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ORIGINAL INVESTIGATION

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Further studies to examine the nature of dexfenfluramine-induced suppression of heroin self-administration

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Abstract The present series of experiments sought to investigate further the mechanism by which dexfenfluramine, a selective 5-HT releaser/reuptake inhibitor, reduces heroin self-administration by male Wistar rats. In experiment 1, the effect of combined intravenous heroin and intraperitoneal dexfenfluramine injections on operant responding for food was examined. In experiment 2, the maintenance of dexfenfluramine suppression of heroin self-administration following chronic (7 day) treatment was evaluated. Finally, in experiment 3, the ability of various 5-HT antagonists to block the dexfenfluramine suppression was examined. The results from experiment 1 suggest that sensorimotor deficits/malaise potentially associated with heroin/dexfenfluramine combinations are unlikely to account for the reductions in heroin self-administration. Experiment 2 suggested that the suppressant effect of dexfenfluramine on heroin responding may diminish rapidly following chronic treatment. Finally, central 5-HT_1 and/or 5-HT_2, but not 5-HT_3, receptors may underlie the suppressant effects of dexfenfluramine on heroin self-administration.

Key words Dexfenfluramine · 5-HT receptor subtypes · Tolerance · Heroin self-administration · Rat · Metergoline

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Introduction

Evidence that the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) can modify behaviours maintained by positive reinforcement, is largely derived from studies of feeding behaviour. Thus, numerous workers have consistently shown reductions in food intake following pretreatment with drugs which enhance the release or reuptake, and hence the physiological impact, of endogenous 5-HT, e.g dexfenfluramine (e.g Blundell 1984; McGuirk et al. 1992). More recent studies, however, indicate that similar findings may be extended to drug reinforcers such as ethanol (Gill and Amit 1989; Higgins et al. 1992; Rowland and Morian 1992), amphetamine (Leccese and Lyness 1984; Smith et al. 1986), and cocaine (Carroll et al. 1990; Richardson and Roberts 1991).

In accordance with these latter findings, we have reported reductions in intravenous heroin self-administration by Wistar rats following dexfenfluramine pretreatment (Higgins et al. 1993, 1994). These reductions are likely to be unrelated to substitution or potentiation of the opioid stimulus, for in a drug discrimination study dexfenfluramine failed to generalise to, or potentiate, a morphine/heroin cue (Higgins et al. 1993). Also, unlike heroin, (dex)fenfluramine does not appear to have reinforcing properties. For instance, it does not support self-administration (Gotestam and Andersson 1975; Papasava et al. 1986), facilitate intracranial self-stimulation (McClelland et al. 1989) or induce a conditioned place preference (Davies and Parker 1993). Rather, the profile of heroin self-administration following dexfenfluramine treatment could be interpreted as a reduction in the reinforcing properties of heroin, since an extinction-like pattern emerged. Thus dexfenfluramine reduced heroin-maintained responding only after an initial 20-min access period (Higgins et al. 1994). Further experiments examining dexfenfluramine pretreatment against the acquisition of a heroin conditioned place

preference (e.g. Koob et al. 1987), or heroin break points under a progressive ratio schedule of availability (Roberts and Bennett 1993) would be alternative approaches to test this hypothesis.

Clearly, from these initial observations, a number of issues remain to be resolved. For instance, using similar schedules of reinforcement, we found much greater suppressions in heroin responding following dexfenfluramine pretreatment compared to food, suggesting that the effect on heroin was not simply due to a drug-induced malaise or sensorimotor deficit. In the aforementioned drug discrimination study, however (Higgins et al. 1993), combinations of heroin and dexfenfluramine produced marked reductions in operant responding far greater than equivalent doses of each drug alone. This implies a synergistic interaction between both drugs to reduce operant performance. Because dexfenfluramine reduced heroin responding only after an initial sampling period (Higgins et al. 1994), we were concerned that a similar interaction may be occurring in the self-administration model. One objective of the present study therefore, was to examine dexfenfluramine/heroin interactions on food maintained responding using conditions approximating to the heroin self-administration task (Higgins et al. 1993, 1994). Previous studies have demonstrated rapid tolerance to various behavioural changes produced by dexfenfluramine, particularly the suppression of food intake (Rowland and Carlton 1986; McGuirk et al. 1992). Therefore a second aim of these studies was to examine whether tolerance also develops to the suppressant effects of dexfenfluramine on heroin self-administration. Accordingly, an experiment was designed to investigate the effect of chronic (7 day) dexfenfluramine pretreatment on the self-administration of heroin. Finally, dexfenfluramine increases 5-HT function by facilitating 5-HT release and inhibiting 5-HT reuptake (Rowland and Carlton 1986; Fuller et al. 1988). This would be expected to produce a global activation of multiple 5-HT receptor subtypes (see Hoyer et al. 1994 for recent review). A further aspect to this research was provisionally to identify which 5-HT receptor subtype(s) might underlie the effect of dexfenfluramine on heroin self-administration by using various 5-HT antagonists.

Experiment 1: assessment of intravenous heroin/systemic dexfenfluramine combinations on food maintained responding

Methods

Twelve male, Wistar rats (Charles River, Quebec, Canada) weighing approximately 300 g on arrival were used. All animals were isolated at this stage and held within wire mesh cages located in a holding room maintained at 22 ± 1°C and 50% humidity (lights on 0700–1900 hours). Following an initial overnight food deprivation to assist acquisition of operant responding, the animals were maintained for the duration of the study on 20 g food per day, which was available as a single meal at 1700 hours. Initially each animal was trained to respond for food under an FR5TO1 min schedule for 1 h each day i.e five presses on the appropriate lever was rewarded with a single food pellet, and this was followed by a 1 min timeout (TO) period during which lever presses were recorded but not reinforced. The operant chambers measured 22 × 22 × 28 cm (L × W × H) (Med Associates, USA). Each chamber was equipped with two response levers and stimulus lights located on one panel on either side of a food dispenser. A houselight positioned on the opposite wall panel provided illumination during the test sessions. Following stable rates of responding, each animal was surgically prepared with a chronic intravenous catheter (see Corrigall 1992 for further detail) under acepromazine (Ayerst, 10 mg/kg IP) and ketamine (Rogar STP, 100 mg/kg IM) anaesthesia. The catheter was implanted into the jugular vein and exteriorised at the animals back between the scapulae. Following a 7 day recovery period, each animal was given ten IV heroin hydrochloride infusions (0.03 mg base/kg per infusion; infusion volume 0.05 ml; Ward Robertson, Scarboro, Ontario, Canada) manually by the experimenter over a 1 h period for 10 consecutive days. Therefore in this particular study, heroin infusions were NOT contingent on the animals' behaviour. This procedure was used to give the animals some experience of heroin approximating to those self-administering this substance. During this stage the animals continued to be trained in the operant boxes responding solely for food reinforcement under the FR5TO1 min schedule. Heroin infusions and operant food sessions were run separately and spaced 2–3 h apart. Heparinised saline (30 units/ml; 0.1 ml) was given daily at the end of each heroin infusion period to assist maintenance of catheter patency; however, by the end of the 10-day habituation phase, one animal had to be excluded from the study because of catheter failure. The eleven remaining rats then entered an eight-cycle study receiving each of the following treatment combinations in a random sequence: pretreatment with either, a) saline or, b) dexfenfluramine hydrochloride (Servier, 1 mg/kg) IP, 30 min before 5 × 0.05 ml IV infusions of a) saline, b) heroin 0.015 mg/kg per infusion, c) heroin 0.03 mg/kg per infusion, d) heroin 0.06 mg/kg per infusion over a 20-min period. Immediately after this treatment the animals were placed in the operant chambers and allowed to respond for food under the FR5TO1 min schedule. Between each cycle the animals had at least 2 days when they were run as during the 10-day aquisition phase.

Results

The results from this experiment were analysed by repeated measures ANOVA and are presented in Fig. 1. As indicated by significant main effects of dexfenfluramine ($F_{1,10} = 29.8$, $P < 0.01$) and heroin concentration ($F_{3,30} = 20.2$, $P < 0.01$) both agents reduced operant responding for food. A significant drug × heroin interaction ($F_{3,30} = 21.9$, $P < 0.01$) reflected a synergistic effect of this combination. However, the actual magnitude of this reduction was small. The number of pellets obtained under the vehicle/saline combination was 57.6 ± 0.2, and this was reduced to a minimal level of 48.2 ± 1.7 under the dexfenfluramine/heroin 0.06 mg/kg per infusion combination. The number of active lever presses were similarly affected by drug ($F_{1,10} = 27.8$, $P < 0.01$) and heroin concentration ($F_{3,30} = 4.2$, $P < 0.05$) (Table 1). The total number of operant responses varied from 935 ± 132 (vehicle/heroin 0.015 mg/kg per infusion) to 426 ± 23 (dexfenfluramine/heroin 0.06 mg/kg per infusion).

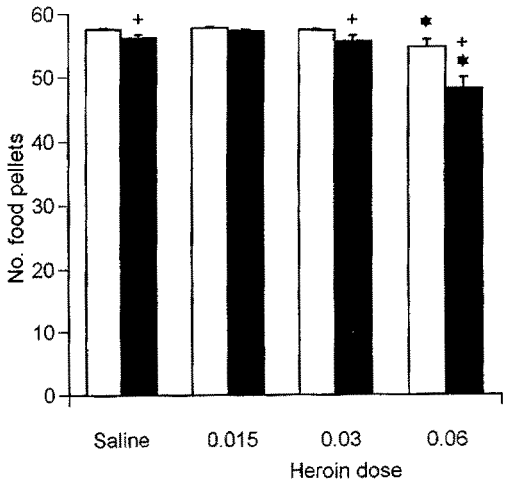

Fig. 1 The number of food pellets obtained by rats receiving either vehicle (□) or dexfenfluramine 1 mg/kg (■) 30 min before five intravenous injections of either saline or heroin at 0.015, 0.03, 0.06 mg/kg per infusion over a 20-min period. This was immediately followed by the 60-min operant session. Eleven rats received all treatments in a counterbalanced design. $*P < 0.05$ vs. saline control under appropriate drug (vehicle/dex) pretreatment, $+P < 0.05$ vs. vehicle control at respective heroin infusion concentration

Table 1 Effect of intravenous heroin and intraperitoneal dexfenfluramine (1 mg/kg) combinations on food maintained responding. The values presented are the number of lever presses recorded during the operant session. $*P < 0.05$, $**P < 0.01$ vs. respective saline infusion. $+P < 0.05$, $++P < 0.01$ vs. respective vehicle/heroin treatment (Tukey's protected *t*-test)

	Saline	Heroin 0.015 mg/kg	Heroin 0.03 mg/kg	Heroin 0.06 mg/kg
Vehicle	832 ± 105	935 ± 132	748 ± 75*	713 ± 72*
Dexfenfluramine	671 ± 60	631 ± 55+	530 ± 34++	426 ± 23**++

Discussion

Both dexfenfluramine and intravenous heroin infusions reduced food maintained responding. Furthermore, the combination of both produced even greater reductions of operant performance. However, despite the highly significant nature of these effects, the actual magnitude of this change was comparatively small. For example, the greatest deficit was observed in animals receiving dexfenfluramine and five heroin infusions of the 0.06 mg/kg per infusion dose; food responding was reduced from a control level of approximately 58 to 48 pellets during the test session. It is important to note that this heroin concentration was double that routinely used in the self-administration experiments reported previously (Higgins et al. 1993, 1994), and also the level of responding necessary to maintain this schedule of food reinforcement was much greater (i.e. 426 ± 23 responses, dexfenfluramine 1 mg/kg-heroin 0.06 mg/kg per infusion compared to the 60–120 responses typically required to attain appropriate heroin reinforcement under control conditions, see Fig. 3B, Higgins et al. 1994; also present study). If the reduction in heroin self-administration produced by dexfenfluramine could be accounted for by a sensorimotor disruption/malaise produced by both drugs in combination, then one would predict far greater reductions in food responding than that recorded in the present study. That such deficits were not seen would probably suggest that dexfenfluramine reduces heroin self-administration by an alternative mechanism, perhaps related to a reduction in heroin reinforcement (see Introduction).

Experiment 2: assessment of chronic dexfenfluramine pretreatment on heroin self-administration

Methods

In this study, a final total of 27 rats were used. Housing conditions and food availability was similar to that described in experiment 1. Following acquisition of food responding, each animal was surgically prepared with a chronic intravenous catheter. Then, after a 7-day recovery period, the animals were trained to respond for heroin within the same operant boxes used in the feeding study. Initially the animals were first habituated to being tethered to the swivel assembly, which connected the drug reservoir to the indwelling catheter, again using food reinforcement. Following one such session, heroin self-administration training began. Only one lever was designated active during these sessions and over the course of 20–25 days the animals were trained to respond for 0.03 mg/kg heroin per infusion (infusion volume = 0.05 ml; infusion rate = 0.01 ml/s). Initial schedule requirements were FR1 which increased in single increments to a final value of FR5. Reinforcement delivery was signalled by a stimulus light positioned above the designated active lever. A 1-min time-out (TO) period followed each infusion and during this period lever presses were recorded but not reinforced, and the houselight was switched off. All self-administration sessions were of 60 min duration, run 7 days/week. Heparinised saline (30 units/ml; 0.1 ml) was given daily at the end of each access session to assist maintenance of catheter patency. When the number of infusions under the FR5 schedule did not vary by more than three, for 3 consecutive days, the animals were then allocated into three groups ($n = 9$ per group) based on similar baseline performance and given the following treatments prior to self-administration sessions. Group 1: saline IP (30 min pretreatment) for 7 consecutive days, followed by dexfenfluramine (1 mg/kg) on day 8. Group 2: dexfenfluramine 1 mg/kg IP (30 min pretreatment) for 8 consecutive days. Group 3: dexfenfluramine 1 mg/kg IP 4 h after self-administration sessions for 7 days, on day 8 dexfenfluramine was given 30 min before heroin availability.

During these self-administration experiments, the animals continued to be fed a single meal of 20 g food at the end of each day. This quantity was selected as it constitutes the recommended daily nutritional requirement for rats (Canadian Council for Animal Care 1980) and is sufficient to allow a monthly weight gain in the order of 15–20 g. This feeding regimen, as with previous studies (Corrigal 1992; Higgins et al. 1994) produces stable levels of heroin self-administration. Furthermore, varying the unit infusion dose of heroin leads to compensatory changes in the number of infusions taken, suggesting that responding is indeed for heroin.

Results

The chronic dosing study consisted of three distinct stages; therefore each was analysed separately. At the

baseline stage, i.e. before dexfenfluramine treatment, the level of heroin self-administration was similar between groups as indicated by ANOVA of treatment groups on the day prior to commencement of drug treatment ($F_{2,24} = 0.1$, NS) (see Fig. 2A). The second stage consisted of the 7-day chronic treatment with either dexfenfluramine or saline vehicle (see Fig. 2B). ANOVA revealed significant main effects of treatment group ($F_{2,24} = 3.8$, $P = 0.03$), days ($F_{6,144} = 20.0$, $P < 0.01$), and treatment × days interaction ($F_{12,144} = 3.3$, $P < 0.01$). Post-hoc within-day comparisons between groups revealed significant differences between 30 min dexfenfluramine pretreatment (group B) and the other groups on days 1–4. Between days 5 and 7 no such difference was apparent. The reason for this decline was due to the magnitude of the dexfenfluramine effect decreasing over days. Responding in the vehicle pretreatment group (group A) remained unchanged over the 7-day period. There was also a tendency towards an increase in heroin responding above saline controls in the 4-h post access heroin group (group C) which actually reached significance on days 4 and 5. The final stage consisted of all three groups receiving 30-min pretreatment with dexfenfluramine before the heroin access period on day 8. Subsequent ANOVA revealed a significant group effect ($F_{2,24} = 4.4$, $P = 0.02$), due primarily to a decrease in heroin self-administration in the rats which had previously received saline during the 7-day chronic period (group A). There was no difference between rats treated with dexfenfluramine either 30 min prior to, or 4 h after, the access period. In neither group was the number of heroin infusions different from baseline or day 7, indicating that tolerance had developed in both groups.

Discussion

These studies reveal that rapid tolerance develops to the suppressions of heroin self-administration produced by dexfenfluramine. Following chronic daily treatment, an attenuated response was noted as early as day 2. By day 5 the effect of dexfenfluramine was indistinguishable from control, i.e complete tolerance had developed. The rapidity of this onset contrasts with the observation that with a suitable interval between consecutive dexfenfluramine doses (approximately 48 h), tolerance does not develop to any measurable level, thus enabling repeated measure designs to study dexfenfluramine (Higgins et al. 1993, 1994; experiment 3).

It is important to note that tolerance also developed in animals which were treated with dexfenfluramine 4 h after the access session. This latter finding suggests that the mechanism for this event was not a conditioned response, but rather the consequence of some physiological adaptation to repeated dexfenfluramine treatment. Presumably, the most likely explanation is a depletion of the releasable pool of 5-HT brought about by chronic dexfenfluramine treatment (Rowland and Carlton 1986; Laferrere and Wurtman 1989).

A final observation from this study was the small increase in the number of heroin infusions taken by the animals treated with dexfenfluramine 4 h after the period of self-administration. This may be related to the aforementioned 5-HT depletion produced by chronic dexfenfluramine, as central 5-HT lesions have been reported to increase opioid self-administration (Smith et al. 1987). However, these increases were inconsistent, only reaching significance on days 4 and 5.

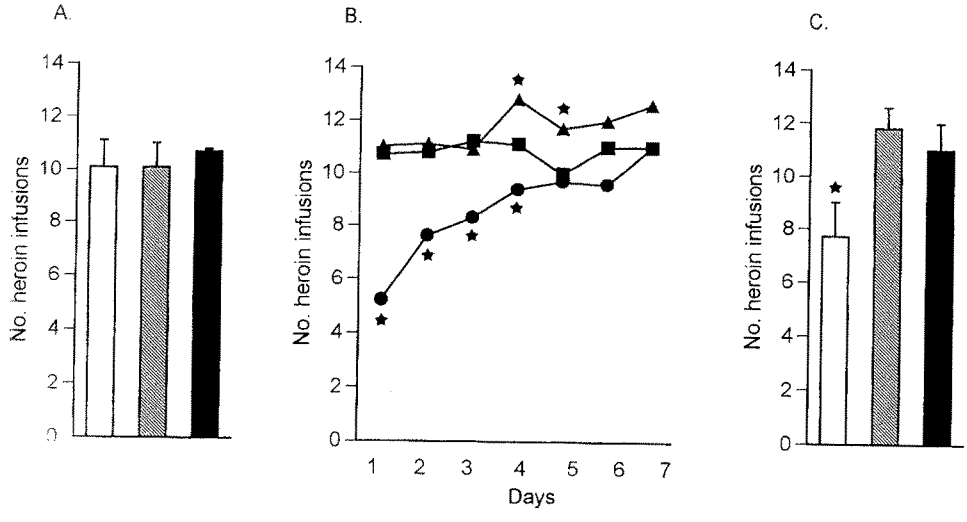

Fig. 2 **A** Heroin self-administration on the final day of the acquisition period immediatly before commencement of drug treatment. There is no difference in the level of responding in each group. (□) group A: saline vehicle 30-min before heroin access session during stage B. (▒) group B: dexfenfluramine 1 mg/kg IP 30 min before heroin access session during stage B. (■) group C: dexfenfluramine 1 mg/kg IP 4 h after heroin access session during stage B. $n = 9$ rats per group. **B** Heroin self-administration in groups A (■), B (●), C (▲) during stage B. $^*P < 0.05$ vs. group A at that day. **C** Heroin self-administration following dexfenfluramine pretreatment (1 mg/kg IP; 30 min) in groups A (□), B (▒), C (■). Only in group A was heroin responding significantly lower than previous day (i.e day 7 in B) or different from other groups at stage C

Experiment 3: assessment of 5-HT receptor antagonists against dexfenfluramine-induced suppression of heroin self-administration

Methods

Squads of male Wistar rats were trained to self-administer intravenous heroin (0.03 mg/kg per infusion; FR5TO1 min schedule) using identical acquisition procedures to those described for experiment 2. Once responding had stabilised, the effects of the 5-HT receptor antagonists metergoline (1 mg/kg), ritanserin (1 mg/kg), ondansetron (0.1 mg/kg) and xylamidine (3 mg/kg), against dexfenfluramine (1 mg/kg)-induced suppressions of heroin self-administration was evaluated. The doses selected for each antagonist were taken from the literature as blocking a relevant 5-HT receptor in vivo (see Discussion). Thus for each antagonist there were four treatments (i.e. vehicle/vehicle, vehicle/dex, antagonist/vehicle, antagonist/dex) which were administered in a counterbalanced sequence to each animal in that particular study. At least 2 drug- free days separated each drug treatment. For the most part, separate squads of animals were run for each antagonist, although occasionally (not more than $n = 4$ per antagonist) some animals were tested in more than one study. The final n for each antagonist study was: metergoline (7), ritanserin (10), ondansetron (7), xylamidine (6). Metergoline (Farmitalia), ritanserin (Janssen Pharmaceuticals), ondansetron hydrochloride (Glaxo) and xylamidine tosylate (Burroughs Wellcome) were all prepared in saline immediately before use. Metergoline was first dissolved in 1 M ascorbic acid before being made up to final volume with saline; ritanserin was initially mixed with 0.01 M tartaric acid before addition of saline. The final pH of these solutions was then adjusted to 5–6. Controls received the appropriate vehicle. All drugs were injected SC except dexfenfluramine (IP). Pretreatment times were 2.5 h (xylamidine), 60 min (ritanserin), 30 min (ondansetron, metergoline) before dexfenfluramine, which was administered 30 min before self-administration sessions at a standard dose of 1 mg/kg. All drug doses refer to that of the base, except dexfenfluramine which is expressed as the salt.

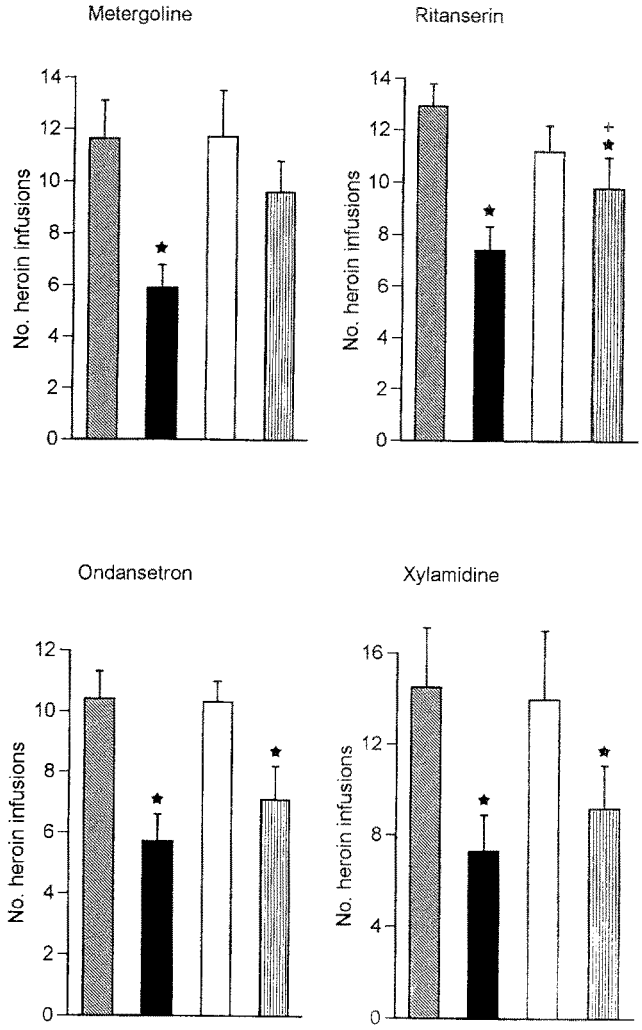

Fig. 3 Effect of various 5-HT receptor antagonists against dexfenfluramine (1 mg/kg IP) reductions in heroin self-administration. (▒) vehicle/vehicle, (■) vehicle/dex, (□) antagonist/vehicle (▥) antagonist/dex. See Methods section for antagonist dose and pretreatment time. $*P < 0.05$ vs. vehicle/vehicle, $+P < 0.05$ vs. vehicle/dex

Results

Dexfenfluramine (1 mg/kg) reduced heroin self-administration in each antagonist interaction study (Fig. 3). Although not significantly altering heroin self-administration alone, metergoline (1 mg/kg) significantly attenuated this effect of dexfenfluramine. Thus two-way repeated measures ANOVA revealed significant main effects of drug (dexfenfluramine: $F_{1,6}$=12.5, P<0.01; metergoline: $F_{1,6} = 8.3$; $P < 0.05$) and a significant dexfenfluramine × metergoline interaction ($F_{1,6} = 18.0$, $P < 0.01$

The effect of ritanserin (1 mg/kg) was less straightforward despite the comparatively large n of 10 which made up the study. Dexfenfluramine produced a significant reduction in responding for heroin (dexfenfluramine main effect: $F_{1,9} = 33.8$, $P < 0.01$) and, if anything, there was also a nonsignificant trend towards a reduction in heroin self-administration following ritanserin alone (vehicle 12.9 ± 0.9 infusions, ritanserin 11.2 ± 1.0 infusions; ritanserin main effect: $F_{1,9} = 0.5$, NS). However, the combination of ritanserin and dexfenfluramine produced an intermediate level of heroin responding, less than ritanserin alone, but greater than dexfenfluramine alone (ritanserin × dexfenfluramine interaction: $F_{1,9} = 10.3$, $P = 0.01$). In other words, ritanserin also appeared to attenuate the dexfenfluramine-induced reduction.

Neither ondansetron (0.1 mg/kg) nor xylamidine (3 mg/kg) affected heroin-maintained responding or affected the dexfenfluramine suppression (in each case dexfenfluramine main effect: $F > 15$, $P < 0.01$; antagonist main effect: $F < 1$, NS; dexfenfluramine × antagonist: $F < 4$, NS).

Discussion

In each study, dexfenfluramine reduced the number of heroin infusions taken by animals self-administering this substance; and, in agreement with an earlier study (Higgins et al. 1993), the 5-$HT_{1/2}$ receptor antagonist

metergoline blocked this effect. In addition, the 5-HT_2 receptor antagonist ritanserin, at a dose reported to block agonist-induced responses at this subtype in vivo (Awouters et al. 1988), attenuated the effect of dexfenfluramine. However, this observation is confounded somewhat by the finding that the attenuation was not complete, and that ritanserin alone slightly reduced responding for heroin. Thus, on the basis of these results the extent to which 5-HT_2 receptors are involved in mediating the effect of dexfenfluramine is unclear. A central site of action for dexfenfluramine is implied by the failure of the peripherally acting 5-HT receptor antagonist xylamidine to modify this response. Xylamidine was tested under conditions reported to block peripherally mediated 5-HT-induced pressor responses (Fuller et al. 1986). Finally, blockade of 5-HT_3 receptors with ondansetron did not modify the effect of dexfenfluramine on heroin self-administration, and neither did ondansetron pretreatment alone affect this parameter. This failure of ondansetron to affect heroin self-administration is consistent with previous results from this laboratory and may be extended to another 5-HT_3 antagonist (MDL72222), and to multiple doses of each drug (Higgins et al. 1994). An involvement of the 5-HT_4 receptor would seem unlikely as metergoline has low affinity for this site (Craig and Clarke 1990).

Recently, a further three 5-HT receptor subclasses, designated 5-HT_{5-7}, have been identified by molecular biological techniques (see Boess and Martin 1994, for a recent review). Metergoline reportedly has high affinity for the 5-HT_6 and 5-HT_7 sites. However, given that these additional sites have yet to be awarded unequivocal receptor status by the Serotonin Nomenclature Committee (Hoyer et al. 1994), we do not speculate on their involvement in the behaviours described in the present report. Nonetheless, it is clear that further studies using more selective drugs, and multiple drug doses, are required to establish the 5-HT receptor types involved in the regulation of the behaviours described in the present report.

General discussion

In keeping with a previous report, dexfenfluramine reduced intravenous self-administration of heroin (Higgins et al. 1994). The results of experiment 1 showed that this reduction in responding is unlikely to result from a combined action of dexfenfluramine and heroin to suppress response rate. The racemic form, fenfluramine, has been reported to elevate met-enkephalin-like immunoreactivity and several other opioid peptides in the rat brain (Dellavedova et al. 1982; Majeed et al. 1986). It might be predicted then that such effects on endogenous opioid function might reduce heroin self-administration in the same way as increases in the unit dose of heroin (Koob et al. 1987). However, this is unlikely to be the mechanism responsible for the dexfenfluramine effect on heroin self-administration for several reasons. Firstly, the doses of fenfluramine required to induce such effects on the opioid system are considerably greater (20-mg/kg, Dellavedova et al. 1982; Majeed et al. 1986) than those used in the present studies, even allowing for the fact that the more active isomer was used in this report. Secondly, the onset of the fenfluramine effect on opioid systems occurs between 4 and 24 h after injection, whereas the effects on heroin self-administration occur within 20 min after a 30 min pre-treatment interval. Thirdly, the effects of fenfluramine on opioid activity appear to result from the decrease in 5-HT function that occurs several hours after injection. Decreased 5-HT activity, at least in the nucleus accumbens, appears to increase responding for IV infusions of opioids (Smith et al. 1987). Furthermore, the 5-HT receptor antagonist metergoline reversed the effects of dexfenfluramine, which implies that increased 5-HT function is responsible for the effect of dexfenfluramine on heroin self-administration. Thus, it seems unlikely that a direct effect of dexfenfluramine on endogenous opioid systems can account for the action of dexfenfluramine to suppress heroin self-administration.

The most widely documented behavioural effect of dexfenfluramine is a suppression of food intake (e.g. Blundell 1984). While the precise mechanism responsible for this effect is not clear, there are a number of similarities between the drug's effects on feeding and heroin self-administration. Against both behaviours the effect of dexfenfluramine is potent and robust. Also, rapid tolerance develops to the suppressant effects of dexfenfluramine on feeding and heroin intake. As shown in the present studies, the effects of dexfenfluramine on heroin were reversed by metergoline, partially reversed by ritanserin and not affected by xylamidine or ondansetron. The pharmacological profile of dexfenfluramine anorexia is similar. Thus, metergoline completely reverses this effect of dexfenfluramine, while xylamidine and the 5-HT_3 receptor antagonist ICS205-903 failed to block dexfenfluramine (Neill and Cooper 1988). In the case of ritanserin, the situation is more complex, since ritanserin has been reported by some authors to reverse dexfenfluramine-induced anorexia (Neill and Cooper 1988), while others have reported that ritanserin is ineffective in this regard (Samanin et al. 1989). However, these unequivocal results could be argued as consistent with the fact that ritanserin did not fully antagonize the effect of dexfenfluramine on heroin self-administration. The similarities of dexfenfluramine on food intake and heroin self-administration suggest that a common mechanism underlies these effects. Both natural rewards such as food, and artificial rewards such as opioids and psychostimulants, may activate the same reward circuitry in the brain (Wise and Bozarth 1987). Thus, it is possible that dexfenfluramine may alter responsivity to

rewarding stimuli in general. At first sight, the observation that in experiment 1 dexfenfluramine only slightly altered responding for food might appear at odds with this suggestion. However, it should be borne in mind that in addition to the large differences in reinforcement density on the two schedules of food and heroin access, these two rewards (food versus heroin) also differ considerably in terms of their sensory properties and their onset and duration of action.

The hypothesis that dexfenfluramine may interact with reward function is supported by evidence from a number of other behavioural paradigms. Thus, dexfenfluramine reduces lateral hypothalamic self-stimulation (McClelland et al. 1989), responding for conditioned rewards and the response potentiating effect of dexamphetamine (Fletcher 1995) and also reduces ethanol consumption (Higgins et al. 1992; Rowland and Morian 1992). As with the effects of dexfenfluramine on feeding and heroin self-administration, several of these effects can be prevented by metergoline (e.g. Higgins et al. 1992; Fletcher 1995) implying that increased 5-HT activity is the primary underlying neurochemical mechanism involved. Taken together, these findings imply a role for brain serotonin neurones in modulating reward-related behaviour. Further evidence to support this hypothesis comes from the observations that reductions in brain 5-HT function, particularly following central 5,7-dihydroxytryptamine lesions, facilitate responding for morphine (Smith et al. 1987), amphetamine (Lyness et al. 1980; Leccese and Lyness 1984), cocaine self-administration (Loh and Roberts 1990) and appear to increase the reinforcing value of sucrose (Wogar et al. 1991). Also, temporary suppressions of central 5-HT function, produced by intra-raphe infusions of the 5-HT_{1A} agonist 8-OH DPAT, are sufficient to induce a conditioned place preference (Fletcher et al. 1993) and increase ethanol intake/preference (Tomkins et al. 1994).

In conclusion, dexfenfluramine reduces heroin self-administration, probably by similar mechanisms to that which reduce food intake. Thus tolerance develops rapidly to both effects, and each appear to show a similar pharmacology. Recent concerns have been expressed in the literature concerning the potential neurotoxic effects of chronic dexfenfluramine treatment (McCann et al. 1994). Together with the issue of rapid tolerance, these findings suggest that the identification of more selective, directly acting 5-HT agonists could result in valuable therapies to assist individuals attempting to cease drug abuse behaviour.

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