Pharmacology Biochemistry and Behavior, Vol. 3, pp. 229–233. ANKHO International Inc., 1975. Printed in the U.S.A.

Self-Administration of Amphetamine Analogues in Rats[1]

K. GUNNAR GÖTESTAM AND BENGT E. ANDERSSON

Psychiatric Research Center, University of Uppsala
Ulleråker Hospital, S-750 17 Uppsala, Sweden

(Received 21 May 1974)

GÖSTESTAM, K. G. AND B. E. ANDERSSON. *Self-administration of amphetamine analogues in rats.* PHARMAC. BIOCHEM. BEHAV. 3(2) 229–233, 1975. – In rats self-injecting amphetamine (0.25 mg/kg/injection) at a stable level during daily 3 hr sessions, three different amphetamine analogues (phenmetrazine, diethylpropion and fenfluramine) were substituted for amphetamine, one at a time on different experimental days. Phenmetrazine (1.0 mg/kg/injection) and diethylpropion (2.0 mg/kg/injection) were self-administered but not fenfluramine (in doses of 0.1, 0.5 and 2.0 mg/kg/injection). It is concluded that amphetamine, phenmetrazine and diethylpropion have reinforcing properties, whereas fenfluramine has not.

Drug dependency d-Amphetamine Phenmetrazine Diethylpropion Fenfluramine Self-administration Rats

IN EXPERIMENTS on intravenous self-administration of drugs by experimental animals, d- and l-amphetamine, methamphetamine, phenmetrazine and methylphenidate have been shown to have reinforcing properties and result in sustained self-administration behavior [1, 18, 23, 24, 25].

The present study was undertaken to compare phenmetrazine, diethylpropion and fenfluramine with regard to their potential for maintaining self-administration in rats. The rats had limited access to the drug for 3 hours/day at FR 50 schedule (i.e., fifty responses per injection). In order to get a stable response pattern the rats were first trained to press a lever for food pellets later followed by intravenous amphetamine as reinforcer.

METHOD

Animals

Eight male Sprague-Dawley rats weighing 300–350 g (Anticimex, Norrviken, Sweden) were kept in a windowless room maintained at 22 ± 1°C and illuminated from 8 p.m.–8 a.m. The training and testing periods started at 9 a.m.

Apparatus

The rats were placed in individual cages, 36 × 26 × 12 cm (Lystedts plast, Bandhagen, Sweden), where they were kept during the entire experiment. On one side of the cage two levers and a food pellet dispenser were positioned (Lehigh Valley Electronics, Inc., Fogelsville, Pa., USA). During the initial training, food pellets (Noyes, 45 mg) were given as reinforcers for lever pressing and a continuous stimulus light was on during the daily training period. When intravenous injections were given contingent on lever pressing the stimulus lamp had an intermittent light. A light flash from a second stimulus lamp accompanied food reinforcements and was presented at the beginning of each drug injection.

Under pentobarbital anesthesia an intravenous cannula was introduced in the right jugular vein [21,22].

The intravenous cannula was connected to an infusion apparatus (Mek. lab. Konstruktioner, V. Frölunda, Sweden), which gave infusions of 1 ml/min, and the infusion time was varied according to the weight of the rat, giving 0.5 ml/kg in each injection. As a consequence of this procedure the infusion time was about 10 sec. The cannula went through a harness on the rat's back and a leak proof swivel (Lehigh Valley Electronics) in the roof of the cage. By this arrangement the rat could move around in the cage relatively freely. Programming and registering was made by means of an electronic equipment (Lehigh Valley Electronics) in an adjacent room.

Drugs

The drugs used were d-amphetamine sulfate 0.25 mg/

[1] Parts of the present results have been presented at the Symposium on Fenfluramine and Derivatives, Marbella 1974, and Colloquio Internazionale Obesita' e Fenfluramina, Rome 1974. This work was supported by the Swedish Medical Research Council (Project No. B74-21X-4243-07) and the Tricentennial Fund of the Bank of Sweden (Grant 150).

kg/injection, phenmetrazine 1.0 mg/kg/injection, diethylpropion, 2.0 mg/kg/injection and dl-fenfluramine-hydrochloride, 0.1, 0.5 and 2.0 mg/kg/injection, all dissolved in saline.

Behavioral Method

Food-reinforced lever pressing. One week after surgery, the rats were placed in the experimental cages. The rat was trained to press the lever with food pellets as reinforcers. Gradually the lever-press reinforcement ratio (fixed ratio, FR) was increased to 50 (FR 50). The harness was put on and the cannula was connected to the swivel. Intravenous self-administration of amphetamine was started when the rat showed a stable level of responding at FR 50 i.e., high response rate without long intermissions [6]. This training procedure lasted for about 20 days.

Self-administration of amphetamine. In a daily session amphetamine 0.25 mg/kg/injection was given as a consequence of lever pressing on a FR 50 schedule. The self-injection sessions were limited to 3 hr a day, or terminated earlier if the rat had received 40 injections (for one rat 70). A noncontingent injection of amphetamine was given immediately before the start of each session. After the session the rat was given about 15 g of food (Anticimex lab chow pellets 210) in the cage. Water was available ad lib.

Experiment. When amphetamine had been self-administered at a relatively stable level for at least 3 days, a new regimen was introduced. Amphetamine was now given every third day and on the days inbetween a test drug or saline was offered for self-administration in a rotated order. The sessions were limited to 3 hr or 40 injections as before. A noncontingent injection of the test drug or saline was given immediately before the start of each session. When amphetamine was available for self-administration, a noncontingent injection of amphetamine was given, and when saline was available, a noncontingent injection of saline was given, etc. Each rat was given only one drug in one dose, besides amphetamine and saline.

Amphetamine and saline as well as the test drug were given for 6 days respectively. The experiment thus lasted 18 days. (Two rats were taken out of the experiment after 9 and 15 days, respectively, because of malfunctioning cannulas; Rat 275 and 307). Experience from other experiments performed in our laboratory has shown that stable level of responding on amphetamine is generally maintained longer than 18 days. No significant weight loss occurred.

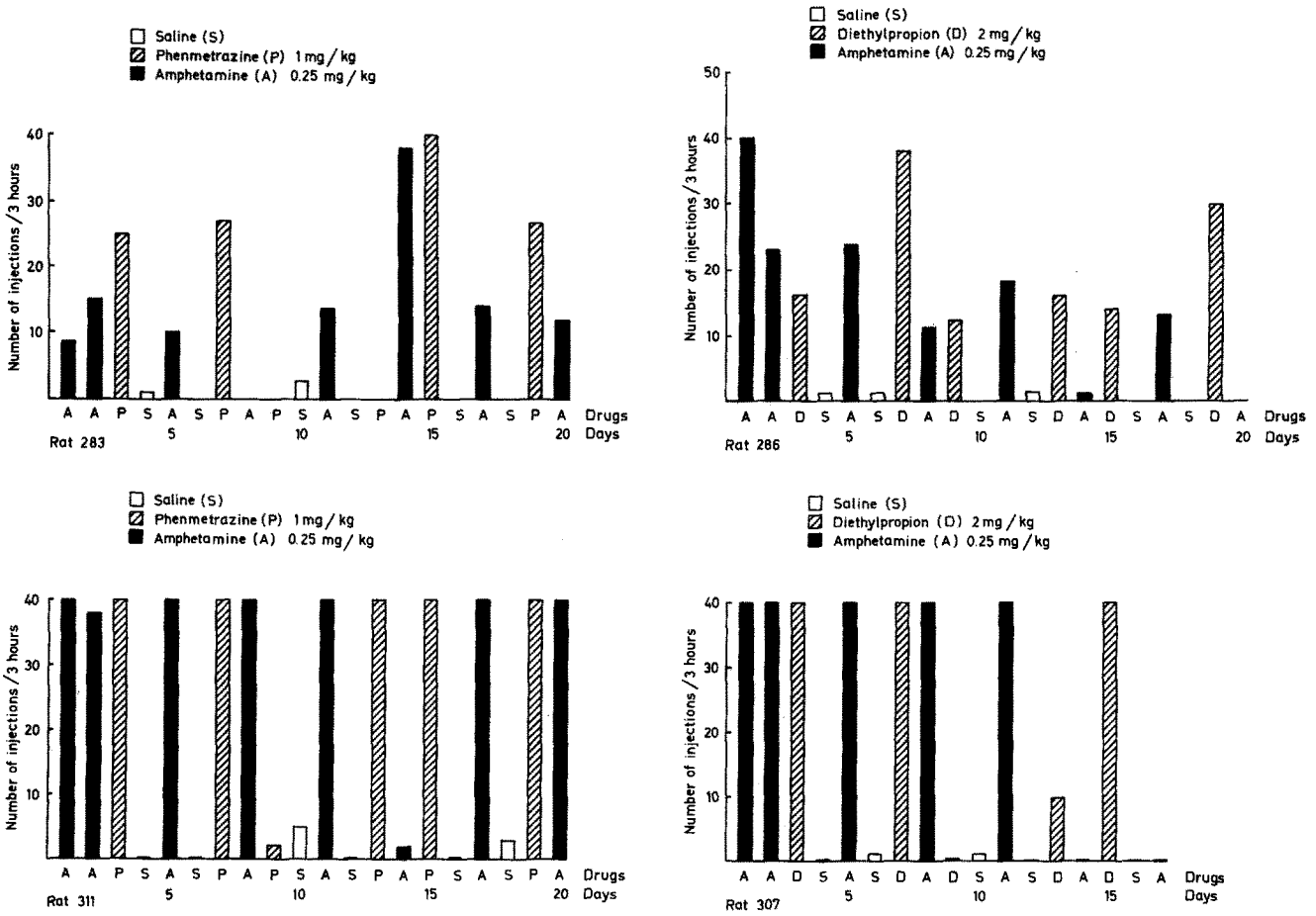

FIG. 1. Self-administration in 2 rats tested with phenmetrazine and 2 rats tested with diethylpropion. Before the 18 days experiment (15 days for Rat 307), the 2 last days of self-administration of amphetamine are shown. Each session lasted 3 hr, or was interrupted when 40 injections had been taken.

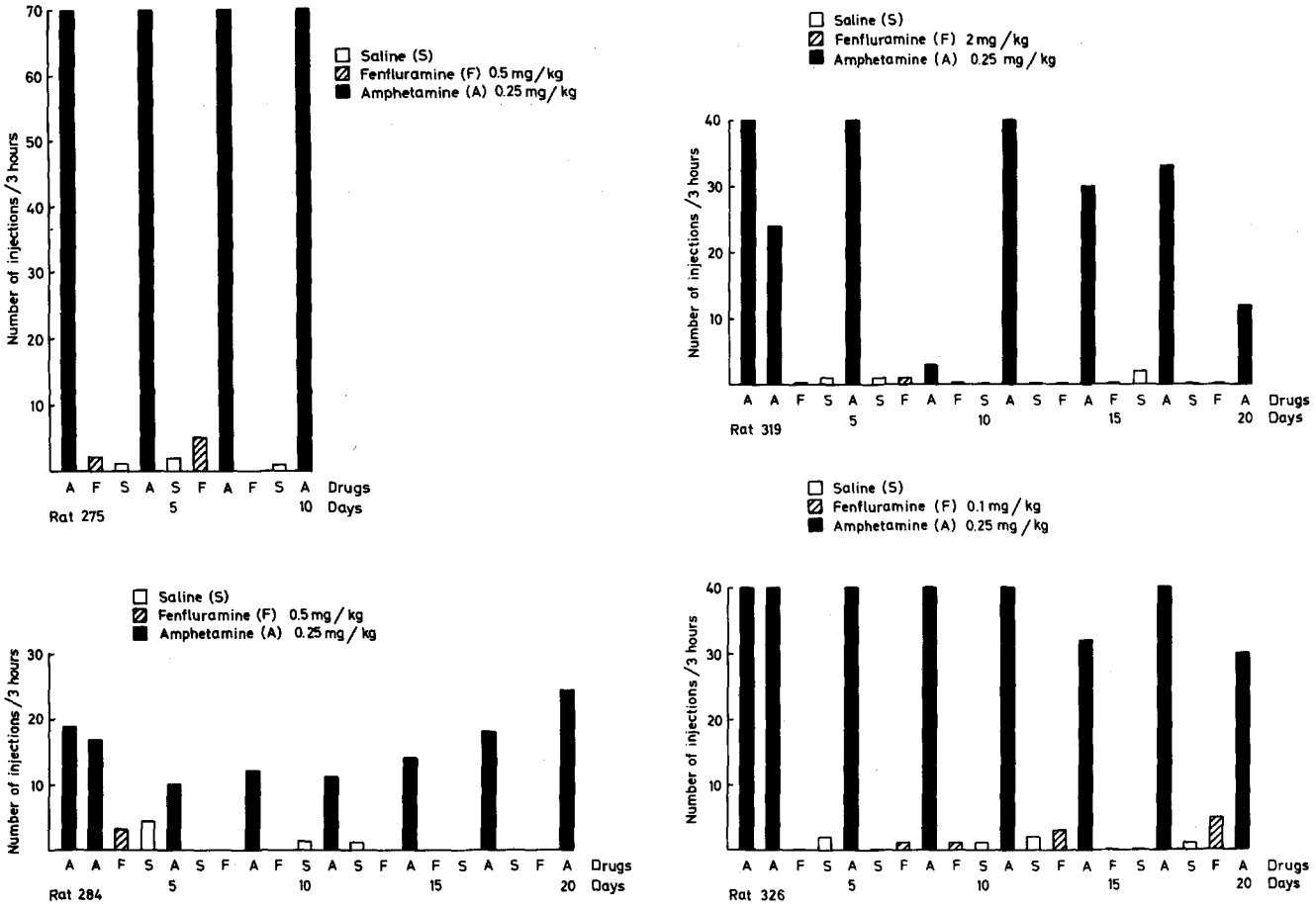

FIG. 2. Self-administration in 4 rats tested with fenfluramine (0.1, 0.5 or 2.0 mg/kg/injection). Before the 18 days experiment (9 days for Rat 275), the two last days (1 for Rat 275) of self-administration of amphetamine are shown. Each session lasted 3 hr, or was interrupted when 40 injections (70 in Rat 275) were taken.

Statistics

Mann-Whitney's U test [19] was used for intraindividual comparisons between drugs.

RESULTS

Figure 1 shows the individual results for the rats tested with phenmetrazine (n = 2) and diethylpropion (n = 2). The two last days of amphetamine self-administration period are shown. The dose of phenmetrazine tested was 1.0 mg/kg/injection. As self-administration behavior occurred to a considerable extent ($p<0.05$) no other dose was tried. The same is true of diethylpropion, where 2.0 mg/kg/injection was tested and found to be self-administered ($p<0.05$).

Figure 2 shows the results for 4 rats tested with fenfluramine. Self-administration of 0.1, 0.5 and 2.0 mg/kg/injection did not differ from saline ($p>0.05$).

The noncontingent injection given at the start of the experimental session seems to control the self-administration behavior. A noncontingent injection of saline or fenfluramine did not start the high rate responding as in the case when a noncontingent injection of amphetamine, diethylpropion or phenmetrazine was given. Some of the days the rats did not take a single injection even when one of the reinforcing drugs was given. In 7% of amphetamine days, 17% of phenmetrazine days, and 9% of diethylpropion days the rats did not start self-administration at all, compared to 57% of fenfluramine days and 45% of saline days.

In Table 1 the number of self-injections per 3 hr (medians) are presented for the 3 test drugs. Intraindividual comparisons are made for each rat. Phenmetrazine and diethylpropion differed from saline, but not from amphetamine. Fenfluramine, however, at all doses tested, differed from amphetamine but not from saline.

DISCUSSION

The present series of experiments showed that phenmetrazine and diethylpropion were self-administered at frequencies (injections/3 hours) not different from self-administration of amphetamine, whereas fenfluramine in the 0.1 to 2.0 mg/kg/injection dose range did not differ from saline.

The drugs examined in the present study are behaviorally active when given intraperitoneally in comparable doses. D-amphetamine (0.43–1.9 mg/kg), phenmetrazine

TABLE 1

NUMBER OF SELF-INJECTIONS PER 3 HR (MEDIANS) FOR THE DIFFERENT TEST DRUGS AND RATS. FENFLURAMINE WAS TESTED AT THREE DIFFERENT DOSES (326, 0.1 mg; 284 AND 275, 0.5 mg; 319, 2.0 mg).

Self-administration of Drug	Dose	Rat Number 283	311	286	307	326	284	275	319
Amphetamine	0.25 mg/kg/inj	13	40	12	40	40	13	70	31.5
Phenmetrazine	1.0 mg	26*	40*						
Diethylpropion	2.0 mg			16*	40*				
Fenfluramine	0.1–2.0 mg					1†	0.5†	1†	0.5†
Saline		0	0	0.5	0	1	0.5	1	0.5

*Difference from saline ($p<0.05$).
†Difference from amphetamine ($p<0.05$).

(1.1–13.0 mg/kg), diethylpropion (1.82–8.2 mg/kg), and fenfluramine (2.0–8.0 mg/kg) have been reported to cause reduction of food intake, and also to affect different behaviors in an open-field setting [4, 8, 14, 16].

The noncontingent injection given prior to each session had priming properties for the subsequent responding an effect which has earlier been reported on rats self-administering d-amphetamine 0.5 mg/kg/injection [15]. High response rate occurred almost immediately after a noncontingent injection of amphetamine, phenmetrazine or diethylpropion. When a noncontingent injection of fenfluramine was given, the rat did not take a single injection in about half of the experimental days. The same effect was seen after a noncontingent injection of saline.

Previous drug experience in the experimental animals seems to be important for the development of self-administration in drug exchange experiments [17]. Self-administration of a drug occurs with increased probability if it has been preceded by self-administration of a drug with similar pharmacologic effects [17]. The results obtained in the present experimental setting might thus partly be caused by similar pharmacological effects (on activity, pulse, blood pressure, temperature, etc.) of amphetamine and diethylpropion. Fenfluramine which did not produce sustained self-administration, has different pharmacological effects, and has been reported to be devoid of central stimulant action [3,12].

The similarity in central pharmacological effects, however, is not a factor that solely determines the occurrence of self-administration of the new drug in drug exchange experiments. Morphine and cocaine, although quite different from each other with respect to central effects, may be substituted for each other in such experiments [9]. Rhesus monkeys previously self-administering cocaine, exhibited self-administration behavior, although at different rates, when given the opportunity to self-administer either amphetamine or morphine [9].

The observation that phenmetrazine and diethylpropion will substitute for amphetamine, whereas fenfluramine will not, confirms two recent preliminary reports on self-administering rats [2] and monkeys [5], respectively.

Earlier studies in humans have indicated that also with regard to subjective effects, fenfluramine seems to differ from amphetamine. The subjective effects of amphetamine and fenfluramine were studied in a controlled drug-free setting on high-dose intravenous amphetamine abusers [7], and on normal subjects with no earlier experience of central stimulants [10]. In these two studies fenfluramine did not show any mood-elevating properties.

Fenfluramine has been on the market in some countries for about 10 years for treatment of obesity, but there has been only one report of abuse of this drug [13]. For amphetamine, phenmetrazine and diethylpropion, on the other hand, there are several reports of abuse [11]. Thus, it seems that self-administration experiments in animals have a potential to predict dependence-producing properties in amphetamine analogues.

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