Pharmacology Biochemistry & Behavior, Vol. 22, pp. 1071–1073, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

BRIEF COMMUNICATION

Self-Administration of Phentermine by Naive Rats: Effects of Body Weight and a Food Delivery Schedule

MICHEAL PAPASAVA, GEORGE SINGER AND CHRISTINE L. PAPASAVA

Department of Psychology, La Trobe University, Bundoora, Vic, 3083, Australia

Received 31 August 1984

PAPASAVA, M., G. SINGER AND C. L. PAPASAVA. *Self-administration of phentermine by naive rats: Effects of body weight and a food delivery schedule.* PHARMACOL BIOCHEM BEHAV 22(6) 1071–1073, 1985.—Food deprivation has been shown to increase intravenous self-administration of amphetamine and cocaine. In the present experiment, the response rates of four groups of eight rats for intravenous infusions of phentermine under free-feeding (FF) and 80% free-feeding weight (FFW) conditions in the presence and absence of a fixed time 1 min (FT-1) food delivery schedule, were compared with those of saline reinforced animals under identical conditions. The findings showed that: (1) Overall, response rates of phentermine-reinforced animals were significantly greater than were those of saline-reinforced animals; (2) 80% FFW animals self-injected significantly greater amounts of phentermine than did FF animals; and (3) the operation of an FT-1 schedule failed to affect the rate of phentermine-reinforced responding.

Food deprivation Stimulant self-administration Phentermine Clinical anorectic
Food delivery schedule Reduced body weight Drug dependence Rats

SCHEDULE-INDUCED Self-Injection (SISI), which combines intravenous self-administration procedures with an intermittent food delivery schedule [9], has been recently employed to induce naive animals to self-administer a range of compounds. These include acetaldehyde [10], d-amphetamine [19], cocaine [14], ethanol [11], heroin [12], and methadone [12,13], as well as diazepam [17], nicotine [9] and Δ^9-THC [19] which in animals, have only weak reinforcing properties (see reviews [4, 5, 6, 22]).

Findings from studies conducted within the SISI paradigm have shown that the type of drug, the nutritional state of the animal and the operation of a fixed time one minute (FT-1) food pellet delivery schedule, either independently or via interactions, may affect the rate of drug-reinforced responding. In the case of acetaldehyde [10], ethanol [11], heroin [12], methadone [12,13], nicotine [9] and Δ^9-THC [19], optimal responding occurs when animals are reduced to 80% of their free-feeding weight (FFW) and are in the presence of an FT-1 food delivery schedule. For d-amphetamine and cocaine, body weight reduction alone is sufficient to induce optimal responding. However, while the operation of an FT-1 schedule suppresses d-amphetamine-reinforced responding [20], responding maintained by cocaine is unaffected [14] (see review by Singer *et al.* [18]). That naive food-deprived rats self-administer psychomotor stimulants vigorously—at doses too low to yield appreciable rates of responding in naive free-feeding (FF) animals—has been demonstrated convincingly in this laboratory [14, 16, 20]. Moreover, that this phenomenon is not an artifact specific to a given laboratory, experimental procedure or species has been confirmed by Carroll *et al.* [1,2], who report that food deprivation alone increases intravenous self-administration of cocaine in rats, and by de la Garza *et al.* [3] who found that in rhesus monkeys, cocaine self-administration was increased several fold when animals were food-deprived.

Based upon the generality of this phenomenon, Papasava *et al.* [14] and Papasava and Singer [16] proposed that if the same effect could be demonstrated with clinically used anorectics, which are in the main structural analogs of amphetamine [21], then it could be argued that the optimal physiological conditions for becoming dependent exist whenever these agents induce weight loss. To test this hypothesis, Papasava and Singer [15] made available various doses of phentermine (Duromine®), a clinically used anorectic shown to maintain significant responding in drug-experienced baboons [7,8], to naive FF and 80% FFW rats. Briefly, findings showed for the first time that: (1) intravenous infusions of phentermine are positively reinforcing in naive rats; (2) irrespective of dose, 80% FFW animals self-administered significantly greater levels than did free-feeding animals; and (3) in accordance with previous findings using both d-amphetamine [20] and cocaine [14,16], phentermine-reinforced responding was characterized by rapid acquisition

of drug intake, erratic alternating periods of high and low intake and large individual differences in amounts self-administered.

The objective in the present experiment was to establish the optimal conditions for maximizing phentermine self-administration within the SISI paradigm, using a dose (0.25 mg/kg/infusion) previously shown to yield the highest level of responding [15].

METHOD

Animals

Sixty-four naive male wistar albino rats weighing between 380 and 400 g were used. The animals were housed individually in a temperature controlled room with a 12 hour light/dark cycle (lights on 0600–1800 hr). Food and water were available ad lib. In experimental conditions where animals were required at 80% of their FFW, they were reduced prior to surgery and were maintained at that weight by restricting the availability of food. For all animals, water was available ad lib in the home cage.

Apparatus

The experimental chamber was identical to that described previously [9–14]. Briefly, an operant box containing a bar and food pellet dispenser with an FT-1 min delivery constituted the drug-taking environment. The bar triggered a syringe infusion pump (Sage Instruments, Model 341) which delivered 70 μl of either phentermine or saline. The infusion system allowed only one infusion per 5 sec interval. Infusion frequency was recorded on a cumulative recorder. When the FT-1 food delivery schedule was operating, a 45 mg Noyes food pellet was dispensed noncontingently every minute.

Drugs

Phentermine hydrochloride (Riker Laboratories Australia Pty. Ltd.) was prepared for intravenous administration daily in sterile physiological saline at a dose of 0.25 mg/kg/infusion: doses refer to the salt. The anaesthetic used for surgery was pentobarbitone sodium (Sagital® May and Baker Pty. Ltd., Australia) and was injected intraperitoneally at a dose of 60 mg/kg (60 mg/ml; 1 ml/kg).

Procedure

The 64 animals were assigned randomly to eight equal sized groups, and the rate of phentermine-reinforced responding at FFW, 80% FFW and FFW and 80% FFW under an FT-1 food delivery schedule, was compared with the level of saline-reinforced responding under similar conditions. All animals were surgically implanted with a chronic jugular vein cannula of SP 28 polythene tubing under Sagital® anaesthesia, according to procedures described elsewhere [9–14]. Following a three day recovery period from surgery, animals were placed in the experimental chamber, connected to a flexible swivel system and tested on six consecutive 1 hr/day sessions beginning at 0900 hr each day. Each experimental session commenced by priming each animal with an initial infusion of either phentermine or saline.

RESULTS

The mean number of infusions/hour over the six day test period for the four saline- and the four phentermine-reinforced groups of animals are presented in Fig. 1.

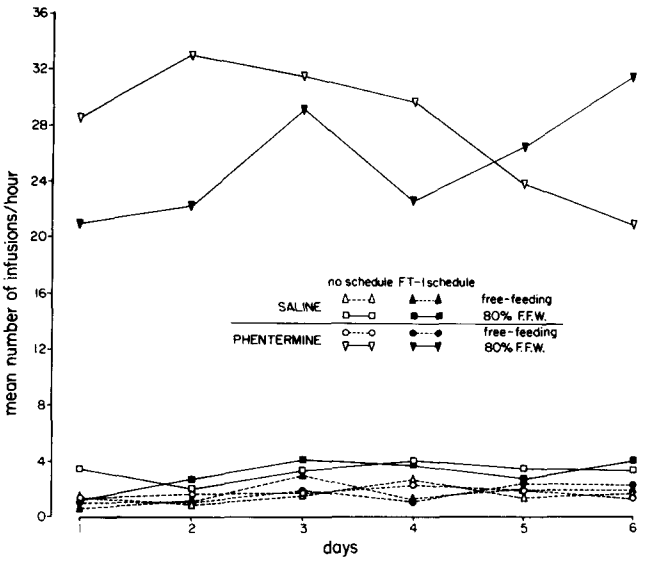

FIG. 1. Mean number of infusions over the six consecutive 1 hour/day test sessions for the four saline- and four phentermine-reinforced groups of animals under free-feeding and 80% FFW conditions in the presence and absence of an FT-1 food delivery schedule.

A four way analysis of variance (ANOVA) with one repeated measure was applied to the data in order to determine main effects for drug conditions, body weight conditions, schedule conditions and days, as well as interactions between them.

Significant main effects were found between the infusion rates of phentermine- and saline-reinforced animals, $F(1,56)=65.859$, $p<0.05$, and between free-feeding and 80% FFW animals, $F(1,56)=83.452$, $p<0.05$. There was no significant difference between the infusion rates of animals in the presence or absence of an FT-1 schedule, i.e., the schedule did not change the rate of phentermine self-administration. A significant interaction was found between the infusion rates of animals in the drug and body weight conditions, $F(1,56)=65.282$, $p<0.05$, indicating that reduced body weight animals reinforced with infusions of phentermine had the highest response rate. There were no other significant effects.

In summary, irrespective of whether or not an FT-1 food delivery schedule was operating, phentermine-reinforced, reduced body weight animals had significantly greater infusions over the six day period than animals in any other condition. The infusion rates of all other groups were very low. This can be seen clearly in Fig. 1.

DISCUSSION

The present findings support previous research from this laboratory with d-amphetamine [20], cocaine [14,16] and phentermine [15], as well as the findings of others who have investigated cocaine-reinforced responding under conditions of food deprivation in both rats [1,2] and rhesus monkeys [3]. Collectively, the data clearly show that stimulant self-administration is amplified by food deprivation. In addition, the present data extend the findings of Griffiths *et al.* [7,8] by showing that phentermine is positively reinforcing in animals with no prior history of drug-reinforced responding.

It is of interest to note that the operation of an FT-1 schedule did not affect the rate of phentermine-reinforced responding, irrespective of whether animals were free-feeding or reduced to 80% FFW. Whilst this finding is consistent with data derived from an earlier investigation with cocaine [14], it is not consistent with the findings of Takahashi *et al.* [20], who reported that the operation of the schedule yielded a significant dose-dependent suppression in the rate of d-amphetamine-reinforced responding in food-deprived rats. Although the explanation for this difference is not apparent, it was proposed by Takahashi *et al.* [20] that the three way interaction between d-amphetamine, physiological factors and schedule conditions gave rise to a 'differential sensitivity' to the pharmacological properties of the drug which resulted in a suppression of drug intake. In neither this nor the cocaine investigation [14] did this interaction occur at the doses tested. Thus, for phentermine, as for cocaine, responding is optimal when animals are body weight reduced and the operation of an FT-1 food delivery schedule appears to be largely irrelevant.

In conclusion, the findings from three different laboratories [1, 3, 14] across two species of animals show clearly that stimulant self-administration is amplified under conditions of food deprivation. The findings of this and an earlier experiment in this laboratory with phentermine [15], indicate that the same relationship exists for a clinically used anorectic. To the extent that one is willing to generalize from animal data, these findings suggest that the use of stimulant-type anorectics in the treatment of obesity may increase the risk of drug dependence when the treatment is successful.

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