Pharmacology Biochemistry & Behavior, Vol. 11, pp. 151–153. Printed in the U.S.A.

The Effects of Fenfluramine on Schedule-Induced Drinking in Rats[1]

D. J. SANGER

Department of Psychology, University College, P.O. Box 78, Cardiff, CF1 1XL, United Kingdom

Received 27 April 1979

SANGER, D. J. *The effects of fenfluramine on schedule-induced drinking in rats.* PHARMAC. BIOCHEM. BEHAV. 11(2) 151–153, 1979.—The lever pressing of rats was maintained by a fixed-interval 60 sec schedule of food reinforcement. Water bottles were available during sessions and high levels of schedule-induced drinking developed. Both fenfluramine (0.5, 1.0, 2.0, 4.0, 8.0 mg/kg) and d-amphetamine (0.25, 0.5, 1.0, 2.0 mg/kg) produced dose related decreases in this drinking with d-amphetamine approximately four times as potent as fenfluramine. d-Amphetamine produced large increases in overall rates of lever pressing and greatly decreased the duration of postreinforcement pauses. Fenfluramine exerted similar actions but at all doses studied these effects were much less than the effects of d-amphetamine on these measures.

Fenfluramine d-Amphetamine Schedule-induced drinking Schedule-controlled behavior

THE pattern of excessive drinking shown by rats receiving intermittently delivered food portions which is known as schedule-induced drinking [5] has been found to be sensitive to the actions on a number of psychoactive drugs [12]. Among the drugs whose actions on schedule-induced drinking have been investigated, amphetamine has on several occasions been reported to produce substantial reductions in drinking [10,17]. This action occurs regardless of whether the food portions are obtained by means of an operant response or are delivered independently of behavior [11]. It has also recently been found that the function relating dose of d-amphetamine to its effect on schedule-induced drinking is very similar to the dose-response function for the action of this drug on drinking in water deprived rats [13].

Fenfluramine is a compound which is structurally related to amphetamine but which is generally reported not to produce increases in locomotor activity in laboratory animals [8, 15, 16, 19]. The reinforcing actions of amphetamine also are not shown by fenfluramine [18]. Both drugs, however, induce anorexia in laboratory rats and other species [1,4], although there is some evidence that the actions of fenfluramine and amphetamine on eating can be distinguished at both a behavioral [2] and a physiological [1, 3, 7, 9] level. The purpose of the present experiment was to investigate the action of fenfluramine on schedule-induced drinking maintained in rats by a fixed-interval schedule of food reinforcement. A comparison was also made between the actions of fenfluramine and those of d-amphetamine.

METHOD

Animals

Four male albino Wistar rats were used. Throughout the experiment they were individually housed and maintained at approximately 85% of their pre-experimental body weights which were between 300–400 g. Water was freely available at all times.

Apparatus

The experiment was carried out in standard operant test chambers (Campden Instruments Ltd.) housed in light and sound attenuating outer cubicles. Available in each test chamber was a spout attached to a plastic water bottle which was fixed behind the chamber wall adjacent to the wall containing the lever and food tray. The spout was approximately 5 mm behind a 12 mm diameter hole in the wall through which the rat was required to lick in order to obtain access to the water. The distance between the water spout and the lever was 15 cm so that it was necessary for the rat to leave the immediate vicinity of the lever and food tray in order to drink. The experiment was controlled by standard electromechanical programming equipment.

Procedure

The rats were trained to press the lever to the left of the food tray to obtain 45 mg food pellets. After several sessions during which each response produced a pellet the schedule was changed to a fixed-interval 60 sec (FI 60 sec) so that a response would only produce a pellet 60 sec after the preceding pellet had been obtained. Each session was terminated when 60 pellets had been delivered.

When the rats had been responding on the FI 60 sec schedule for approximately 30 sessions and were showing relatively steady rates of lever pressing and drinking, drug administration was begun. Each animal received injections of several doses of fenfluramine hydrochloride (0.5, 1.0, 2.0,

[1]Fenfluramine was generously supplied by Servier Laboratories Limited.

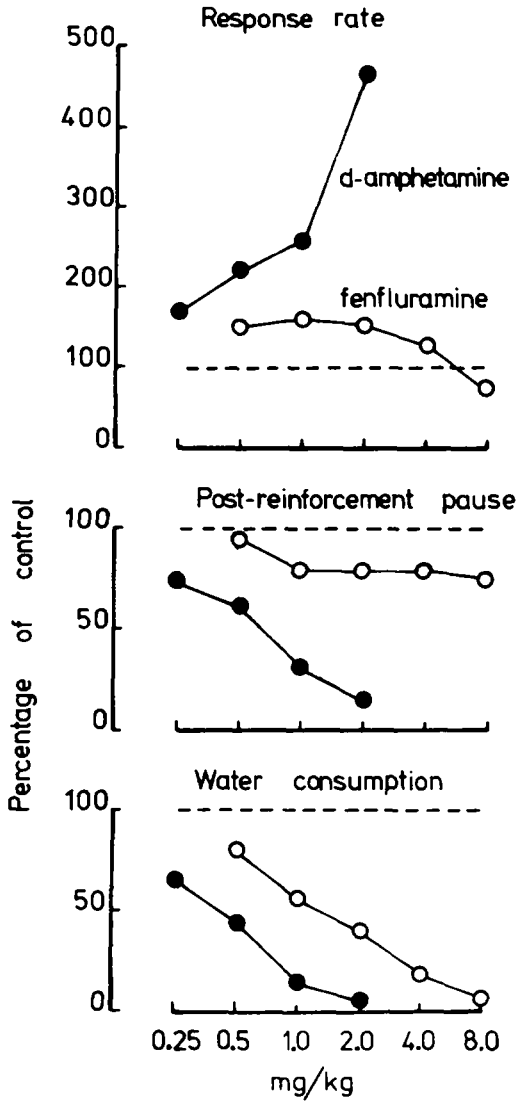

FIG. 1. Dose response curves showing the effects of d-amphetamine and fenfluramine on overall response rates maintained by the FI schedule, mean postreinforcement pause durations and volumes of water consumed during schedule-induced drinking. Values have been converted to percentages of the corresponding measure taken on the immediately preceding session and combined for the four rats. Thus each point is the mean of at least eight determinations.

4.0, 8.0 mg/kg) and also several doses of d-amphetamine sulfate (0.25, 0.5, 1.0, 2.0 mg/kg). Both drugs were dissolved in physiological saline to give injection volumes of 1 mg/kg body weight and were administered by intraperitoneal injection immediately before a session. Each animal received each dose on at least two occasions and doses of the two drugs were given in a mixed order which was different for each animal. At least three non-drug days intervened between successive drug administrations. Saline was injected on all non-drug days.

RESULTS

The FI 60 sec schedule maintained patterns of responding typical of such schedules and consisting of a pause after each pellet delivery followed by either a constant rate or an accelerating rate of responding until the next reinforcer. The schedule also generated high levels of schedule-induced drinking. Table 1 shows mean values of overall response rates, postreinforcement pause durations and volumes of water consumed taken from non-drug sessions for each of the four rats.

TABLE 1

AVERAGE VALUES FOR RESPONSE RATES, POSTREINFORCEMENT PAUSE DURATIONS AND WATER CONSUMPTION FOR THE FOUR INDIVIDUAL RATS DURING CONTROL SESSIONS. EACH VALUE IS THE MEAN ± SD OF VALUES TAKEN FROM DAYS PRECEDING DRUG DAYS (AT LEAST 18 VALUES IN EACH CASE)

Animal	Response Rate (r/min)	Postreinforcement pause (sec)	Water consumption (ml)
R1	7.3 ± 1.6	40 ± 4	20 ± 2
R2	16.7 ± 4.2	41 ± 4	28 ± 3
R3	19.5 ± 4.3	37 ± 5	19 ± 6
R4	7.0 ± 2.6	54 ± 4	32 ± 3

The effects of d-amphetamine and fenfluramine on both operant behavior and schedule-induced drinking are presented in Fig. 1. The drug effects were essentially similar in the four animals and thus the data have been converted to percentages of control values (measures taken after drug administration were converted to a percentage of the corresponding measures on the immediately preceding day) and combined for all animals. Statistical comparisons were made using the Friedman two-way analysis of variance. d-Amphetamine substantially increased rates of lever pressing ($\chi r^2=28$, $p<0.001$) while reducing post-reinforcement pause durations ($\chi r^2=29$, $p<0.001$) and also reducing levels of schedule-induced drinking ($\chi r^2=25$, $p<0.001$). Fenfluramine also produced a dose-related decrease in drinking ($\chi r^2=36$, $p<0.001$) although it was approximately 4 times less potent than d-amphetamine in this respect. Fenfluramine, however, did not produce such marked disruptions of operant behavior as did d-amphetamine. The statistical analysis showed that overall response rates were significantly affected by administration of fenfluramine ($\chi r^2=13.4$, $p<0.001$). Further analysis of the effects of individual doses was carried out using the Wilcoxon matched pairs signed ranks test. This showed that doses of 0.5, 1.0 and 2.0 mg/kg produced statistically significant increases in rates of responding (for 0.5 mg/kg, T=1, $p<0.01$; for 1.0 mg/kg, T=0, $p<0.005$; for 2.0 mg/kg, T=3, $p<0.025$). The two higher doses of fenfluramine did not produce statistically significant changes in overall rates of responding. The drug also reduced the average duration of postreinforcement pauses ($\chi r^2=15$, $p<0.01$) but again this effect was much smaller than the corresponding action of d-amphetamine. The rats were observed to consume all the food pellets delivered during sessions even after administration of the highest doses of the two drugs.

DISCUSSION

The present experiment confirmed the results of previous

studies in showing that d-amphetamine can greatly reduce levels of schedule-induced drinking while increasing rates and disrupting temporal patterns of fixed-interval responding [11, 12, 17]. Fenfluramine was also found to reduce the volumes of water consumed but without producing such marked disruptions of operant performance.

The behavioral effects of fenfluramine are often quite different from those of amphetamine, as described above. Harris and his colleagues [6], however, recently studied the actions of several drugs with stimulant and anorexigenic properties on the responding of rats maintained by a FI 120 sec schedule and found that both d-amphetamine and fenfluramine disrupted the temporal patterning of responding and produced dose-related decreases in overall response rates. This is in contrast to the results of the present experiment in which d-amphetamine produced substantial increases and fenfluramine small increases in overall response rates, and fenfluramine also exerted quantitatively much smaller effects on temporal patterning as indicated by the reduced postreinforcement pause durations. Harris *et al.* [6] also found that d-amphetamine exerted quantitatively greater effects than fenfluramine on the temporal pattern of responses. The reasons for the different drug effects on response rates observed in the two studies probably lie in a number of procedural and other differences which distinguish the experiments. In particular, control rates of responding were considerably lower in the animals studied in the present experiment than in those used by Harris *et al.* [6].

As noted earlier, both fenfluramine and amphetamine are known to reduce food intake. These drugs have also been shown to reduce water intake produced by fluid deprivation, e.g., [8,14]. It is not clear at present whether these actions are related to the effects of these drugs on schedule-induced drinking observed in the present experiment. It is relevant to note, however, that drugs do not invariably affect water consumption induced by fluid deprivation and by schedule-induction in identical ways [13]. To clarify this matter it would be of some interest to investigate the mechanisms, both behavioral and physiological, by means of which d-amphetamine, fenfluramine and other agents affect schedule-induced drinking.

REFERENCES

1. Bizzi, A., S. Bonnaccorsi, S. Jespersen, A. Jori and S. Garatini. Pharmacological studies on amphetamine and fenfluramine. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini, New York: Raven Press, 577–595, 1970.
2. Blundell, J. E., C. J. Latham and M. B. Leshem. Differences between the anorexic actions of amphetamine and fenfluramine—possible effects on hunger and satiety. *J. Pharm. Pharmac.* **28:** 471–477, 1976.
3. Carey, R. J. Effects of selective forebrain depletions of noradrenaline and serotonin on the activity and food intake effects of amphetamine and fenfluramine. *Pharmac. Biochem. Behav.* **5:** 519–523, 1976.
4. Dobrzanski, S. and N. S. Doggett. The effects of (+)-amphetamine and fenfluramine on feeding in starved and satiated mice. *Psychopharmacology* **48:** 283–286, 1976.
5. Falk, J. L. The nature and determinants of adjunctive behavior. *Physiol. Behav.* **6:** 577–488, 1971.
6. Harris, R. A., D. Snell and H. H. Loh. Effects of stimulants, anorectics, and related drugs on schedule-controlled behavior. *Psychopharmacology* **56:** 49–55, 1978.
7. Jespersen, S. and J. Scheel-Kruger. Evidence for a difference in mechanism of action between fenfluramine and amphetamine induced anorexia. *J. Pharm. Pharmac.* **25:** 49–54, 1973.
8. Le Douarec, J. C. and C. Neveu. Pharmacology and biochemistry of fenfluramine. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini, New York: Raven Press, 75–105, 1970.
9. Samanin, R., D. Ghezzi, L. Valzelli and S. Garattini. The effects of selective lesioning of brain serotonin or catecholamine containing neurons on the anorectic activity of fenfluramine and amphetamine. *Eur. J. Pharmac.* **19:** 318–322, 1972.
10. Sanger, D. J. d-Amphetamine and adjunctive drinking in rats. *Psychopharmacology* **54:** 273–276, 1977.
11. Sanger, D. J. The effects of d-amphetamine and scopolamine on drinking induced by a multiple schedule. *Psychopharmacology* **58:** 311–315, 1978.
12. Sanger, D. J. and D. E. Blackman. The effects of drugs on adjunctive behavior. In: *Contemporary Research in Behavioral Pharmacology*, edited by D. E. Blackman and D. J. Sanger, New York: Plenum Press, 239–287, 1978.
13. Sanger, D. J. and P. K. Corfield-Sumner. Schedule-induced drinking and thirst: A pharmacological analysis. *Pharmac. Biochem. Behav.* **10:** 471–474, 1979.
14. Soulairac, A. and M. L. Soulairac. Effects of amphetamine-like substances and L-DOPA on thirst, water intake and diuresis. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini, New York: Raven Press, 819–837, 1970.
15. Tang, A. H. and J. D. Kirch. Appetite suppression and central nervous system stimulation in the rhesus monkey. *Psychopharmacologia* **21:** 139–146, 1971.
16. Tessel, R. E., J. H. Woods, R. E. Counsell and M. Lu. Structure-activity relationships between meta-substituted N-ethyl amphetamines and locomotor activity in mice. *J. Pharmac. exp. Ther.* **192:** 310–318, 1975.
17. Wayner, M. J., I. Greenberg and J. Trowbridge. Effects of d-amphetamine on schedule-induced polydipsia. *Pharmac. Biochem. Behav.* **1:** 109–111, 1973.
18. Woods, J. H. and R. E. Tessel. Fenfluramine: Amphetamine congener that fails to maintain drug-taking behavior in the rhesus monkey. *Science* **185:** 1066–1070, 1974.
19. Ziance, R. J., I. G. Sipes, W. J. Kinnard and J. P. Buckley. Central nervous system effects of fenfluramine hydrochloride. *J. Pharmac. exp. Ther.* **180:** 110–117, 1972.