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RAPID COMMUNICATION

Preliminary Findings with the Indirect 5-HT Agonist Dexfenfluramine on Heroin Discrimination and Self-administration in Rats

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HIGGINS, G. A., Y. WANG AND E. M. SELLERS. *Preliminary findings with the indirect 5-HT agonist dexfenfluramine on heroin discrimination and self-administration in rats.* PHARMACOL BIOCHEM BEHAV 45(4) 963–966, 1993.— In the present study, the effect of the 5-HT releaser/reuptake inhibitor dexfenfluramine in heroin self-administration and morphine (3 mg/kg) drug discrimination paradigms was examined. Dexfenfluramine (1 mg/kg) reduced heroin self-administration (heroin dose 0.03 mg/kg/infusion; FR5 schedule; 1-h session/day). This effect was antagonised by the 5-$HT_{1/2}$ receptor antagonist metergoline (1 mg/kg). In the drug discrimination model, dexfenfluramine (0.5–2.5 mg/kg) produced no significant generalisation to a morphine cue, and also failed to modify the generalization curve to heroin. Dexfenfluramine (1 mg/kg) produced a slight decriment in response rate in the drug discrimination model and this effect was potentiated by heroin. The mechanism(s) by which dexfenfluramine reduces heroin self-administration remain to be determined, however substitution for heroin would seem unlikely. Furthermore, this effect of dexfenfluramine is probably mediated by either 5-HT_1 or 5-HT_2 receptors.

Heroin self-administration Dexfenfluramine Morphine drug discrimination Rat Metergoline

INTRODUCTION

AT present the role for 5-HT systems in modulating drug reinforced behaviour is unclear (e.g., see ref 13). However, one reasonably consistent preclinical finding is that drugs which enhance the functioning of this neurotransmitter system, notably selective 5-HT reuptake inhibitors (e.g., fluoxetine, zimelidine), reduce IV cocaine (2,9), amphetamine (7), and ethanol (4,8,12) self-administration. At present there is little information relating to the effect of these drugs on opioid self-administration with the exception of a single report describing reductions in the oral intake of a morphine solution following zimelidine pretreatment (10). Because the majority of studies involve opioid (principally heroin) self-administration by the IV route, the present investigation examined the effect of acute pretreatment with dexfenfluramine on IV heroin self-administration in rats. Dexfenfluramine was chosen, because in addition to blocking the reuptake of 5-HT, it also directly releases this neurotransmitter and therefore produces a more profound enhancement of 5-HT function (3,11). A further advantage of dexfenfluramine is that unlike fluoxetine, its pharmacological effects have been consistently shown to be blocked by 5-HT antagonists, such as metergoline (4,11,14).

Initial studies showed that dexfenfluramine reduced heroin self-administration. Because a similar effect may be produced by an opioid preload or by increasing the unit infusion dose of heroin (6), in a separate study we then examined the ability of dexfenfluramine to either a) substitute for a morphine cue, or b) modify a heroin generalization curve in rats trained to discriminate morphine. If dexfenfluramine was indeed substituting for heroin in the self-administration paradigm, then it could be predicted to either generalize to, or potentiate, an opioid cue.

METHODS

Animals and Housing

Male Wistar rats (approx. starting weight 300 g) were used throughout. All animals were maintained in a light and temperature controlled holding room, and singly housed in hang-

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ing wire mesh cages except during the operant session. Food (20 g lab chow) was available as a single supplement at approximately 17:00 h daily. Water was available ad-lib except during operant testing.

Apparatus

Testing was conducted in four identical operant chambers (22 × 22 × 28 cm, L × W × H; Med Associates Inc., East Fairfield, VT) each equipped with two response levers mounted 7 cm above a gridded floor and positioned on either side of a pellet dispenser. Stimulus lights were mounted 5 cm above each lever. A house light was positioned at the back of the chamber. This was illuminated for the duration of all sessions except during the time-out phase of the self-administration schedule.

Heroin Self-administration Paradigm

Following initial shaping to press for food reinforcement, six animals were surgically implanted with an IV catheter under acepromazine (10 mg/kg IP) and ketamine (100 mg/kg IM) anaesthesia. The catheter was inserted into the right jugular vein and was exteriorised on the back of the animal between the scapulae. Following 5–7 days recovery, the animals were returned to the operant chambers and connected to the drug delivery line via a steel spring, which screwed into a pedestal assembly mounted on the animals back around the catheter. At this stage IV drug self-administration training was started. The animals were tested 7 days a week at approximately the same time each day. Prior to each session the catheters were infused with 0.1-ml physiological saline to ensure patency and after each session a further infusion of 0.1 ml of heparinized saline (30 IU/ml) was made. Each session was of 60-min duration and began with a priming heroin (0.03 mg/kg IV) injection delivered by the experimenter. During the session, depression of a designated active lever resulted in the delivery of 0.03-mg/kg heroin (Ward Robertson, Scarboro, Ontario) in a volume of 0.05-ml saline over a 5-s period. A stimulus light positioned above the active lever was activated during each infusion. For a 60-s period after each infusion, the house light was switched off and during this time lever presses were recorded but did not result in an infusion (time out period). Over a 3- to 4-week period, the schedule of reinforcement was gradually increased to FR5 (i.e., 5 presses on the designated lever resulted in the delivery of a single infusion). Once the number of infusions under this schedule did not vary by more than 3, for 3 consecutive days, drug testing began.

All animals received each of the following treatments administered in a random order: saline SC/saline IP; saline SC/dexfenfluramine 1 mg/kg IP; metergoline 1-mg/kg SC/saline IP; metergoline 1-mg/kg SC/dexfenfluramine 1 mg/kg IP.

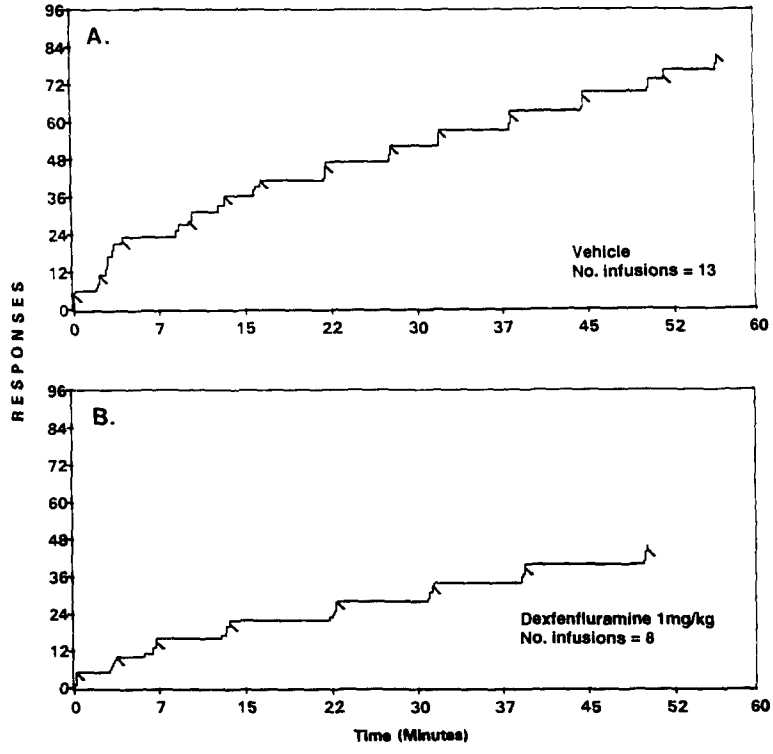

FIG. 1. Response trace of a single animal showing the profile of heroin self-administration (0.03-mg/kg/infusion) following (A) saline and (B) dexfenfluramine (both IP route) pretreatment. The vertical axis represents the number of lever presses made by the animal during the test session. Note the regularity of each heroin infusion (illustrated by the angled strokes) during the test session and the burst of responding leading to reinforcement. Dexfenfluramine did not appear to influence this response burst, however, each infusion was spaced at longer time intervals compared to controls.

An exception to this was one animal where due to catheter failure it did not receive the metergoline/vehicle treatment. Each treatment was separated by at least 1 day of baseline. Metergoline (Farmitalia) or its vehicle was administered 60 min before dexfenfluramine (Servier), which in turn was administered 30 min before the session started.

Drug Discrimination Paradigm

A separate group of 10 rats were trained using standard procedures to discriminate morphine (3 mg/kg) from saline using a two-lever food-reinforced paradigm (see 5 for further detail). Briefly, schedule requirements were FR10 on the designated lever and during generalisation tests both levers were active. Testing was conducted on Wednesdays and Saturdays subject to sustained critereon on intervening days; that is, no more than 16 responses on both levers before the delivery of the first food pellet. Operant sessions terminated either after the delivery of 50 pellets or after 15 min had elapsed.

Morphine sulphate (Macfarlan Smith) and heroin hydrochloride were administered sc 30 min prior to test session. Dexfenfluramine was administered ip either 30 min before test or 30 min before heroin. All doses refer to that of base except dexfenfluramine were doses are expressed as salt. This was to allow comparison with other studies.

RESULTS

Heroin Self-administration

Following a 3–4 week training period all animals showed stable rates of heroin self-administration across sessions and approximately 80% responding was on the drug associated lever (i.e., vehicle/vehicle group: 10.5 ± 1.6 infusions; active lever presses = 78 ± 15, inactive lever presses = 20 ± 10). Dexfenfluramine (1 mg/kg) pretreatment reliably suppressed heroin self-administration. This effect appeared to be the result of an increase in the interresponse interval between infusions; response control, as assessed by appropriate lever selec-

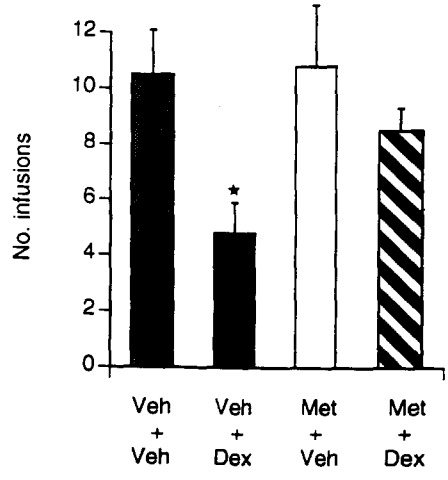

FIG. 2. Antagonism of dexfenfluramine (DEX; 1 mg/kg)-induced suppression of heroin self-administration by the 5-$HT_{1/2}$ antagonist metergoline (MET; 1 mg/kg). Metergoline was administered sc 1 h prior to dexfenfluramine, which was administered ip 30 min before session. $N = 6$ rats. *$p < 0.05$ vs. vehicle/vehicle group (Dunnetts t-test).

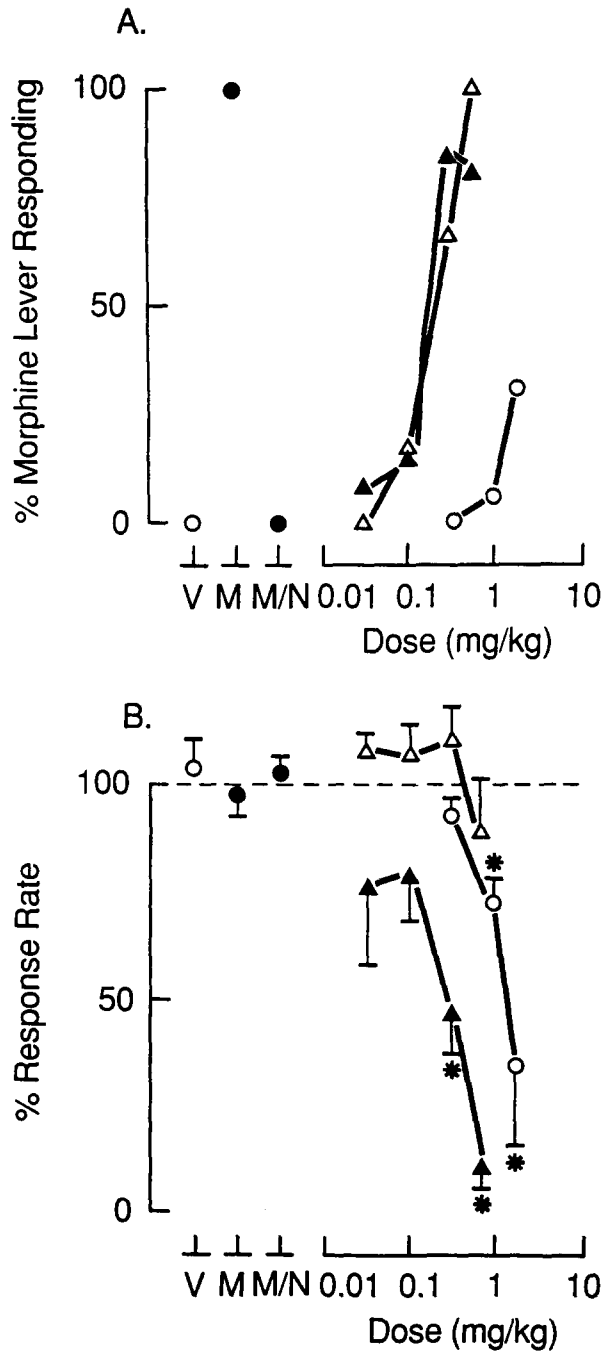

FIG. 3. Effect of dexfenfluramine in rats trained to discriminate morphine (3 mg/kg) from saline using a standard 2-lever operant procedure. (A) Tests of generalization to the morphine cue: (○) dexfenfluramine, (△) heroin + saline, (▲) heroin + dexfenfluramine (1 mg/kg). Also shown is antagonism of the morphine (M) cue following naloxone (N; 0.25 mg/kg 15 min pretreatment). Note that at doses ranging from 0.5–2.5 mg/kg, dexfenfluramine failed to occasion any significant morphine lever responding, and that dexfenfluramine failed to modify heroin generalization to a morphine cue. $N = 5$–8 rats per treatment. (B) Rates of responding during this test expressed as a percentage of the rate observed from the vehicle session immediately preceding the test (normal range 1–2 responses/s). *$p < 0.05$ vs. rate on saline session (Wilcoxan test). Note that dexfenfluramine (1–2.5 mg/kg) reduced response rate, as did the combination of dexfenfluramine (1 mg/kg) and heroin (0.3–0.5 mg/kg).

tion and temporal patterning of lever pressing was largely unaffected by this treatment (e.g., see Fig. 1). At a dose that did not influence self-administration behaviour alone, metergoline (1 mg/kg) pretreatment attenuated this effect of dexfenfluramine (Fig. 2).

Drug Discrimination

In a generalization test, dexfenfluramine (0.5–2.5 mg/kg) did not evoke any significant morphine lever responding (Fig. 3A). Response rates were, however, reduced at both the 1-, and especially 2.5-mg/kg, doses of dexfenfluramine (see Fig. 3B). When administered as pretreatment, dexfenfluramine (1 mg/kg) did not produce any apparent shift in a heroin generalization curve (Fig. 3A). However, the rate suppressant effect of dexfenfluramine was potentiated by heroin doses of 0.3 mg/kg and above (Fig 3B).

DISCUSSION

In the present study we found that the 5-HT releaser/reuptake inhibitor dexfenfluramine reduced heroin self-administration in rats. This effect was blocked by the 5-$HT_{1/2}$ receptor antagonist metergoline confirming an involvement of 5-HT systems in this effect. It also seems likely that the receptors involved belong to either the 5-HT_1 or 5-HT_2, but not 5-HT_3, class (1). The drug discrimination studies clearly showed that dexfenfluramine across a range of doses did not generalize to a morphine cue. Also dexfenfenfluramine did not seem to shift the generalization curve to heroin. Taken together, these findings suggest that the reduction in heroin responding was probably not due to dexfenfluramine either a) producing or b) potentiating, a heroin-"like" stimulus and hence reducing the animals subsequent requirement for heroin (6). Of further note, the observation that following dexfenfluramine (1 mg/kg) pretreatment rats still maintained fairly high rates of food responding, suggests the decline in heroin self-administration was probably not the result of a drug-induced malaise.

Examination of response rates from the drug discrimination studies did reveal that at doses of 1 mg/kg and above, dexfenfluramine suppressed rates of responding for food. Furthermore, this effect appeared to be potentiated by heroin. It must, therefore, be considered whether the reduction in heroin responding was the result of a drug-induced motoric impairment. Of note, the baseline rate of responding in the drug discrimination paradigm was approximately 1–2 responses/s, far above the requirement to maintain baseline responding for heroin infusions. At a dose of 1 mg/kg, dexfenfluramine produced only a modest decrease (approximately 25%) of this higher rate. However, the potentiation of this suppressant effect in heroin (0.3 mg/kg and above) treated rats could also conceivably be occurring in the self-administration model, resulting in a reduction of operant performance. Examination of response traces from the self-administration paradigm, however, revealed that animals pretreated with dexfenfluramine showed comparable response profiles to saline pretreatment, with rapid bouts of lever pressing leading to reinforcement. The main difference between the groups was that the infusions were spaced farther apart. Control of response lever selection was similarly unaffected by dexfenfluramine. These observations suggest that the heroin/dexfenfluramine interaction on response rate may have a relatively unimportant role in the self-administration model.

In conclusion, the present studies suggest that the 5-HT uptake blocker/releaser dexfenfluramine reduces heroin self-administration in rats. This decline in responding would not seem to be a consequence of drug-induced malaise or substitution for heroin. Further studies are now in progress to more clearly elucidate the nature of this effect, not least to determine the influence of dexfenfluramine/heroin combinations on rate measures of operant behaviour.

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