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Effects of *d*-Amphetamine and *d*-Fenfluramine on Performance of Rats in a Food Maze

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RECH, R. H., F. BORSINI AND R. SAMANIN. *Effects of d-amphetamine and d-fenfluramine on performance of rats in a food maze.* PHARMACOL BIOCHEM BEHAV 20(4) 489–493, 1984.—*d*-Amphetamine and *d*-fenfluramine caused different patterns of disruption in a learned maze performance reinforced with food. A 0.8 mg/kg dose of amphetamine increased correct and incorrect (errors) alley entrances as well as earned reinforcers consumed. Larger doses (1.6–3.2 mg/kg) decreased correct responses, increased errors, and resulted in earned reinforcers not being consumed. Metergoline pretreatment did not reverse these deficits. *d*-Fenfluramne (1.5 and 3.0 mg/kg) reduced correct responses dose-relatedly with a slight increase in errors after the larger dose; all earned reinforcers were consumed. Pretreatment with metergoline reversed the deficit in correct responses but not the errors. Combinations of *d*-amphetamine and *d*-fenfluramine produced greater deficits than each drug separately, with fewer correct responses and an increase in reinforcers earned but not consumed. Metergoline pretreatment before the combination did not reverse these effects but increased alley entrances scored as errors. The results indicate that the *d*-fenfluramine but not the *d*-amphetamine deficit relates to a 5-hydroxytryptamine (5-HT) mechanism. Furthermore, the enhanced effect of the combination appears to relate to drug interactions not dependent upon a 5-HT component.

d-Amphetamine *d*-Fenfluramine Food reward Maze performance Rats

AMPHETAMINE and fenfluramine are similar in chemical structure and in the effect of inducing anorexia, but differ markedly for influences on brain neurotransmitters and psychomotor responses [8, 10, 22, 24]. Amphetamine acts on central catecholamine mechanisms to generally enhance behavioral output [16,21], whereas fenfluramine appears to inhibit behavioral responding by an increase in serotonin (5-HT) activity [9,14]. Thus, the anorectic as well as other behavioral effects of amphetamine and fenfluramine undoubtedly relate to different mechanisms of action.

Interactions between amphetamine and fenfluramine have been examined by several laboratories. Amphetamine toxicity in grouped mice is antagonized by fenfluramine [11], amphetamine-induced locomotor activity is attenuated [20], and the initial rise in body temperature induced by amphetamine is counteracted [13]. However, *d*-amphetamine stereotypy is markedly prolonged, as is the concentration of *d*-amphetamine in the brain, when the stimulant is combined with fenfluramine [13]. The combination was also studied in humans for effects on a battery of psychomotor tests [3]; the effects of *d*-amphetamine on these tests were unaltered by pretreatment with fenfluramine. Therefore, the effects of *d*-amphetamine, at least in experimental animals, may be potentiated or attenuated by interactions with fenfluramine. It may be proposed that potentiation relates to inhibition of amphetamine metabolism by fenfluramine [12], whereas antagonistic effects of the combination presumably depend upon the opposing roles of brain catecholamines and 5-HT in modulating neurophysiological and behavioral responses.

The present study examined the effects of *d*-amphetamine and *d*-fenfluramine, separately and in combination, on a conditioned behavioral task performed by rats working for food in an X-shaped maze. We measured the number of correct alley entrances, errors committed and reinforcers consumed per daily session, so that drug effects were expressed as alterations in baseline control levels of correct and incorrect alley entrances and number of food pellets ingested in a daily 15-min session.

METHOD

Animals

Male CD-COBS (Charles River, Italy) rats, initially weighing 175–200 g, were housed under conditions of con-

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stant temperature (21±1°C) and relative humidity (50%) with a conventional 12-hr light-dark cycle, the light period commencing at 7:30 a.m. The rats were caged in groups of 3 except when being trained or tested in the maze (see below) or for about one hour thereafter when supplementary food was presented to isolated subjects as needed to maintain the desired body weight range. Subjects were allowed enough 90 mg Noyes-type food pellets earned in the maze plus Altromin MT food blocks (Rieper, Italy) to maintain 75–80% of their free-feeding weight, adjusted by calculating from a table of food intake in free-feeding rats of comparable ages. Body weights were monitored daily and adjustments made in food rations to assure that the desired body weight range was achieved in each rat.

Maze Apparatus and Training

An X-shaped maze was constructed with a hexagon-shaped central arena approximately 20 cm in width from which 4 alleys radiated at 90°C angles. Holes in the appropriate walls of the central arena allowed access by a rat to each alley. The alleys were 32 cm in length and 10 cm in width and contained a smaller hole in the end-walls allowing access to a food cup. All walls were ten cm in height and the entire maze was covered with hinged panels to facilitate introduction, containment and removal of a subject. The panel over the central arena consisted of clouded Plexiglas, allowing the investigator to observe the subject's behavior during the session. Alleys were arbitrarily numbered clockwise as 1, 2, 3, and 4. The rats were intially reinforced for any alley entrance by introduction of a food pellet into the respective food cup. However, all alleys had to be visited in sequence before entrance into the first alley would again be reinforced. An alley entrance was defined as the subject entering the alley at least up to the base of his tail. Rats seldom entered an alley during control days without traversing its length and investigating the food cup. This behavior was established with minimal errors in 3–5 days; furthermore, the optimal daily session time of 15 min was established, since the better performers dropped off prominently in rate of alley entrances after 15 min. Thenceforth, half the subjects were reinforced for entrances into adjacent alleys 1 and 2, and the other half received reinforcement for entrances into alleys 3 and 4 during daily 15 min sessions. The subjects were trained to near-asymptotic performance (maximum reinforcers consumed with minimum errors), which required another week, before drug studies were initiated. Training and later testing was accomplished between 3 and 6 p.m. for 5–6 days per week.

Drug Tests

Drugs were generally administered in a random design to one of 4 groups of 5 rats each, although in some cases an n of 10 was used and in two other instances an n of 6 and 8 was used. Drug treatments were tested by IP injection (concentrations adjusted to contain the dose in 0.2 ml per 100 g body weight) over a period of 3 months. Each group received 4–6 treatments, the treatments being spaced at intervals of at least 2 weeks. Vehicle treatments were administered on interim days. *d*-Amphetamine sulphate (Recordati, Milan, Italy) in distilled water was administered 30 min before a test session, *d*-fenfluramine HCl (Servier Laboratories, France) in distilled water was injected one hr before, and metergoline (Farmitalia Carlo Erba, Milan, Italy) in 1.0% ascorbic acid was given 3 hr before a test session. When multiple drugs were administered the appropriate vehicles were injected at the designated times on the preceding control day. Doses of *d*-amphetamine and *d*-fenfluramine refer to the weight of the salts.

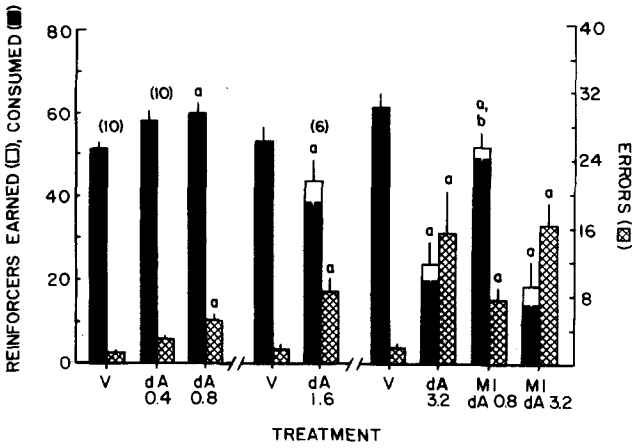

FIG. 1. *d*-Amphetamine effects on performance of rats in the food maze. Number of reinforcers consumed (filled bars) and correct responses without consumption of reinforcers (unfilled extensions of filled bars) are indicated by the left ordinate scale, and number of errors (hatched bars) are indicated by the right ordinate scale. Treatments indicated on the abscissa: V=vehicle, dA=*d*-amphetamine, M=metergoline, numbers=mg/kg by IP injection. Each set of bars represents the means (vertical lines=S.E.M.) from 5 rats, except where indicated in parenthesis above the bars. a=Sign. diff. from vehicle control, b=sign. diff. of the combination of drugs from the respective *d*-amphetamine dose alone.

Statistical Analysis

Baseline control values for statistical comparisons were calculated from the performance of the day preceding each drug test day. Single drug treatments were analyzed by *t*-tests for related measures. Multiple drug treatments were compared by a two-way ANOVA followed by Duncan's multiple range test to evaluate individual differences. For illustrative purposes only in the figures below, control baseline (V) values were calculated as the mean±S.E. of the average of three vehicle measures for each subject taken at various times over the 4- to 7-week period of each testing series. The analyses were restricted to comparisons of number of reinforcers consumed and errors made per daily session, although the figures also depict, where appropriate, the number of correct alley entrances without food ingestion (reinforcers earned but not consumed). The level of significance was set at $p<0.05$.

RESULTS

The subjects acquired the behavior in the maze to a high level of performance in about one week, although the number of pellets earned during control sessions generally increased very gradually for each subject over the 3 months of testing. Baseline control values for reinforcers consumed (same as reinforcers earned for control sessions) varied among subjects from 40 to 76 per 15-min daily session, with an overall mean of about 55 per session. The number of errors gradually decreased during training to asymptote at values that varied among subjects from 0 to 5 per daily control session, with an overall mean of about 2 per session.

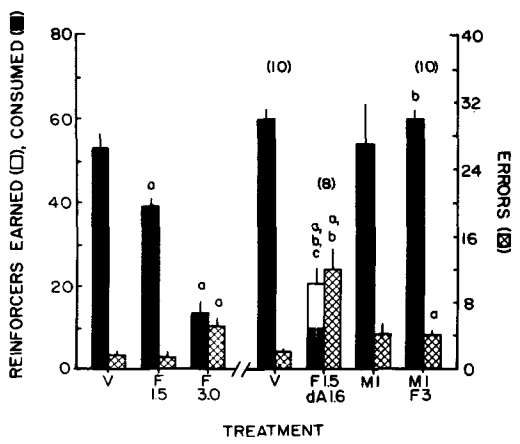

FIG. 2. *d*-Fenfluramine effects on performance of rats in the food maze. Treatments indicated on the abscissa: F=*d*-fenfluramine. a=Sign. diff. from vehicle control, b=sign. diff. of the combination of drugs from fenfluramine alone, c=sign. diff. of the combination of drugs from the respective d-amphetamine dose alone. See Fig. 1 legend for other details.

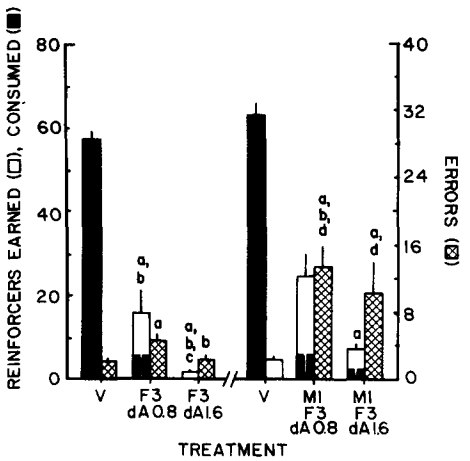

FIG. 3. Effects of combined amphetamine-fenfluramine treatments on performance of rats in the food maze. a=Sign. diff. from vehicle control, b=sign. diff. of the combination of drugs from the respective *d*-amphetamine dose alone, c=sign. diff. of the combination of drugs from the respective fenfluramine dose alone, d=sign. diff. of the combination after meterogoline pretreatment from the respective combinations without meterogoline pretreatment. See Fig. legends 1 and 2 for other details.

Figure 1 illustrates dose-related effects of *d*-amphetamine on performance of these subjects in the X-maze. Treatment with 0.4 mg/kg *d*-amphetamine tended to increase the number of reinofrcers consumed and errors committed, but these trends were not significant. At 0.8 mg/kg the stimulant did significantly increase reinforcers consumed and errors made. However, a dose of 1.6 mg/kg significantly decreased reinforcers consumed as well as further increasing the number of errors. In addition, subjects made correct alley entrances (mean of about 6) after which they failed to consume the reinforcer, sniffing at it or picking it up in their mouth and then dropping it in the alley. These responses appeared to be distributed randomly throughout the 15-min session. After 3.2 mg/kg *d*-amphetamine reinforcers consumed were further decreased while errors were increased. It is noteworthy that the overall alley entrances after the 1.6 and 3.2 mg/kg doses were not greatly altered from control values. Nevertheless, the animals' rates of responding had increased so that they spent relatively more time in the central arena, engaged during those periods in stereotypic patterns. Pretreatment with the 5-HT antagonist metergoline (ineffective by itself, see Fig. 2) reduced slightly the number of reinforcers consumed after 0.8 mg/kg *d*-amphetamine and resulted in a lack of consumption of a few earned pellets. The metergoline pretreatment did not alter the effects of 3.2 mg/kg *d*-amphetamine on maze performance.

The effects of *d*-fenfluramine are depicted in Fig. 2, along with several drug interactions. A 1.5 mg/kg dose of this anorectic significantly decreased reinforcers consumed without affecting the errors committed. Increasing the dose of *d*-fenfluramine to 3 mg/kg further decreased the number of food pellets consumed and also slightly increased the number of errors. Grossly observing these subjects, it was difficult to discern any difference from vehicle-treated controls in the behavior of the rats treated with 1.5 mg/kg *d*-fenfluramine, especially at the beginning of the session. Later in the session, however, these subjects noticeably decreased their rate of responding. The demeanor of the animals treated with 3 mg/kg indicated some depression, with ptosis and decreased rate of responding even at the beginning of the session. Nevertheless, responses that were made were concentrated early in the session and these subjects spent the remaining time in the central arena grooming or dozing. In every case that a fenfluramine-treated subject entered a correct alley, he also consumed the reinforcer. Therefore, the pattern of decreased responding after *d*-fenfluramine was very different from that observed after larger doses of *d*-amphetamine and resembled very much, except for timing, the pattern of satiation in untreated rats run for a daily session longer than 15 min. Treatment with metergoline, 1 mg/kg, alone did not significantly affect maze performance (Fig. 2). Pretreatment with metergoline before 3 mg/kg fenfluramine was found to completely reverse the reduction in food pellets consumed that was induced by this dose of fenfluramine alone. On the other hand, the increase in errors seen after 3 mg/kg *d*-fenfluramine alone was not antagonized by pretreating with metergoline.

The effects of the combination of 1.5 mg/kg fenfluramine with 1.6 mg/kg amphetamine are also indicated in Fig. 2. There was an augmentation of the reduction in reinforcers consumed, with reference to either the fenfluramine or the *d*-amphetamine dose alone. The pattern of the effect still resembled the *d*-amphetamine alterations, with a large number of reinforcers being earned but not consumed and a prominent increase in errors over vehicle control or fenfluramine values alone.

Other dose combinations of *d*-fenfluramine and *d*-amphetamine were examined and the results graphed in Fig. 3. Combining 3 mg/kg fenfluramine with 0.8 mg/kg amphetamine yielded values of reinforcers consumed and errors not significantly different from 3 mg/kg *d*-fenfluramine alone. Still, the *d*-amphetamine pattern of disrupted performance was manifested by this combination in that a prominent number of reinforcers earned were not consumed. Responses were almost eliminated by the combination of 3 mg/kg fenfluramine and 1.6 mg/kg amphetamine, and the few

reinforcers earned were not consumed. This latter combination resulted in a decrease in errors from the error score after 1.6 mg/kg *d*-amphetamine alone (Fig. 1), but the relevance of this change is questionable since the subjects treated with the 3 mg/kg fenfluramine-1.6 mg/kg amphetamine combination manifested such a low score of total alley entrances.

On observing the animals treated with the fenfluramine-amphetamine combinations indicated in Fig. 3, we noted less stimulant properties than with *d*-amphetamine alone (especially concerning the 1.6 mg/kg dose), but also did not observe the sedative features of fenfluramine alone. Another curious phenomenon was the behavioral pattern of these rats in the central arena (particularly evident after the combination of 3 mg/kg fenfluramine with 1.6 mg/kg amphetamine). These subjects would begin to enter an alley, but then would back out and direct attention to an adjacent alley. After inserting the head into this alley, a subject would again back out and face another alley, repeating the sequence over and over. This ritual dominated the behavior of the rats administered these combinations for most of the 15-min session.

Pretreatment with 1 mg/kg metergoline of subjects receiving the fenfluramine-amphetamine combinations (Fig. 3) had some consequences. These animals demonstrated a more typical *d*-amphetamine-like stimulation, and alley entrances were increased, for the total and the number of errors. However, the number of reinforcers consumed was still markedly decreased in comparison with the scores after *d*-amphetamine alone. Furthermore, the reinforcers earned but not consumed after the 1 mg/kg metergoline, 3 mg/kg fenfluramine, 0.8 mg/kg amphetamine combination reached a mean of about 19, whereas there were no reinforcers earned but not consumed in the group treated with 0.8 mg/kg *d*-amphetamine alone (Fig. 1). Therefore, pretreatment with metergoline did not act to simply nullify completely the interactions dependent on fenfluramine.

DISCUSSION

A previous investigation by one of the authors has examined straight runway performance for food reinforcement and described different patterns of reduced feeding after treatment with *d*-amphetamine and *d*-fenfluramine [24]. In that study 1 mg/kg *d*-amphetamine did not affect running performance or feeding, while 1.5 mg/kg reduced somewhat the running speed in early trials but decreased food intake during later trials. On the contrary, *d*-fenfluramine even at the lower dose (2 mg/kg) markedly reduced running speed and food intake during the early trials, a pattern more consistent with the behavior of a satiated animal. In the results of the present study, a smaller dose of *d*-amphetamine (0.8 mg/kg) actually increased the number of alley entrances as well as the number of reinforcers consumed. Larger doses of the stimulant decreased food consumption with an associated increase in incorrect alley entrances. In addition, some reinforcers earned throughout the session were not consumed. It is important to emphasize that total alley entrances after 1.6 and 3.2 mg/kg *d*-amphetamine were essentially at the same level as during control sessions. Thus, the subjects' overall response rates were little affected by this drug. *d*-Fenfluramine, on the other hand, reduced the rate of alley entrances in a dose-related manner with an associated decrease in pellets consumed. After 3 mg/kg *d*-fenfluramine the rats were reduced in total alley entrances by more than half of the control values while errors were increased only modestly; in every case with regard to the effects of this latter drug treatment, reinforcers that were earned were also consumed.

The present study differed from the previous design [24] in that a conditioned choice behavior was available to the subjects, the daily session was limited by time (15 min) rather than number of trials (18), and reinforcement after each successful response consisted of access to one food pellet rather than a dish of 25 available for a 2-min period. Furthermore, in the previous study a treated rat that had failed to run to the food by 30 sec was then placed at the food dish for the usual 2-min period. As in the runway study [24], the findings here indicate that the rate of instrumental responding may be little influenced even by large doses of *d*-amphetamine that result in reduced consumption of the reinforcer. This is clearly indicated by the failure of *d*-amphetamine-treated subjects to consume all earned reinforcers (Fig. 1). Fenfluramine showed a different pattern, in that the instrumental response decayed in rate in association with the decrease in food pellets consumed. Such differences have prompted suggestions [16,19] that amphetamine-type agents disrupt sequencing of different types of behavior, perhaps by inducing perseverative responding or by uncovering competing responses that were suppressed as a result of prior conditioning.

The pattern of change induced by fenfluramine is more consistent with the behavior of a satiated subject, and, in fact, mimics in an accelerated manner the behavioral sequence occurring during the process of satiation. Since fenfluramine is well-known as an agent which increases the release of 5HT in the brain [8, 10, 22, 23] and 5-HT mechanisms in the hypothalamus are thought to relate to satiation [5, 9, 22, 24], it is not surprising that pretreatment with the 5-HT antagonist metergoline was effective in completely reversing the reduced alley entrances and decrease in food intake induced by 3 mg/kg fenfluramine (Fig. 2). It is interesting that metergoline pretreatment did not reverse the increase in errors in the maze following the 3 mg/kg dose of fenfluramine, which may indicate that this effect of fenfluramine is mediated by an action other than on serotonin systems (for example, dopamine blockade: see [20]). A recent study has proposed that fenfluramine may produce anorexia primarily by way of a peripheral action to delay gastric emptying time [4].

Metergoline pretreatment was not effective in reversing the disruptive effects of *d*-amphetamine but actually appears to enhance them (Fig. 1). This is consistent with a marked augmentation of catecholamine activities that brings about disrupted behavior, including anorexia, and may actually be exaggerated by interference with 5-HT functions [17,18]. The amphetamine anorectic effect has been related to the subjects' sense of the reinforcing value of food [1, 5, 15, 16, 25] rather than to a satiating mechanism. The enhancement of feeding behavior by low doses of amphetamine has been reported previously [2,5]. This effect is probably accounted for in some measure by the dual role of norepinephrine in hypothalamic feeding centers [1,15], although a generalized increase in response output associated with heightened arousal and/or motivation has also been proposed [7].

Interactions between *d*-amphetamine and fenfluramine have been investigated by several groups [3, 11–14], but apparently not with regard to anorexia. The effects of the combination mutually attenuated separate effects of the drugs in some instances [11,13], but enhanced the effects of *d*-amphetamine in others [12,13]. Results of the present study show that the combination markedly enhanced the

anorectic effects relative to food consumed after either drug separately (Fig. 2: 1.5 fenflruamine plus 1.6 amphetamine; Fig. 3: 3 fenfluramine plus 1.6 amphetamine). The propensity of amphetamine to block consumption of earned reinforcers was also potentiated by combination of the stimulant with fenfluramine. However, the combination did not result in an increase in errors relative to effects of *d*-amphetamine alone. The potentiation of anorexia may be explained as the combined effects of the catecholamine-type and 5-HT-type of anorectic mechanisms. This is supported by a study [6] which demonstrated a significant potentiation of the anorectic potency of amphetamine by pretreating rats with 30 mg/kg of 5-hydroxytryptophan, the precursor of 5-HT. Alternatively, this potentiation may relate to the prolongation of *d*-amphetamine half-life by interference with its *p*-hydroxylation shown to be exerted by fenfluramine [12]. The fact that metergoline pretreatment did not reverse the enhanced anorexia of the combination argues against a specific 5-HT agonistic component as being involved (Fig. 3). Nevertheless, the gross appearance of the subjects after the various treatments indicated that amphetamine stimulation and fenfluramine sedation were mutually antagonized by combining the drugs. Since pretreatment with metergoline reinstated the gross appearance of amphetamine stimulation with the combination, the fenfluramine interaction in this case seems to depend upon a 5-HT mechanism.

In conclusion, the results of this study support previous investigations indicating that *d*-amphetamine and fenfluramine disrupt food-reinforced behavior in different patterns and by different mechanisms. Furthermore, interactions between the agents demonstrated mutual antagonism of general effects on central exictability but an enhancement of the anorexia with reference to the separate effects of each agent.

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