59 male hooded rats (300–500 g). In 20 rats, anesthetized with pentobarbital, bipolar electrode pairs were implanted in the left hippocampus and the right parietal neocortex using standard techniques (4). In the neocortex, one electrode of each pair was placed on the pial surface while the other electrode penetrated to a depth of about 1.0 mm. In the hippocampus one electrode of each pair was placed on the alvear surface of CA1 while the other electrode penetrated approximately to the hippocampal fissure.

Recording Cortical Activity and Behavior

Rats with implanted electrodes were placed on a magnet-and-coil type of movement sensor platform (33 × 33 cm surface, placed 61 cm above a laboratory bench) and polygraphic records were taken of hippocampal and neocortical slow wave activity occurring during spontaneous behavior (28). Activity in both cortices was recorded with a band-pass of 1–75 Hz, but hippocampal activity was also more sharply filtered (6–12 Hz band-pass), rectified, and integrated over 1-sec intervals. Records were taken during waking immobility (standing motionless, head up and

eyes open) and during walking (either spontaneous or elicited by light pushing of the hindquarters) during a period of about 5–10 min. After these initial observations were completed the rats were given scopolamine hydrobromide (SC in the neck, 5 mg/kg). After a delay of 15 min, additional records were taken during waking immobility and walking for an additional 15–30 min. A third set of records was taken after a delay of about 24 hr.

Drugs

Parachlorophenylalanine (PCPA; 500 mg/kg, IP) was injected as a fine suspension (50 mg/ml) in a solution of gum acacia (0.5%) and saline (0.9%). Equivolume control injections consisted only of gum acacia and saline. Both types of injections were given once/day for 3 days.

Scopolamine hydrobromide was dissolved in saline and given subcutaneously (5 mg/kg) in the neck (5 mg/ml solution). This dose was chosen on the basis of evidence that it produces a total blockade of cholinergic activation of the neocortex (23). Equivolume control injections consisted, in this case, of saline given subcutaneously.

Maze Test

After a recovery period of 2–3 weeks, rats with implanted electrodes were habituated to a 22-hr food deprivation schedule (a wet mash of Purina lab chow available for 2 hr/day; water continuously available) for one week. Feeding occurred on an open stand to accustom the rats to the test room. Weights were recorded daily.

Next, the rats were given 5 trials/day for 16 days on a Lashley No. 3 maze (11) made of unpainted plywood. The outside dimensions of the maze, exclusive of the goal and start boxes, were 122×47 cm with walls 22 cm high. There was a detachable Plexiglas lid for the maze and hinged Plexiglas lids for the goal and start boxes. There were 8 blind alleys and the true path consisted of a series of 5 alternating right and left turns. The alleys were 10.5 cm wide. The start box, measuring 29×10.5 cm, communicated with the alleys via a guillotine door. The goal box measured 38×10.5 cm. Errors (entries into blind alleys) and total running time were recorded on each trial. About ¼ teaspoon of wet Purina mash was used as a reward for reaching the goal box.

At the end of training the rats were divided into 2 equivalent groups. One group ($N = 10$) received PCPA while the other ($N = 10$) received control injections. On the day following the third injection, polygraphic records of neocortical and hippocampal activity and behavior were taken both before and after the administration of scopolamine. Two additional days were allowed for recovery from the effects of scopolamine. The next 3 days the rats were tested on the Lashley maze. On the last of these test days all rats were given scopolamine about 15 min prior to testing on the maze.

Swim-to-Platform Test

Separate groups of rats (different from those used in the maze test which were also used in the recording experiment and the neurochemical assays) were tested in a rectangular aquarium (22) measuring 43×90 cm and 45 cm deep was filled with water at 20°C to a depth of 25 cm. A wire mesh platform measuring 21.5×18.5 cm and 26 cm in height was placed in the centre, its long axis parallel to the long axis of the aquarium. Thus, the water level was 1 cm below the top of the platform. After measuring rectal temperature (with a 2 mm diameter probe inserted to a depth of 6.5 cm) rats were placed individually in one corner of the tank and both the number of passes past the platform down the long axis of the aquarium as well as the time taken for the rat to reach the platform (to a maximum of 60 sec) were recorded on 10 trials (intertrial interval of 10–20 sec). If a rat was unable to reach the platform in 60 sec it was placed there manually. Times to reach the platform that were greater than 10 sec were considered errors. After completion of 10 trials the rectal temperature was measured again. Rectal temperature was monitored because we have found that swim-to-platform performance in normal rats deteriorates if the mean of the temperatures at the start and end of a 10 trial test falls below about 30°C.

On the 4th, 5th, and 6th day after training the rats were given PCPA, equivalent volume of drug vehicle, or no treatment. Twenty-four hours after the last injection (on the 7th day after training), and 15–30 minutes prior to testing, either scopolamine or saline was given. This made a total of 6 groups: 1) PCPA + scopolamine; 2) PCPA + vehicle; 3) vehicle + scopolamine; 4) vehicle + vehicle; 5) no treatment + scopolamine; and 6) no treatment + vehicle. The rats were then tested in the aquarium again following the same procedure as before.

Neurochemical Procedures

Several hours after completion of the Lashley maze tests, the rats with implanted electrodes were killed by cervical fracture followed immediately by decapitation. The brain was removed rapidly and cooled in ice-cold saline for 1 min before dissection into: a) neocortex plus cingulate cortex; b) hippocampal formation, including the entorhinal cortex; and c) the remainder of the brain. Dissection was carried out in a pool of ice-cold saline. Samples were immediately frozen in a bath of isopentane over solid carbon dioxide and stored at −70°C. Subsequently, the brain samples were packed in solid carbon dioxide and shipped by air from London, Ontario, to Edmonton, Alberta. Homogenization of brain samples and high pressure liquid chromatographic determination (using electrochemical detection) of the concentrations of amines, their metabolites, and tryptophan was done according to the procedures of Baker *et al.* (1) except that a voltage setting of 0.85 was used in the HPLC analysis.

Statistical Procedures

Data were analyzed with the help of nonparametric statistical tests (19), a computer software parametric analysis of variance package (5), and a Pearson coefficient of correlation (8).

RESULTS

Neurochemical Observations

Table 1 shows that the treatment with PCPA reduced 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) levels to 1.8–8.3 percent of the control values in all 3 brain regions examined. Noradrenaline, dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid and tryptophan also tended to be reduced, though less severely than 5-HT and 5-HIAA.

Cortical Electrical Activity

The polygraphic records, taken after the initial 16 days of maze training and subsequent treatment with PCPA or gum acacia, revealed mainly irregular activity in the hippocampus during waking immobility and RSA during walking. Following the administration of scopolamine, RSA persisted in the control group (previously treated with the gum acacia vehicle) during walking, but in the PCPA-treated rats, RSA tended to be replaced by large

TABLE 1

BRAIN CONCENTRATIONS OF SOME AMINES, AMINE METABOLITES, AND TRYPTOPHAN IN RATS TREATED WITH PARACHLOROPHENYLALANINE (500 mg/kg/DAY × 3)

	NA	DA	DOPAC	HVA	5-HT	5-HIAA	Trypt
Neocortex	48.0†	36.6†	21.7†	7.8†	4.7‡	1.9‡	67.1†
(N = 10)	±5.0	±7.5	±9.0	±7.8	±0.6	±0.8	±5.8
	(209.0	(220.0	(26.7	(25.6	(317.7	(174.3	(2349.3
	±13.0)	±45.0)	±3.4)	±6.2)	±15.6)	±9.1)	±210.9)
Hippocampal Formation	51.1‡	69.5	11.2†	N.M.	1.8‡	2.3‡	60.4*
(N = 10)	±4.5	±16.5	±6.5		±0.4	±1.0	±8.3
	(239.8	(60.7	(16.9		(408.6	(303.2	(3010.3
	±6.8)	±7.4)	±4.1)		±52.2)	±21.7)	±391.9)
Remainder	64.2†	84.1†	50.0‡	53.3†	8.1‡	8.3‡	61.7†
(N = 10)	±4.4	±2.9	±3.2	±7.1	±0.7	±1.0	±6.1
	(324.2	(962.6	(106.1	(73.2	(426.2	(287.7	(2608.0
	±11.6)	±24.9)	±4.9)	±5.7)	±12.6)	±9.0)	±221.8)

Concentrations (mean ± standard error of the mean) are presented outside the parentheses as percentages of the concentrations determined in a group of 10 control rats that received only drug vehicle. *Differs from control $p<0.02$; †differs from control, $p<0.01$; ‡differs from control, $p<0.00001$. Control concentrations are given in brackets (ng/g). NA, noradrenaline; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindoleacetic acid; Trypt, tryptophan; N.M.; not measurable.

amplitude irregular activity even though the rats walked about very actively. Correspondingly, the levels of integrated 6–12 Hz activity were initially higher during walking than during waking immobility in all 16 of the rats in which adequate records of integrated activity are available (Table 2). Following the administration of scopolamine, the level of integrated 6–12 Hz activity fell significantly in the PCPA-treated group, but did not change in the control group (Table 2). An additional effect observed in some of the PCPA-treated rats was that 5–6 Hz RSA occurred, at times, during waking immobility.

TABLE 2

EFFECT OF SCOPOLAMINE ON INTEGRATED 6–12 Hz HIPPOCAMPAL ACTIVITY IN RATS TREATED WITH *p*-CHLOROPHENYLALANINE

	PCPA Only			PCPA + SCOP		
	Immobile	Walk	D	Immobile	Walk	D
PCPA Group	7.4	13.5	6.1	7.5	11.6	4.1*
(N = 9)	±0.6	±1.1	±0.6	±0.8	±1.5	±1.1
	VEH Only			VEH + SCOP		
	Immobile	Walk	D	Immobile	Walk	D
Control Group	8.4	13.9	5.5	7.4	14.0	6.5
(N = 7)	±0.6	±1.3	±0.9	±0.3	±1.4	±1.1

Analysis of variance of D scores revealed an interaction between group and drug condition ($p<0.02$). *Differs from PCPA only condition, $p<0.02$, Walsh test. Integrated 6–12 Hz activity is larger during walking than during immobility in all conditions ($p<0.01$ or better, Walsh test).

PCPA, parachlorophenylalanine (5000 mg/kg, IP/day for 3 days); SCOP, scopolamine hydrobromide (5 mg/kg, SC); VEH, gum acacia vehicle (0.5% solution, IP). Numbers refer to mean ± S.E.M. of arbitrary units of integrated 6–12 Hz activity; D, difference between immobility and walking conditions.

Satisfactory records of neocortical activity were obtained in 19 of the 20 rats with implanted electrodes. The remaining rat displayed a depressed almost isoelectric record, suggesting accidental local injury. The control rats (N = 10) at first displayed continuous LVFA, regardless of behavior, but following the administration of scopolamine they displayed large amplitude irregular slow waves during walking immobility and other Type 2 behavior. However, clear LVFA persisted during walking, head movement, and other Type 1 behavior (Fig. 1). The PCPA-treated rats at first displayed either continuous LVFA (5 cases) or LVFA interrupted by bursts of 6–10 Hz spindles (4 cases). Following the administration of scopolamine, large amplitude irregular slow waves occurred, not only during waking immobility, but also during walking and head movement (Fig. 1). In each rat, 20 or more episodes of walking (each of 1–2 sec duration) were examined for the presence of LVFA of at least 1 sec duration/episode. In 2 of the 9 PCPA-treated rats, LVFA was totally abolished during walking. In the remaining 7 rats LVFA was partially abolished, but occurred on some occasions during walking.

Both the control and PCPA-treated rats were very active after treatment with scopolamine. However, the control rats remained on the movement sensor platform while the PCPA-treated rats frequently attempted to walk off the edge. In 6 of the 10 cases, it was necessary to restrain these rats (holding the tail or pushing them back repeatedly) throughout the recording session after the scopolamine had taken effect.

Twenty-four hours after the administration of scopolamine, the electrographic effects of the drug had completely disappeared. Hippocampal RSA and neocortical LVFA had recovered their prescopolamine appearance and relation to behavior in all rats, suggesting that the scopolamine had been largely eliminated.

Maze Test

On the Lashley maze, each of the 20 rats displayed a clear decrease in errors (Fig. 2) and in running time (not shown) over

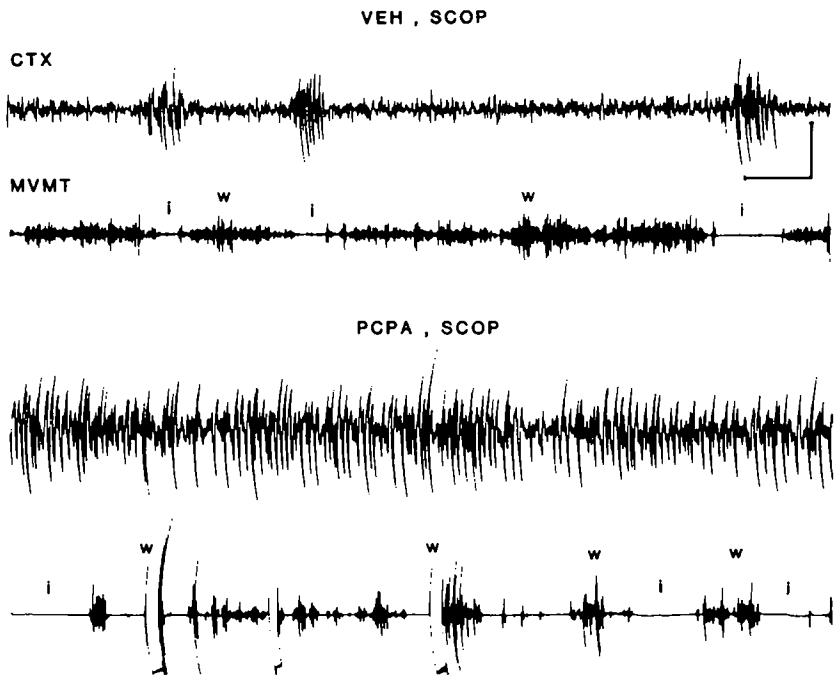

FIG. 1. Effects of *p*-chlorophenylalanine and scopolamine on the electrocorticogram in relation to behavior. CTX, slow wave activity from parietal neocortex, surface-to-depth electrodes. MVMT, output from magnet-and-coil type of movement sensor. VEH, SCOP; rat treated with 3 daily injections of drug vehicle plus scopolamine (5 mg/kg, SC). PCPA, SCOP; rat treated with 3 daily injections of *p*-chlorophenylalanine (500 mg/kg, IP) plus scopolamine (5 mg/kg, SC). i, immobile; w, walking. Note that in the PCPA, SCOP rat large amplitude irregular slow waves occur continuously, but that in the VEH, SCOP rat such waves occur only during behavioral immobility. Cal.: 1 mV, 5 sec.

the course of the 16 days of initial training. Following the drug treatments and a 6-day hiatus in testing, the rats were returned to the maze. Both groups performed at the same level as prior to the drug treatments. PCPA did not result in a loss of the maze habit (Fig. 2). However, when scopolamine was administered, performance in both groups deteriorated. Each of the 20 rats made more errors when tested after scopolamine than on either of the 2 preceding test days ($p<0.01$ in each group, Walsh test). However, the PCPA-treated rats made even more errors than the control rats after scopolamine treatment (Fig. 2; $p<0.05$; Mann-Whitney U-test). There was no significant difference between the groups in total time taken to complete a run through the maze.

The scopolamine injections had the effect of totally suppressing feeding in the rats in the maze. This was confirmed in a supplementary experiment in which 3 rats, habituated to a 22-hr schedule of food deprivation for 8 days, were treated with either scopolamine or saline on 2 successive days. After saline injections the rats increased their weight by 21–35 g after exposure to food for 90 min. After scopolamine injections their weight decreased by 2–3.5 g after the same exposure to food (presumably due to loss of urine, feces, and expired water vapor).

Treatment with PCPA had significant effects on body weight in the experimental rats. At the start of training in the Lashley maze, the experimental group (later to receive PCPA) weighed 454.5 ± 19.7 g. The control group weighed 448.2 ± 8.7 g. The food deprivation schedule produced a mean loss of 4.9% in the experimental group and a mean loss of 5.4% in the control group (no significant difference between the groups). However, the drug injection procedure resulted in an additional loss of weight amounting to 20.6% of the initial weight of the experimental group and 16.1% of the initial weight of the control group. This difference between the groups is significant ($p<0.002$, Mann-Whitney test).

Swim-to-Platform Test

All 36 rats acquired a swim-to-platform habit readily. Errors, occurring almost entirely on the first trial, ranged from 1.3 ± 0.2 to 2.0 ± 0.6 among the 6 groups during training (N.S.). Figure 3 shows performance during retention testing after a delay of 7 days plus various drug or control treatments. It is evident that the PCPA plus scopolamine group made a large number of errors (8.3 ± 1.5 in the 10 trials) while the other groups usually made an average of less than one error. Both parametric and nonparametric tests revealed significant between-groups variation (ANOVA, $p<0.00001$; Kruskal-Wallis test, $p<0.05$). Mann-Whitney tests revealed that the PCPA plus scopolamine group differed significantly from every other group ($p<0.02$) and that the remaining groups did not differ among themselves. The rather poor performance of the no treatment/scopolamine group is due mainly to one aberrant rat that made 6 errors.

Similar, but more variable results were obtained upon analysis of the occurrence of passes (swimming past the platform without climbing up). The 6 groups did not differ significantly on this measure during training. During retention testing the groups differed significantly (Kruskall-Wallis test, $p<0.05$; between-groups ANOVA, $p<0.00004$), with the PCPA plus scopolamine group averaging 35.2 ± 8.8 passes, i.e., more than 11 times the mean of the other 5 groups.

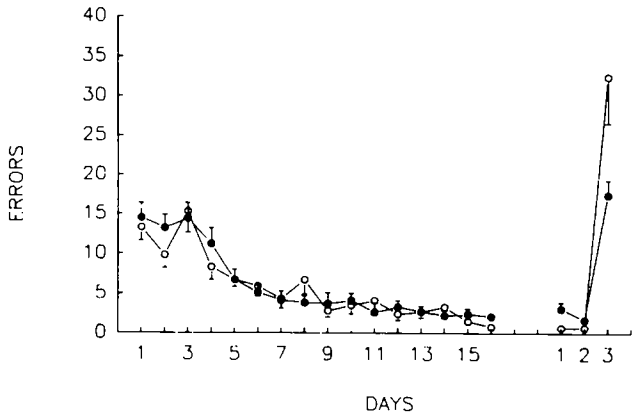

FIG. 2. Effects of *p*-chlorophenylalanine and scopolamine on performance in a Lashley No. 3 maze. Rats were trained for 16 days and divided into 2 groups. *p*-Chlorophenylalanine (PCPA, 500 mg/kg, IP, N = 10) or an equivalent volume of drug vehicle (N = 10) were administered on each of 3 successive days. After a further delay of 3 days (during which brain activity was recorded) the rats were given 3 days of testing on the maze. Scopolamine HBr (5 mg/kg, SC) was given 15 min prior to testing on the last day (day 3, far right). Open circles, PCPA group; filled circles, control group. PCPA treatment alone had no effect on maze performance, but when scopolamine was given, performance deteriorated in all rats ($p<0.01$ in each group; Walsh test). The PCPA-treated rats made more errors than the control rats ($p<0.05$; Mann-Whitney test).

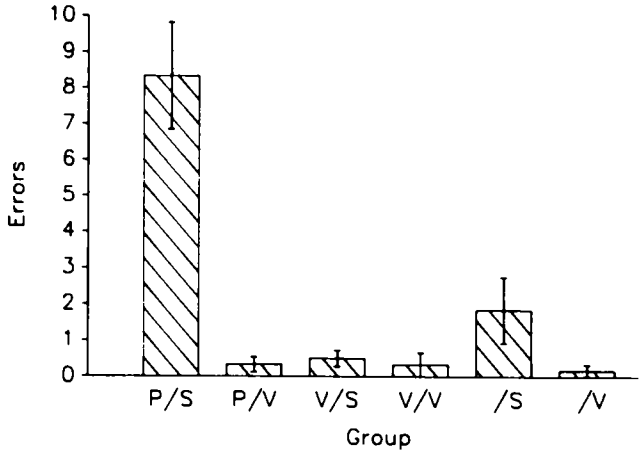

FIG. 3. Effects of PCPA and scopolamine on performance in a swim-to-platform test. Rats were given 10 training trials (not shown) followed by 10 retention trials 7 days later. On successive days, prior to retention testing, groups P/S and P/V received 3 daily doses of PCPA (500 mg/kg, IP); groups V/S and V/V received 3 daily doses of drug vehicle; groups /S and /V received no treatment. Groups P/S, V/S and /S received scopolamine (5 mg/kg, SC) 15–30 min prior to retention testing; groups P/V, V/V and /V received saline injections (SC) 15–30 min prior to retention testing. Six rats/group. Group P/S differs from each of the other groups ($p<0.02$ in each case, Mann-Whitney tests), but the latter do not differ among themselves.

The pass scores and error scores over all 36 rats correlated +0.25 during training ($p<0.01$), but correlated +0.90 ($p<0.01$) during retention, presumably as a result of the increased variability of the scores.

The rectal temperature was usually higher before swimming than after swimming. This decline was especially pronounced during retention testing in the PCPA plus scopolamine group (mean decline from 38.0 ± 0.3 to 30.9 ± 1.2) which spent a longer time in the water than the other groups. Since the mean of these temperatures is well above 30°, the poor performance of this group cannot be attributed to hypothermia.

DISCUSSION

The neurochemical assay data show that 6 days after treatment with large doses of PCPA there were 95–98 percent reductions in cortical levels of serotonin and 5-hydroxyindoleacetic acid plus more moderate reductions in the levels of tryptophan, noradrenalin, dopamine, 3,4-dihydroxyphenylacetic acid and homovanillic acid. Similar depletions were observed when rats were killed for assay one day after the PCPA treatment (24) indicating that serotonin levels remain low for a period of many days after PCPA treatment (9,16). The effect of PCPA on catecholamines and their metabolites and on tryptophan may be due to an influence on amino acid transport (6,21). However, since the PCPA-treated rats lost more weight than the control rats, reduced dietary intake of amino acids might also play some role in the nonspecific effects of PCPA.

In confirmation of previous work (24,26) in which records were also taken 24 hr after PCPA treatment, we have shown that large doses of PCPA suppress, partially or completely, scopolamine-resistant hippocampal RSA and scopolamine-resistant neocortical LVFA. This suppression is probably due to blockade of central serotonergic transmission since other means of depleting brain serotonin have the same effects. This has been shown for reserpine (12) and intracerebral injections of 5,7-dihydroxytryptamine, a specific serotonergic neurotoxin (29). Procedures that selectively block central catecholaminergic transmission have no direct effect on atropine- (or scopolamine-) resistant RSA and LVFA (10, 17, 31).

A combination of PCPA and scopolamine produced severe impairments in behavioral performance which were revealed most clearly in the experiments using the swim-to-platform test. Neither scopolamine nor PCPA alone had any effect on retention of swim-to-platform behavior, but when the two drugs were combined the rats swam around the water tank repeatedly, failing to climb up on the central platform. Very similar results were obtained when training was given for the first time after combined PCPA plus scopolamine treatment (22). As in the present experiments, swim-to-platform training was given on the day after completion of the PCPA treatment in this work. Therefore, the disrupting effects of the combined drug treatment are not reduced by previous experience with the test while in the normal state. In contrast, scopolamine or PCPA, given alone, produce a significant impairment when given prior to training, but no significant impairment when given prior to retention testing.

The results using the Lashley maze, though less complete, were consistent with those in the swim-to-platform test. Treatment with PCPA alone had no effect on retention of maze running, but a combination of PCPA and scopolamine resulted in more errors than a combination of the drug vehicle and scopolamine.

The swim-to-platform test, first devised by Morris (14), appears to be more useful in behavioral pharmacology than the Lashley maze. Maze training required adaptation to a schedule of food deprivation plus daily testing for over 2 weeks. When scopolamine was given, deficits in performance may have been partly due to loss of the ability to follow the true path accurately, but may also have been, in part, a secondary consequence of inability to eat the food reward. [It has long been known that antimuscarinic drugs block feeding (20).] In contrast, training or

testing a rat on the version of the swim-to-platform test used here took 5–10 min, and food deprivation and feeding were not involved. It should, perhaps, be pointed out that the swim-to-platform test used here is easier and probably less sensitive to defective brain function than the hidden platform type of test generally used by Morris. Further, Morris' tank was round while the one used here is rectangular.

It is unlikely that the behavioral deficit produced by PCPA plus scopolamine is restricted to learned behavior. Behavioral performances that are not dependent on any specific previous experience such as stopping and turning away from a sudden vertical decline (PCPA plus scopolamine-treated rats repeatedly walked off the edge of the recording platform while polygraphic records were being taken) or grooming the fur when wet (22) are disrupted in much the same way as are specially trained behaviors. Neither can the deficit be attributed to a low level motor impairment since rats treated with PCPA plus scopolamine run and swim as well as control rats (22). It may be that the behavioral deficit in rats treated with a combination of PCPA and scopolamine is due primarily to a generalized dysfunction of the activity of the cerebral cortex. Rats whose cerebral cortex has been surgically removed walk about actively with a nearly normal posture but, in the absence of cerebral control, their behavior is erratic and aimless (27,30). When the cerebral cortex is physically present, but the cholinergic and serotonergic inputs to it have been blocked by PCPA and scopolamine, its activity is clearly abnormal. For example, neocortical activity in a normal rat always consists of LVFA as the rat walks about, but large irregular slow waves occur during walking in a rat treated with PCPA and scopolamine. A syndrome of profound behavioral disorganization, large amplitude irregular slow activity in the electroencephalogram, and preservation of relatively normal waking postures and movements is also observed in human dementia (13). Since dementia of the Alzheimer type is also associated with a loss of cholinergic and serotonergic inputs to the cerebrum (2, 3, 18, 32), it is likely that the disorders in the PCPA-plus-scopolamine-treated rat and the demented human patient are fundamentally similar. Further research making use of animal preparations in which cholinergic and serotonergic inputs to the cerebrum have been partially or totally eliminated may ultimately be of benefit in the treatment of human dementia.

ACKNOWLEDGEMENTS

This research was supported by grants from the Natural Sciences and Engineering Research Council (C.H.V.) and the Alberta Heritage Foundation for Medical Research (G.B.B.). We thank R. K. Cooley and M.-E. Kelley for assistance in the experiments and L. Goyette for typing the manuscript. Part of the results of the swim-to-platform experiment reported here have previously been summarized by Vanderwolf, Baker and Dickson; in press.

REFERENCES

1. Baker, G. B.; Coutts, R. T.; Rao, T. S. Neuropharmacological and neurochemical properties of N-(2-cyanoethyl)-2-phenylethylamine, a prodrug of 2-phenylethylamine. Br. J. Pharmacol. 92:243–255; 1987.
2. Bowen, D. M.; Davison, A. N. Biochemical studies of nerve cells and energy metabolism in Alzheimer's disease. Br. Med. Bull. 42(1): 75–80; 1986.
3. Collerton, D. Cholinergic function and intellectual decline in Alzheimer's disease. Neuroscience 19:1–28; 1986.
4. Cooley, R. K.; Vanderwolf, C. H. Construction of wire leads and electrodes for use in slow wave recording in small animals. Brain Res. Bull. 3:175–179; 1978.
5. de Catanzaro, D. Practical statistics. West Flamborough, Ontario, Canada: Canadian Academic Technology; 1988.
6. Fuller, R. W. Drugs altering serotonin synthesis and metabolism. In: Green, A. R., ed. Neuropharmacology of serotonin. Oxford: Oxford University Press; 1985:1–20.
7. Green, J. D.; Arduini, A. A. Hippocampal electrical activity in arousal. J. Neurophysiol. 17:533–557; 1954.
8. Kenny, J. F.; Keeping, E. S. Mathematics of statistics. Toronto: D. Van Nostrand Co.; 1954.
9. Koe, B. K.; Weissman, A. *p*-Chlorophenylalanine: A specific depletor of brain serotonin. J. Pharmacol. Exp. Ther. 154:499–516; 1966.
10. Kolb, B.; Whishaw, I. Q. Effects of brain lesions and atropine on hippocampal and neocortical electroencephalograms in the rat. Exp. Neurol. 56:1–22; 1977.
11. Lashley, K. S. Brain mechanisms and intelligence: A quantitative study of injuries to the brain. Chicago: University of Chicago Press; 1929.
12. Leung, L.-W. S. Pharmacology of theta phase shift in the hippocampal CA1 region of freely moving rats. Electroencephalogr. Clin. Neurophysiol. 58:457–466; 1984.
13. Mahendra, B. Dementia: A survey of the syndrome of dementia. Lancaster: MTP Press Ltd.; 1984.
14. Morris, R. G. M. Spatial localization does not require the presence of local cues. Learn. Motiv. 12:239–260; 1981.
15. Moruzzi, G.; Magoun, H. W. Brainstem reticular formation and activation of the EEG. Electroencephalogr. Clin. Neurophysiol. 1:455–473; 1949.
16. Reader, T. A.; Briere, R.; Grondin, L.; Ferron, A. Effects of *p*-chlorophenylalanine on cortical monoamines and on the activity of noradrenergic neurons. Neurochem. Res. 11:1025–1035; 1986.
17. Robinson, T. E.; Vanderwolf, C. H.; Pappas, B. A. Are the dorsal noradrenergic bundle projections from the locus coeruleus important for neocortical or hippocampal activation? Brain Res. 8:75–98; 1977.
18. Rossor, M.; Iversen, L. L. Non-cholinergic neurotransmitter abnormalities in Alzheimer's disease. Br. Med. Bull. 42(1):70–74; 1986.
19. Siegel, S. Non-parametric statistics for the behavioral sciences. New York: McGraw-Hill; 1956.
20. Stein, L. Anticholinergic drugs and the central control of thirst. Science 139:46–48; 1963.
21. Tagliamonte, A.; Tagliamonte, P.; Corsini, G. V.; Mereu, G. P.; Gessa, G. L. Decreased conversion of tyrosine to catecholamines in the brain of rats treated with *p*-chlorophenylalanine. J. Pharm. Pharmacol. 25:101–103; 1973.
22. Vanderwolf, C. H. Near-total loss of "learning" and "memory" as a result of combined cholinergic and serotonergic blockade in the rat. Behav. Brain Res. 23:43–57; 1987.
23. Vanderwolf, C. H. Cerebral activity and behavior: Control by central cholinergic and serotonergic systems. Int. Rev. Neurobiol. 30:225–340; 1988.
24. Vanderwolf, C. H.; Baker, G. B. Evidence that serotonin mediates non-cholinergic neocortical low voltage fast activity, non-cholinergic hippocampal rhythmical slow activity and contributes to intelligent behavior. Brain Res. 374:342–356; 1986.
25. Vanderwolf, C. H.; Baker, G. B.; Dickson, C. Serotonergic control of cerebral activity and behavior: models of dementia. Ann. NY Acad. Sci.; in press.
26. Vanderwolf, C. H.; Harvey, G. C.; Leung, L.-W. S. Transcallosal evoked potentials in relation to behavior in the rat: Effects of atropine, *p*-chlorophenylalanine, reserpine, scopolamine and trifluoperazine. Behav. Brain Res. 25:31–48; 1987.
27. Vanderwolf, C. H.; Kolb, B.; Cooley, R. K. The behavior of the rat following removal of the neocortex and hippocampal formation. J. Comp. Physiol. Psychol. 92:156–175; 1978.
28. Vanderwolf, C. H.; Leung, L.-W. S. Brain electrical activity in relation to behavior. In: Boulton, A. A.; Baker, G. B., eds. Neuromethods, Series 1, General neurochemical techniques. Clifton, NJ: Humana Press; 1985:305–341.
29. Vanderwolf, C. H.; Leung, L. W. S.; Baker, G. B. The role of serotonin in the control of cerebral activity: Studies with intracerebral 5,7-dihydroxytryptamine. Brain Res. 504:181–191; 1989.
30. Whishaw, I. Q.; Kolb, B.; Sutherland, R. J. The analysis of behavior in the laboratory rat. In: Robinson, T. E., ed. Behavioral approaches to brain research. New York: Oxford University Press; 1983:141–211.

31. Whishaw, I. Q.; Robinson, T. E.; Schallert, T.; De Ryck, M.; Ramirez, V. D. Electrical activity of the hippocampus and neocortex in rats depleted of brain dopamine and norepinephrine: Relations to behavior and effects of atropine. Exp. Neurol. 62:748–767; 1978.
32. Whitford, G. M. Alzheimer's disease and serotonin: A review. Neuropsychobiology 15:133–142; 1986.