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Differential Effects of *d*-Amphetamine on Vigilance in Younger and Older Male Rats

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GRILLY, D. M. AND B. B. SIMON. *Differential effects of* d-*amphetamine on vigilance in younger and older male rats.* PHARMACOL BIOCHEM BEHAV **49**(3) 497-502, 1994.—After training to comparable levels of performance on a two-choice, discrete-trial vigilance task, younger (9 mo) and older (26 mo) male F344xBN rats were tested after SC injections of *d*-amphetamine (0.125, 0.25, 0.50, and 1.0 mg/kg). Relative to their saline treatment performance levels, both groups exhibited decreases in choice latencies under the lower doses of amphetamine and an increase in food retrieval latencies after 1.0 mg/kg amphetamine. The percentage of correct responses in the older animals was lower than in the younger animals at all doses of amphetamine, and the groups differed significantly at the 0.25 and 0.50 mg/kg doses. There were no significant differences between the groups in either of the latency measures at any of the doses of amphetamine. These results suggest, as has been demonstrated with cocaine, that the alertness-altering properties of amphetamine are qualitatively different in older and younger adult organisms.

Amphetamine Performance Vigilance Age Rats

ALTHOUGH there has been little systematic research into the potential changes in the behavioral effects of psychostimulants as organisms age, a considerable body of literature indicating dramatic age-related declines in presynaptic and postsynaptic components of dopaminergic systems (20,21,23) suggests that the behavioral effects of dopamine (DA) agonists should change considerably in aged organisms.

For example, virtually all studies with humans have suggested that aging results in a decrease in sensitivity to the effects of amphetamine (an indirect DA agonist), since the therapeutic benefits of amphetamine (e.g., mood elevation and enhanced alertness) appear to decrease in elderly patients (1,3,4,16,17,22), although the side-effects may increase (4). In contrast, the majority of studies with nonhumans have indicated that older animals may be more sensitive to the effects of amphetamine with respect to food intake (5), body temperature increases (7,25), motor activity (25), and stereotypy (6,13,24).

Cocaine is an indirect DA agonist with properties similar to amphetamine, and it has recently been demonstrated that the effects of cocaine also change in aged animals (9). In Grilly (9) different aged adult rats were trained to perform a task in which performance was heavily dependent on vigilance (sustained attention) and then tested after acute administration of cocaine. The results indicated that, relative to baseline (saline) levels of performance, a low dose (2.5 mg/kg) of cocaine produced significant increases in accuracy and decreases in choice latency in 6- to 18-month-old rats, whereas none of the low doses of cocaine (1.25, 2.5, and 5.0 mg/kg) enhanced accuracy in 21- to 36-month-old rats and the decreases in choice latency were less reliable. Furthermore, a 15 mg/kg dose of cocaine, which increased the variability in the accuracy and choice latency measures in the 6- to 18-month-old rats without changing mean performance levels, significantly reduced accuracy and increased choice latency in 25- to 36-month-old rats. It was concluded from these results that there is a qualitative change in cocaine's behavioral effects as rats age, rather than a simple increase or decrease in sensitivity to cocaine's effects.

It was also suggested that, because of the biochemical and behavioral similarities between cocaine and amphetamine, these findings could reconcile the long-standing discrepancies in the literature regarding age-related changes in the behavioral effects of amphetamine. That is, because the studies with humans used doses of amphetamine that were considerably lower than those used with nonhumans, as was demonstrated with cocaine, the type of effect may depend more on the interaction between age and dose of amphetamine than to species differences.

Therefore, the purpose of the present study was to test

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the hypothesis that amphetamine would produce qualitatively different dose-dependent effects in younger and older animals with respect to vigilance task performance. Previous studies (11,12) using this paradigm have shown that in young to middle-aged adult rats low doses of amphetamine (0.125–0.5 mg/kg) enhance choice accuracy, whereas moderate doses of amphetamine (1.0–1.5 mg/kg) increase the variability among animals in choice accuracy without producing significant changes in the average group accuracy level. Thus, it was predicted that: (a) low doses of amphetamine (0.125–0.5 mg/kg) would produce less of a facilitative effect on task accuracy of older adult rats; and (b) a moderate dose of amphetamine (1.0 mg/kg) would produce greater disruptions in the accuracy of older adult rats. We also used a different strain of rats (Fischer 344 Brown Norway [F344xBN] vs Sprague-Dawley) to establish whether the effects were specific to the particular strain of rat. Finally, we eliminated some of the confounding factors that could have influenced the results of (9). Other than differences in age and body weights at the time of drug testing, in the present study all animals were maintained on the same food restriction diet for several months prior to testing, had no previous drug exposure, had the same amount of practice on the task, and were tested at the same time of the year.

METHOD

Animals

Male F344xBN rats (obtained from Charles River Laboratories) were caged in pairs. Water was available ad lib in their home cages. The animals were maintained in a 22°C, 50% humidity facility under a 12-h light-dark cycle (lights on 0800 h).

Upon arrival in the laboratory, the animals were 3 mo (N = 15) and 20 mo (N = 15) of age, at which time their mean weights were 336 g and 564 g, respectively. The older rats were immediately placed on a food restriction diet of 10 g of rodent chow (Agway Prolab RMH 2000) a day. Two weeks after arrival, the older rats (M weight = 533 g) were allowed access to the pellets used as reinforcers in the vigilance task (45 mg Bioserv dustless precision pellets) for 1 h. None of the rats ate the reward pellets. One week later, the older rats (M weight = 493 g) were again allowed access to the reward pellets, which the majority of rats ate. One week later, the older rats (M weight = 469 gm) began the training phase. Five and a half months after arrival, the older rats (M weight = 466 gm) began the drug testing phase. (One rat from this group developed a tumor and was discarded.)

After their arrival in the laboratory, the younger rats were initially fed ad lib for 4 weeks (M weight = 349 g) and then placed on a food restriction diet of 10 g rodent chow a day. Four weeks later, the younger rats (M weight = 346 g) began the training phase. Five and a half months after arrival, the younger rats (M weight = 365 g) began the drug testing phase.

In summary, drug tests were conducted when the animals were approximately 9 mo (younger adults) and 26 mo (older adults) of age. While the older rats weighed approximately 100 g more than the younger rats during the drug test phase, it is unlikely that differences in the task performance of the two groups were due to potential age-related differences in food motivation (2) because both groups had been maintained on the same food restriction diet for approximately 4.5 months, and both groups exhibited comparable baseline levels with respect to choice latency and food retrieval latency (see Results).

Apparatus

Two operant chambers were interfaced with Apple IIe 64K microprocessors, which controlled experimental events and collected data. Two levers were located at one end of the chambers. Located between the two levers was a food tray, into which single 45-mg food pellets were delivered as reinforcers. A microswitch was activated when the rat's head was inserted into the opening. The cue lights were located directly above each lever, and a house light was located in the middle of the ceiling. Further details of the apparatus can be found in Grilly (10).

Procedure

During the training and test sessions (100 trials per session), there was no illumination in the room containing the operant chambers. Trials began with the house light in the chamber coming on. Prior to cue light presentation, the rat had to have its head out of the food tray and had to refrain from pressing either lever for 1.0 s. The cue light above one of the levers was then illuminated briefly (there was a minimum of 1.7 s between house light onset and cue light onset). Cue light duration was individually determined as described below. Following cue light termination, if the lever beneath the cue light was pressed, food was delivered (accompanied by a 40-ms light presentation inside the food tray), and 1.0 s after the rat inserted its head in the food tray, the house light was turned off. If the other lever was pressed, the house light was turned off. If no response occurred within 10 s the trial was terminated. Intertrial intervals were between 7 and 10 s. The position of the cue light was randomly determined except that there were no more than six successive trials with the light present in the same position. Within a session, the total number of trials with each cue did not differ by more than two. Sessions were approximately 21 to 35 min long (the latter occurred if the animal made no responses in a session).

All animals began training with the cue light staying on until the animal made a choice. Upon reaching a criterion of at least 95% correct responses with this procedure, the cue light duration was set at 1.8 s. If an animal's correct responses exceeded 75%, the cue light duration was decreased by 0.3 s in the next session. Once correct responses dropped below 75%, the cue light duration for the next session was increased by 0.15 s. If correct responses were still below 75%, cue light duration was increased by 0.15 s every two sessions until 75% correct responses was achieved. If the animal exceeded 87% correct responses, the cue duration was again decreased by 0.3 s followed by increases of 0.15 s, if needed, until accuracy was within the criteria for four successive 100 trial sessions without a change in cue light duration. The drug treatment phase began once the animals met the criteria of 75% to 87% correct choices for four consecutive 100 trial sessions. These criteria were chosen so that ceiling and basement effects would not obscure drug-induced effects. The top criterion (87%) allows for detection of drug enhancement effects, and the bottom criterion (75%) allows for detection of detrimental drug effects above chance levels.

Mean final cue light durations were M = 1.13 s (range = 0.90–1.65 s) for the younger animals and M = 1.28 s (range = 0.75–2.10 s) for the older animals. The average number of training trials on the task (including initial discrimination training trials) was 2990 (SD = 180) and 3300 (SD = 250) for the younger and older animals, respectively.

Drug test sessions (conducted between 1100 and 1400 h) consisted of 100 trials each and were conducted a minimum of

5 days apart. Saline or doses of *d*-amphetamine sulfate of 0.125, 0.25, 0.50, and 1.0 mg/kg were administered SC 30 min prior to test sessions. The order of these treatments was randomly determined for each rat. Amphetamine was diluted with 0.9% saline, and solutions were prepared so that all injections were given in a volume of 1.0 ml/kg. All doses are expressed as the salt.

RESULTS

The following behavioral measures were derived for each animal under each drug treatment: (a) accuracy (percent correct choices); (b) median choice latency (time between cue light offset and lever press); and (c) median food retrieval latency (time between lever press and food tray entry). Because of the expected increase in the variability of the scores as the dose of amphetamine increased, particularly in the older animals, measures of central tendency and variability were derived using the trimmed means approach (27), with 20% trimming. Statistical comparisons between the groups were conducted using Yuen's (28) method based on trimmed means. Values of T_y derived through this method were evaluated for significance at the 0.05 level (one tailed), with the prediction that the younger animals would exhibit higher accuracy scores than the older animals. The two groups were not predicted to be significantly different in the choice latency and food retrieval measures, since a previous study with cocaine had indicated that older rats did not differ from young adult rats in these measures until very old age, at which point motor disabilities may become a factor (9). For statistical comparisons between the groups under the four dose levels of amphetamine, all individual animals' drug treatment scores were first transformed into percentage change scores, i.e., (Drug − Saline)/Saline) × 100.

The dose-related effects of amphetamine on the trimmed means of the untransformed measures in the two groups are shown in Table 1. Choice accuracy in the younger rats was increased following doses of 0.25 and 0.50 mg/kg amphetamine. This group's mean accuracy decreased somewhat after the 1.0 mg/kg dose of amphetamine, and within subject variability was increased (one rat did not complete any trials at the 1.0 mg/kg dose). In contrast, none of the doses of amphetamine enhanced accuracy in the older rats, and the 1.0 mg/kg dose produced a greater decrease in accuracy in this group as well as increasing within subject variability. Within group statistical comparisons (two tailed *t*-tests for correlated measures, $\alpha = 0.05$) indicated that compared to saline levels: (a) mean percent correct responses for the younger group was significantly higher after 0.25 mg/kg amphetamine; and (b) mean percent correct responses for the older group was significantly lower after 1.0 mg/kg amphetamine. Between group comparisons of the percentage change in accuracy scores indicated that the groups were significantly different at the 0.25 and 0.50 mg/kg doses [$T_y(17) = 1.83$ and $T_y(19) = 2.92$, respectively].

As shown in Table 1, mean choice latency scores were decreased in both groups at all four doses of amphetamine; none of the between group comparisons of the percentage change in choice latency were statistically significant. Mean food retrieval latency scores were increased in a dose-dependent fashion in both groups, but none of the between group comparisons of percentage change scores were significant. Within group statistical comparisons (two tailed *t*-tests for correlated measures, $\alpha = 0.05$) indicated that compared to saline performance levels: (a) mean choice latency scores for the younger group were significantly lower after 0.125, 0.25, and 0.5 mg/kg amphetamine; and (b) mean choice latency scores for the older group were significantly lower after 0.25 and 0.5 mg/kg amphetamine. Statistical comparisons between saline and 1.0 mg/kg amphetamine for the latency measures were not performed because of the considerable variability both between and within animals across trials at the 1.0 mg/kg dose, e.g., the number of choice response trials ranged between 0 and 100, and the number of trials in which food retrieval latencies exceeded 10 s ranged from 0–31. However, all animals showed an increase in their median food retrieval latency scores at the 1.0 mg/kg dose.

Although previous studies utilizing this task have shown that the overall measures of accuracy and choice latency may be independently affected by a variety of treatments (10,12), we have also demonstrated that overall percent correct responses is to some extent related to choice latency, i.e., the

TABLE 1

TRIMMED MEANS FOR PERCENT CORRECT CHOICE, MEDIAN CHOICE LATENCY, AND MEDIAN FOOD RETRIEVAL LATENCY FOR THE TWO GROUPS AS A FUNCTION OF DOSE OF *d*-AMPHETAMINE (mg/kg)

Amphetamine Dose	Group	Percent Correct (SEM)	Choice Latency (sec)	Food Retrieval Latency (sec)
Saline	Younger	79.2 (2.4)	0.63 (0.07)	0.55 (0.05)
	Older	81.0 (1.7)	0.71 (0.05)	0.58 (0.04)
0.125	Younger	82.3 (1.8)	0.48 (0.04)	0.57 (0.06)
	Older	80.8 (1.9)	0.59 (0.06)	0.66 (0.05)
0.25	Younger	85.3 (2.4)*	0.53 (0.08)	0.59 (0.05)
	Older	81.7 (1.8)	0.53 (0.08)	0.62 (0.04)
0.50	Younger	84.6 (2.5)*	0.49 (0.07)	0.61 (0.07)
	Older	77.7 (2.2)	0.49 (0.03)	0.71 (0.05)
1.0	Younger	78.9 (2.6)	0.42 (0.03)	0.89 (0.10)
	Older	74.6 (3.1)	0.49 (0.05)	0.89 (0.06)

*Groups significantly different in terms of percentage change from saline levels of performance; SEM in parentheses.

faster a choice is made the higher the probability of a correct response. Thus, to further explore the differences between the two age groups in this study, we derived mean percent correct responses for four types of trials: (a) trials in which a lever press was initiated prior to cue light termination and was being maintained at the moment the cue light was turned off (choice latency = 0 sec); and (b) trials in which a lever press was made within 1.5 s of cue light termination ($0 < CL < 1.5$ sec), between 1.5 and 3.5 s ($1.5 < CL < 3.5$ sec), and between 3.5 and 7.5 s ($3.5 < CL < 7.5$ sec). (Trials in which the choice latency exceeded 7.5 s were not analyzed since there were so few of them.) To construct the means in these categories, all trials for all rats of each group at each treatment were pooled. Trials were then categorized and group mean percent correct and mean number of each choice latency category were derived. This approach allows for a more reliable description of group performance than would be obtained from deriving a percent correct score for each animal for each category and then computing group means from these (because some animals had few or no trials in some categories). Mean percent correct responses in each of these categories is shown in Table 2, which also indicates the mean frequency of each type of trial.

As can be seen in Table 2, the dose-related effects of amphetamine on the two groups' mean percent correct were quite different. For the older animals, as amphetamine dose increases (in the table from left to right) and as choice latency increases (in the table from top to bottom), percent correct generally declines (except for the 3.5–7.5 s category for which percent correct is basically at chance levels under all treatments). Thus, in the older animals, percent correct generally declined in both short and long choice latency trials as a function of dose of amphetamine. However, because the frequency of short latency choices increased with the lower doses of amphetamine, there was little net change (relative to saline) in the number of reinforced trials at these doses.

In contrast, in the younger animals percent correct responses were increased in at least one choice latency category after all doses of amphetamine. The most consistent elevation occurred at the 0.25 mg/kg dose in which percent correct was higher than saline treatment in all four choice latency categories. In addition, as was the case with the older animals, the frequency of the two shortest choice latency categories also increased, which resulted in an overall increase in percent correct trials. Similar effects were evidenced at the 0.125 and 0.50 mg/kg doses, but not to the same degree as at the 0.25 mg/kg dose. However, as can be seen in Table 2, the effect of 1.0 mg/kg was quite variable; at this dose there was an increase in the frequency of choice latencies = 0 s and an increase in the percent correct in this category. On the other hand, the frequency of choice latencies between 0 and 7.5 s declined and the percent correct responses in these categories also declined. Finally, on approximately 20% of the trials, no response at all was made within the 10 s time limit (which occurred on <5% of trials under saline treatment). A similar pattern was also seen in the older animals at the 1.0 mg/kg dose, with the exception that in the older animals percent correct choices declined even on trials in which the response was initiated prior to cue light termination.

DISCUSSION

The present results with F344xBN rats are in agreement with those of previous studies with Sprague-Dawley rats demonstrating that doses of amphetamine between 0.125 and 0.5 mg/kg may enhance the vigilance task performance of young adult and middle-aged rats (11,12). Also as predicted by Grilly's (9) findings with cocaine, amphetamine induced differential effects on younger adult and older rats with respect to choice accuracy. In terms of percentage change in accuracy, the younger adults performed better than the older adults under all four doses of amphetamine, and the two groups differed significantly in the 0.25 and 0.50 mg/kg dose tests. Although not statistically significant, as predicted the highest dose of amphetamine (1.0 mg/kg) produced a greater disruption in the mean choice accuracy of the older rats. In both groups there was a considerable increase in variability of choice accuracy at this dose. In addition, both groups exhibited dose dependent decreases (relative to saline treatment) in mean choice latency, but there was no significant difference between the groups at any of the doses used. Finally, amphetamine produced comparable dose-dependent increases (relative to saline treatment) in food retrieval latencies in both groups, with notable increases being obtained at the 1.0 mg/kg amphetamine dose.

Because of altered pharmacokinetics due to age and/or

TABLE 2

MEAN PERCENT CORRECT RESPONSES FOR YOUNGER AND OLDER RATS AS A FUNCTION OF CHOICE LATENCY AND DOSE OF AMPHETAMINE

	Amphetamine Dose (mg/kg)				
CL in sec	Saline	0.125	0.25	0.50	1.0
Younger Animals					
CL = 0	84% (31)	86% (32)	90% (35)	89% (35)	91% (36)
0 < CL < 1.5	85% (38)	85% (42)	88% (42)	88% (38)	80% (29)
1.5 < CL < 3.5	72% (17)	69% (12)	75% (13)	74% (12)	51% (10)
3.5 < CL < 7.5	59% (7)	58% (5)	61% (6)	57% (6)	44% (5)
Older Animals					
CL = 0	90% (22)	87% (26)	86% (26)	84% (27)	84% (27)
0 < CL < 1.5	84% (48)	83% (49)	85% (51)	79% (53)	79% (45)
1.5 < CL < 3.5	73% (15)	64% (15)	69% (12)	60% (11)	52% (9)
3.5 < CL < 7.5	50% (8)	55% (5)	47% (5)	57% (5)	45% (5)

CL = choice latency; the mean number of trials for each CL category is in parentheses.

weight differences, it is possible that different brain levels of amphetamine were achieved in the two groups despite the administration of amphetamine on a mg/kg basis. This in turn could have produced the differential effects of amphetamine in the two groups. However, this possibility is unlikely based on the observation that there was no difference between the groups with respect to amphetamine's effects on the choice latency and food retrieval latency measures. Secondly, with the amphetamine dose range used (from minimally effective to task-disrupting doses), altered pharmacokinetics would have resulted in the older rats exhibiting a dose-response function for accuracy to the left or to the right of that produced in the younger animals—rather than the downward shift in their dose-response function.

The finding that both the younger and older animals were comparable in terms of baseline levels of accuracy, choice latency, and food retrieval latency and that only accuracy of the two groups was differentially affected by amphetamine is a rather unique finding since virtually all studies comparing the behavioral effects of drugs in old and young animals are confounded by potential differences in weight, motor functions, baseline performance measures, and level of motivation (2,13–15,24,26). In particular, our results suggest that the differential effect of amphetamine on accuracy was more likely due to amphetamine's affecting higher order psychological processes, e.g., information processing capabilities or attentional processes, rather than being due to its interactions with one or more of these confounding factors.

As several authors have pointed out, the effects of amphetamine on learned behavior are complex (8,19). For example, amphetamine often has biphasic effects on task-related performance. Low doses may enhance the organism's reaction to discriminative stimuli and may activate behaviors that facilitate task-oriented performance. However, higher doses tend to activate behaviors (e.g., stereotypy) that are incompatible with these and disrupt task performance. In short, the ability of rats to organize behavior into functional sequences under amphetamine is highly dependent on the dose of amphetamine and the task demands (12,18). The present results indicate that the age of the organism is also important.

One explanation for the results is that the task performance of the younger animals may have been enhanced by the lower doses of amphetamine because the animals were more attentive to the cue light stimuli and the levers. However, the 1.0 mg/kg dose may have produced considerable variability in terms of what stimuli the animal attended to from moment to moment. That is, on some trials, the animal may have attended to the cue light and the appropriate lever, on others the levers but not the cue light, and on others it may have attended to some stimulus unrelated to the task. Thus, on the first type of trial, choices were highly likely to be correct; on the second type, choices would likely be at chance levels; and on the third type, no choices would be made. In contrast, the older animals, possibly because of CNS deterioration, may have been more susceptible to amphetamine's disruptive effects on attentional processes, such that the lower doses of amphetamine may have disrupted their ability to attend to the cue light, but not disrupt their attention to the levers. Thus, their choices were made more quickly, but not more accurately. And under higher doses, the disruption of the animal's attention to both the cue light and the levers would be evidenced in both fewer lever presses and a lower percentage of correct responses when a response was made.

In summary, these results support the suggestion that there is a qualitative change in some of the behavioral effects of indirect dopamine agonist stimulants as organisms age. That is, some of the performance-enhancing effects of low doses appear to decline with aging while the disruptive effects of higher doses, e.g., amphetamine-induced stereotypy, appear to increase. These results also indicate that discrepancies in the literature with respect to amphetamine's effects in aging humans and nonhumans have more to do with dose than species. That is, in studies with elderly humans in which low doses of amphetamine are used therapeutically, the mood-elevating and alertness-enhancing effects of amphetamine have been shown to decline (see introduction). In contrast, in studies with nonhumans, in which considerably higher doses of amphetamine are typically used, aged animals appear to be more affected by amphetamine than younger animals (see Introduction).

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