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P-Chloroamphetamine and a Side-Chain Fluorinated Analog: Effects on Brain Amine Levels and Behavior[1]

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BECK, C. H. M., H. L. CHOW, G. B. BAKER AND R. T. COUTTS. *P-chloroamphetamine and a side-chain fluorinated analog: Effects on brain amine levels and behavior.* PHARMACOL BIOCHEM BEHAV **20**(2) 215–220, 1984.—Reserpinized (1 mg/kg, IP—24 hr) and saline-pretreated male rats were subdivided into groups receiving p-chloroamphetamine (pCA, 5.2 mg/kg, IP), 1-fluoromethyl-2-p-chlorophenylethylamine (FpCA, 5.6 mg/kg, IP), or saline, 90 minutes before the testing of behavior in the open-field and 150 minutes before sacrifice for assay of brain levels of amines. FpCA and pCA produced identical investigative and social patterns of behavior in saline pretreated animals in spite of the fact that pCA reduced serotonin levels whereas FpCA did not. Both pCA and FpCA enhanced dopamine and noradrenalin levels compared to saline controls. The behavioral syndrome common to FpCA and pCA animals was one of increased sitting still, and decreased locomotion and self-grooming while alone, and decreased locomotion, and social behavior but increased sniffing of the environment while in the company of an untreated male rat. Rerserpine pretreatment exacerbated this syndrome of inactivity in pCA more than in FpCA rats even though the reserpinized groups did not differ from each other in the concentrations of the three amines.

Para-chloroamphetamine 1-Fluoromethyl-2-parachlorophenylethylamine Reserpine Serotonin
Noradrenalin Dopamine Open-field Exploratory behavior Social behavior

THE continuing interest in the role of 5-hydroxytryptamine (5-HT) in depression has led to a concerted effort to profile the therapeutic efficacy of serotonergic agonists (cf., [38]). Para-chloroamphetamine (pCA), noted for its rapid release of 5-HT [13] showed therapeutic promise in improvement of mood, motility and work interest of depressed patients [39]. Therapeutic contraindication of pCA because of its neurotoxic properties [16] led to a search for pCA analogs with reduced serotonin depleting action. A side-chain fluorinated analog of pCA, 1-fluoromethyl-2-p-chlorophenylethylamine (FpCA) compared to pCA resulted in smaller reductions in brain 5-HT concentration and in reduced release of [^{3}H]-5-HT from striatal slices [2,6].

The purpose of the present study was to compare the acute effects of pCA and FpCA on the short-term changes in concentrations of whole brain noradrenalin (NA) and dopamine (DA) as well as 5-HT. The action of pCA is attenuated by reserpine-induced depletion of amine stores [30,31]. The potential significant interaction of the effects of reserpine with the differential serotonergic effects of pCA and FpCA warranted the comparison of the behavior and brain amine levels of FpCA and pCA animals following saline or reserpine pretreatment. Alternating periods of lone investigative behavior and periods of social interaction with a same-sex conspecific were used to compare the behavioral effects of pCA and FpCA. The exploration of a novel environment by a single animal has been the staple behavioral paradigm in psychopharmacological studies of anxiety and depression in general [7,17] and in pCA studies in particular [18,34]. Observation of the short term effects of pCA on social behavior of animals has not been reported although the paradigm is gaining currency in the psychopharmacological literature [11,23] and would appear to be of particular relevance for describing behavioral sequelae of serotonergic action [8].

METHOD

Animals

Seventy-two male Sprague Dawley rats from the University of Alberta breeding colony, with a body weight range of 275 to 305 g, were housed individually in a room maintained at a temperature of 19°C and a relative humidity of 51%. Food and water were freely available in the home cages but were not available in the test apparatus. The animals had been previously adapted to a lighting cycle in which the lights were off between 0800 and 2000 hr. During the two weeks prior to testing, the animals were adapted to handling. Before testing began, the animals were randomly paired and the pairs assigned to six groups of six pairs per group. One

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animal of each pair was designated as the experimental animal and the other as the unobserved-animal.

Drug Treatments

The drugs used were (±)-para-chloroamphetamine hydrochloride (Sigma), (±)-1-fluoromethyl-2-p-chlorophenylethylamine hyrochloride [6] and reserpine (Serapsil injection, CIBA). All drugs were dissolved in 0.9% saline immediately before use.

Half of the experimental animals were pretreated with saline (2 ml/kg, 0.9% NaCl, IP) and half with reserpine (1 mg/kg, IP). "Unpublished work" in this laboratory showed that at higher doses of reserpine the rats became completely inactive behaviorally. Twenty-four hours later, six of the saline-pretreated and six of the reserpinized animals were given saline (2 ml/kg, 0.9% NaCl, IP, saline-saline group and reserpine-saline group respectively). Comparable groups were given pCA (5.2 mg/kg, IP, saline-pCA and reserpine-pCA groups) or the mole equivalent dose of FpCA (5.6 mg/kg, IP, saline-FpCA and reserpine-FpCA groups). The rats serving as unobserved social partners were not injected.

Behavioral Procedure

The rats were tested behaviorally during a preinjection injection session immediately before the initial pretreatment injection and were tested again during a postinjection session 1 hr after the treatment injection. Each session included 25 minutes of adaptation to the open-field test chamber, followed by one hour of observation in the open-field. The stereotypic behaviors elicited by pCA in the first half hour postinjection were not studied since these have been well documented [18]. All behavioral testing took place between 0900 and 1600 hours in the dark phase of the light cycle to ensure that a full range of activity would be observed. Animals from different groups were counterbalanced for time of testing and were randomly assigned to their order in the testing-sequence over days.

The experimental rats were observed through a one-way mirror as they moved about a 66 cm by 66 cm by 63 cm high open-field. The floor of the open-field was divided into 30 equal squares and was illuminated dimly by a 40 watt red light bulb hung 90 cm above the floor. The floor and walls were scrubbed after the testing of each rat.

The behavior of the experimental rat in the open-field was recorded during 15 two-minute observation periods spaced over a 60 minute session. The observation periods were clustered into five trials of three periods in each trial. The intertrial interval was five minutes and the interperiod interval within trials was one minute. The experimental rat's unobserved partner was present in the open-field during the second and fourth trial, referred to as *pair* trials. During the intertrial intervals and during the remaining three trials, trials one, three and five, referred to as *alone* trials, the experimental rat was alone in the field. The rats were placed into and removed from the open-field by hand.

The observer recorded the experimental rat's behavior continuously throughout each observation period by entering coded symbols for each behavior on a microprocessor keyboard. The microprocessor was programmed to store the behavior codes and their time of occurrence. The behaviors used were: *locomote*, moving body forward, backward or turning; *rear*, raising the forepaws so that they were not touching the floor or the unobserved animal; *sniff-field*, sniffing the environment as indicated by nose and whisker twitching while otherwise sitting still; *self-groom*, licking, combing, mouthing or scratching itself; *allogroom*, grooming the unobserved rat in a nonaggressive manner; *allosniff*, sniffing the unobserved animal; *aggress* and *submit*, included all such behaviors as described by [25]; *inactive*, immobile while not exhibiting any of the other behaviors.

Aggressive and submissive behaviors were accorded preferential recognition over other behaviors. For example, if the experimental rat arched its back, reared, bent over the back of the unobserved rat and nibbled its neck fur, this behavior was scored as aggression, and not as allogroom or rear. Since the behaviors constituted a mutually exclusive and exhaustive rendering of the rat's repertoire, it was possible to compute the frequency and duration of each bout of behavior and the percent of total session time spent on each behavior. Frequency was defined as the number of bouts of a behavior per trial. Duration was the mean duration (sec) of the bouts of a behavior per trial. Percent total time was the sum of all bout durations of a behavior in a trial expressed as a percent of the total trial duration. Test-retest and interjudge agreement on behavior coding was in the 80 to 90% range.

TABLE 1
MEAN WHOLE BRAIN CONCENTRATIONS OF 5-HT, DA, AND NA

Group	Amine		
	5HT	DA	NA
Saline-saline	100*	100†	100†
Saline-FpCA	89*	146*	121*
Saline-pCA	27†	136*	116*
Reserpine-saline	29†	56‡	43‡
Reserpine-FpCA	37†	63‡	33‡
Reserpine-pCA	21†	66‡	34‡

Expressed as a percent of saline-saline group values. Groups n=6 rats. *, †, ‡Duncan multiple range differences between groups, $p<0.05$. Means with identical postscripts are not significantly different from each other. Means with different postscripts are significantly different from each other.

Biochemical Analysis

Immediately after the postinjection observation session, that is 2.5 hr after the treatment injection, the experimental rats were decapitated. Extracts of their brains, excluding the pineal glands, were assayed by gas chromatography for the concentration of 5-HT [1] and by a radioenzymatic procedure for concentrations of DA and NA [21].

Statistical Evaluation

Analysis of variance was used to determine the significance of group main effects of brain amine concentrations. Differences between the groups was assessed by the Duncan multiple range test.

The three dependent measures of each behavior, bout, frequency, bout duration, transformed, square root (x+1), and percent total time were subjected to repeated measures analysis of variance to determine the significance of main effects (groups, sessions, trials and conditions) and interactions for each behavior. Differences between components within significant main effects were assessed by the Duncan

TABLE 2

MEAN PERCENT TIME SPENT ON BEHAVIORS IN ALONE CONDITION

Group	Behavior				
	Locomote	Rear	Sniff-field	Inactive	Self-groom
Saline-saline	3.5*	5.7*	44.0*	26.4†	20.4*
Saline-FpCA	1.0†	2.0†	29.0*†	65.7*	2.3†
Saline-pCA	0.3†	0.0†	37.0*	60.9*	1.8†
Reserpine-saline	0.2†	0.1†	13.1†‡	64.6*	22.0*
Reserpine-FpCA	0.0†	0.1†	7.8‡	79.1*	13.0*†
Reserpine-pCA	0.0†	0.0†	16.5†‡	81.8*	1.7†

All data from postdrug session. Group n=6 rats. *, †, ‡Duncan multiple range differences between groups, $p<0.05$. Refer to Table 1 for elaboration.

multiple range test. The Michigan Terminal System Revised SPSS programs (Anova and Anovar) were used in computations.

RESULTS

Significant group main effects were obtained for whole brain concentrations of each of the amines: for 5-HT, $F(5,30)=31.43$, $p<0.0001$; for DA, $F(5,30)=34.3$, $p<0.0001$; for NA, $F(5,30)=96.4$, $p<0.0001$. Amine whole brain levels for each group relative to the saline-saline group are presented in Table 1. Mean (±SEM) whole brain concentrations (ng/g) for the saline-saline group were: for 5-HT 652.6 (±60.5); for DA 709.0 (±43.9); for NA 386.5 (±11.6). The Duncan multiple range analysis in Table 1 shows that the three reserpine pretreated groups had significantly lower levels of 5-HT, DA and NA than the saline-saline group. Both the FpCA and pCA groups pretreated with saline had significant elevations of DA and NA relative to the saline controls. Concentrations of 5-HT in the saline-pCA animals were significantly lower than those of the saline-saline and saline-FpCA groups. The saline-FpCA group did not differ significantly from the saline-saline group in the concentration of 5-HT.

The behavioral pattern of drug effects did not differ significantly among the three dependent measures (bout frequency, bout duration and total time spent). Percent total time spent was chosen as the measure to represent the data in this report since it is a composite measure reflecting changes in both frequency and duration. The percent time spent on each behavior in the preinjection session did not differ significantly among the six groups. The saline-saline group's preinjection behavioral measures did not differ from those obtained for the same group in the postinjection session. As the latter set of values were the most appropriate control for proactive temporal effects, the postinjection scores were used as control values for comparison with the other groups' postinjection behavior scores. Analysis of variance of percent time spent on each behavior in the postinjection session revealed significant group main effects for all behaviors in the alone and pair conditions except for rear and self-groom in the pair condition. For the alone condition, the significant group effects were: locomote $F(5,30)=3.61$, $p<0.011$, rear $F(5,30)=5.09$, $p<0.002$, sniff-field $F(5,30)=4.84$, $p<0.002$, inactive $F(5,30)=3.88$, $p<0.008$, and self-groom $F(5,30)=3.66$, $p<0.011$. For the pair condition the significant group effects were: locomote $F(5,30)=7.09$, $p<0.001$, sniff-field $F(5,30)=4.89$, $p<0.002$, inactive $F(5,30)=11.36$, $p<0.001$, allogroom $F(5,30)=3.62$, $p<0.011$, aggress $F(5,30)=4.72$, $p<0.003$, and allosniff $F(5,30)=7.53$, $p<0.001$. Significant trial main effects were obtained only for alone self-groom $F(2,60)=6.26$, $p<0.003$ and pair locomote $F(1,30)=13.89$, $p<0.001$, rear, $F(1,30)=9.29$, $p<0.005$ and aggress $F(1,30)=6.74$, $p<0.014$. None of the group by trial interactions was significant.

The percent of time spent by each group on each behavior in the postinjection session is shown for the alone condition in Table 2 and for the pair condition in Tables 3 and 4. None of the comparisons of the groups pretreated with saline revealed significant behavioral differences between animals treated with pCA and those treated with FpCA. These comparisons included the direct comparison of saline-pCA with saline-FpCA group scores and the comparison of the pattern of differences both of these groups had with saline-saline group scores. This pattern of differences from the saline-saline group for both the pCA and FpCA groups was, in the alone condition, increased inactivity but decreased locomotion, rear and self-groom, and in the pair condition, increased sniff-field but decreased locomotion, allogroom, aggress and allosniff (Tables 2, 3, 4).

In contrast to the lack of significance between the behavioral scores of the saline-pCA and saline-FpCA groups, comparison of the effects of pCA with those of FpCA in rats pretreated with reserpine revealed several significant behavioral differences. The reserpine-FpCA group did not differ from the reserpine-saline group, whereas the reserpine-pCA group spent significantly less time in self-groom while alone, and less time in locomote and allosniff and more time being inactive while paired than did the reserpine-saline animals. Direct comparison of the reserpine-pretreated pCA and FpCA groups revealed only the effect on inactivity to be significant. Finally the two groups showed the same pattern of differences from the reserpine-saline group (Tables 2, 3, 4).

Reserpine had several effects on the percent of time spent on various behaviors. When alone, rats in the reserpine-saline group compared to those in the saline-saline group showed more inactivity and less locomotion, rear and sniff-field. When paired they showed more self-groom, but less locomote and aggression. Reserpine-FpCA rats compared to saline-FpCA rats when alone, indulged in less sniff-field. Finally reserpine-pCA rats compared to saline-pCA rats when alone, engaged in less sniff-field and, when paired with another rat, were more inactive but less likely to locomote or sniff-field (Tables 2, 3, 4).

TABLE 3
MEAN PERCENT TIME SPENT ON NONINTERACTIVE BEHAVIORS IN PAIR CONDITION

Group	Behavior				
	Locomote	Rear	Sniff-field	Inactive	Self-groom
Saline-saline	25.6*	5.9*	16.0‡	5.2‡	3.9†
Saline-FpCA	10.7†	2.8*	45.0*†	10.0†‡	9.8*†
Saline-pCA	11.8†	3.6*	55.0*	10.0†‡	3.5†
Reserpine-saline	10.4†	2.8*	35.0†‡	6.7†‡	12.7*
Reserpine-FpCA	8.3†‡	1.8*	35.0†‡	23.1†	5.1*†
Reserpine-pCA	0.6‡	0.0*	24.0‡	46.9*	5.7*†

All data from postdrug session. Group n=6 rats. *, †, ‡Duncan multiple range differences between groups, $p<0.05$. Refer to Table 1 for elaboration.

TABLE 4
MEAN PERCENT TIME SPENT IN INTERACTIVE BEHAVIORS IN PAIR CONDITION

Group	Behavior			
	Allogroom	Aggress	Submit	Allosniff
Saline-saline	13.8*	5.7*	10.3*	13.6*
Saline-FpCA	0.3†	0.2†	17.3*	3.9‡
Saline-pCA	3.3†	0.3†	9.9*	2.6‡
Reserpine-saline	6.7*†	2.5†	12.1*	11.1*†
Reserpine-FpCA	1.1†	0.2†	19.5*	5.9†‡
Reserpine-pCA	0.0†	0.0†	22.5*	0.3‡

All data from postdrug session. Group n=6 rats. *, †, ‡Duncan multiple range differences between groups, $p<0.05$. Refer to Table 1 for elaboration.

The effect of social stimulation on the treated animals is shown in Table 5. When paired with another rat, compared to being alone, the saline-saline rats spent 43% of their time in social interaction (Table 4), increased their level of locomote, and decreased the time spent on self-directed or field-directed behaviors (Table 5). Considering all drugged animals together, social stimulation greatly reduced inactivity and enhanced sniff-field (Table 5), but failed to generate as much social interaction (Table 4) or locomote (Table 5) as in saline-saline controls. The reserpine-pCA group was the group least affected by the introduction of a partner into the field.

DISCUSSION

In agreement with published reports, reserpine reduced whole brain concentrations of 5-HT [20, 31, 32], NA, and DA [31]. The observation that pCA depleted whole brain 5-HT confirmed the classic action of this drug (cf., [12]) and replicated an earlier report from this laboratory that the effect is greater than that obtained with a mole equivalent dose of FpCA [2]. Our finding that pCA raised the concentration of dopamine supports the consensus that pCA has a short-lived dopaminergic action [4, 5, 9, 19, 35, 36]. As in this study, others have reported significant increases in NA levels shortly after pCA administration [15, 26, 28]. Increased levels of normetanephrine, a noradrenaline metabolite, have been observed by others after pCA treatment [9, 34, 37]. However, it has not been previously reported that FpCA augments DA and NA levels. A subsequent dose of FpCA or pCA did not change the amine depleting effects of reserpine as measured by whole brain levels of those amines. In summary, the side-chain monofluorinated analog of p-chloroamphetamine mimicked the pCA enhancement of whole brain DA and NA levels but, unlike pCA, FpCA failed to significantly deplete whole brain 5-HT.

There is general agreement that reserpine acutely decreases locomotor activity scores [10, 20, 30, 31]. Our results confirm and extend those observations to include reduced rearing, sniffing the environment, and reduced social interaction. The enhancement of self-grooming by reserpine has not been previously reported in rodents, although increased self-huddling and social withdrawal has been observed in chronically reserpinized monkeys [22]. The addition of pCA decreased reserpine-induced grooming in the present study. To summarize, reserpine depressed activity directed toward the environment and toward another rat but increased self-directed activity.

Para-chloroamphetamine, compared to saline, decreased the frequency of walking, rearing, and self-grooming by a lone animal in an open-field [18]. The methodology used in that experiment was very similar to that of the alone condition in the present study. Our results support and extend these observations to include other effects not measured in

TABLE 5

ALONE TO PAIR CONDITION MEAN PERCENT TIME INCREASE (+) OR DECREASE (−)

	Behavior				
Group	Locomote	Rear	Sniff-field	Inactive	Self-groom
Saline-saline	+22.1*	+0.3*	−27.7†	−20.8*	−16.5†
Saline-FpCA	+ 9.8†	+1.0*	+15.3*	−53.1†‡	+ 7.6*
Saline-pCA	+11.6†	−3.6*	+18.3*	−52.9†‡	+ 1.7*†
Reserpine-saline	+10.3†	−2.8*	+21.7*	−59.8‡	− 9.0*†
Reserpine-FpCA	+ 8.3†‡	+1.8*	+26.7*	−52.6†‡	− 8.2*†
Resrpine-pCA	+ 0.6‡	0.0*	+ 7.5*	−24.3*†	+ 4.0*

Mean percent time spent on noninteractive behaviors in the postdrug session. Group n=6 rats.
*, †, ‡Duncan multiple range differences between groups, $p<0.05$. Refer to Table 1 for elaboration.

the previous study [18]. Specifically these effects were increased sniffing the environment and decreased locomotion, allogrooming, allosniffing, and aggression while in the open-field in the company of an untreated animal.

In contrast to Kutscher's [18] and our results, several studies have noted increased locomotor activity following pCA treatment (cf., [33]). Differences in methodology such as time of testing, length of test sessions, environmental novelty, and size of test apparatus have been suggested to account for the disparate effects of pCA on gross bodily activity [14]. It is worth remarking that although the level of activity in our pCA animals was low, the activity was reduced even more by the addition of reserpine in agreement with the literature [3, 27, 29, 30]. Specifically, the reserpine-pCA group showed depressed sniff-field, depressed locomotion and increased inactivity compared to the saline-pCA animals.

FpCA and pCA behavioral effects may be compared in several ways. Saline-FpCA and saline-pCA groups did not differ from each other, nor did they differ in the way in which they deviated behaviorally from saline-saline controls. By contrast the reserpine-pCA group was more inactive than the reserpine-FpCA group. In addition reserpine-pCA rats, compared to reserpine-saline rats, spent less time sniffing the environment when alone, more time inactive, and less time in locomotion and in sniffing the environment when paired with another rat. However reserpine-FpCA rats behaved like reserpine-saline animals. A similar pattern of FpCA to pCA differences emerged from the comparison of the effects of reserpine on the two treatments: viz. saline-pCA vs. erserpine-pCA compared to saline-FpCA vs. reserpine-FpCA.

To summarize, the FpCA animals did not differ behaviorally from the pCA animals following saline pretreatment, despite the lower 5-HT levels in the pCA rats. Paradoxically, reserpine pretreatment revealed behavioral differences between FpCA and pCA rats but no differences in whole brain concentrations of the amines. Recent reports suggest that regional brain concentrations of amines [28] or amine release and receptor kinetics [24] might reveal the latent linkage between behavior and neurochemistry. Finally, it is noteworthy that the significant behavioral differences between FpCA and pCA animals involved social stimulation in 4 out of 5 instances and involved behaviors other than locomotion in 4 out of 5 cases. If the behavioral paradigm had focused on the locomotor activity of the lone rat, as is often the case (cf., [14]), no significant differences in behavior between FpCA and pCA animals would have been observed.

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