# Phentermine and Fenfluramine

## Preclinical Studies in Animal Models of Cocaine Addiction

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**ABSTRACT: Combined dopamine (DA) and 5-hydroxytryptamine (5-HT) releasers such as phentermine (PHEN) and fenfluramine (FEN) are reported, in open label studies, to reduce craving for alcohol and cocaine and to prevent relapse. The objective of the studies reported here was to assess the actions of these agents alone and in combination in various animal models of drug addiction. *Study 1. In vivo* microdialysis experiments demonstrate that these agents preferentially release mesolimbic DA (PHEN) and 5-HT (FEN). Patients who relapse and use cocaine while taking these medications report diminished cocaine-like subjective effects. Microdialysis experiments were performed in awake rats, and dialysate samples were analyzed for DA and 5-HT. PHEN (1 mg/kg, intravenously (i.v.)) elevated DA (2–3-fold) for over 1.5 hr. Administration of cocaine (3 mg/kg, i.v.) increased DA 6-fold in saline-treated rats, but only 3-fold in PHEN-treated rats. PHEN did not reduce cocaine-induced increases in 5-HT. *Study 2.* These agents were assessed in a mouse model of cocaine-conditioned motoric activity (CCMA). Pretreatment with non-activating doses of PHEN (4.6 mg/kg, intraperitoneally (i.p.)) enhanced CCMA, whereas non-depressing doses of FEN (0.1 mg/kg, i.p.) did not alter CCMA or the PHEN-induced increase in CCMA. In contrast, sub-effective doses of FEN reduced CCMA stereotypy-like locomotion, whereas sub-effective doses of PHEN were without effect. PHEN reversed the FEN-induced increase in CCMA stereotypy-like locomotion. *Study 3.* PHEN and FEN were assessed in the conditioned place preference model. FEN produced marked aversions for an environment previously associated with its administration and the minimum dose producing this effect was 3.0 mg/kg. In contrast, administration of PHEN, amphetamine (1.0–3.0 mg/kg) or morphine (3.0–5.0 mg/kg) produced dose-related preferences for the drug-paired place. However, the magnitude of the response to PHEN was less than that produced by the other prototypic drugs of abuse. In rats that received FEN (0.3 or 3.0 mg/kg) in combination with PHEN (3.0 mg/kg), the conditioned rewarding effects of PHEN were abolished. These data demonstrate that the rewarding effects of PHEN can be conditioned to stimuli previously associated with its administration. However, the conditioned response to this agent is less then that produced by prototypic drugs of abuse. The finding that PHEN-induced place preferences were attenuated by doses of FEN demonstrates that the combination of FEN/PHEN is devoid of motivational effects. The preclinical data obtained with PHEN/FEN in various models of drug provide a strong rationale for pursuing controlled clinical trials in humans with agents that act via a similar mechanism of action.**

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## INTRODUCTION

Converging lines of evidence indicate that withdrawal from chronic cocaine in rats is associated with abnormalities in dopamine (DA) and 5-hydroxytryptamine (serotonin, 5-HT) function.[1–5] These findings led us to propose a 'dual deficit model' of cocaine addiction. According to this model, DA dysfunction may underlie the anhedonia experienced by abstinent human addicts,[6–7] whereas 5-HT dysfunction could be responsible for disturbances in mood and impulse control.[8,9] A prediction of this model is that medications that increase both dopaminergic and serotonergic tone, but not one or the other, will help patients stop their use of cocaine and maintain abstinence. Open-label studies, which demonstrate that coadministration of DA- and 5-HT-releasing agents facilitate abstinence in cocaine- and alcohol-dependent patients,[10–13] support this hypothesis. These observations, and other data supporting the 'dual deficit model' of cocaine addiction led us to investigate the actions of medications that release DA and 5-HT, administered alone and conjointly, in various models of cocaine addiction. The medications we focused on are phentermine (PHEN), which preferentially releases DA, and fenfluramine (FEN), which selectively releases 5-HT.

## METHODS

### *General Procedures*

Experimental procedures reported here were carried out in accordance with the Declaration of Helsinki and with the Guide for the Care and Use of Laboratory Animals as adopted by the NIH.

### *In Vivo Microdialysis Studies*

The *in vivo* microdialysis experiments were performed according to published procedures.[14] Briefly, male Sprague-Dawley rats (Charles River, Wilmington, MA) were anesthetized with Equithesin (3 ml/kg) and fitted with indwelling jugular catheters and intracerebral guide cannulae (model CMA 12, Bioanalytical Systems, Inc., West Lafayette, IL) aimed at the nucleus accumbens (mediolateral ± 1.5, anteroposterior + 1.6, dorsoventral + 6.2 relative to bregma).[15] After 7–10 days, rats were lightly anesthetized with metofane. Microdialysis probes (CMA 12, 2 mm × 0.5 mm) were lowered into guide cannulae and polyethylene extensions were attached to jugular catheters. Artificial Ringers' solution (147.0 mM NaCl, 4.0 mM KCl, 2.0 mM $CaCl_2$, unadjusted pH 6.5) was pumped through the probe at 0.5 µl/min. Beginning 2–3 hr after probe insertion, 10-µl dialysate samples were collected at 20-min intervals and immediately assayed for DA and 5-HT by microbore high-pressure liquid chromatography with electrochemical detection (HPLC – EC).[14] The first 3 samples collected before any treatment were considered baseline samples, and all subsequent monoamine measures were expressed as a percent of this baseline. Data were evaluated by repeated measures analysis of variance (ANOVA). When significant $F$ values were obtained Newman-Keuls post-hoc tests were performed to compare group means. $p < 0.05$ was chosen as the minimum criterion for statistical significance. All drugs were obtained from the NIDA Addiction Research Center pharmacy. In some cases, drugs were administered via the microdialysis probe, and in other cases by intravenous (i.v.) or intraperitoneal (i.p.) routes.

### *Conditioned Place Preference*

Place conditioning was conducted in 28.5 cm × 28.5 cm × 28.5 cm Plexiglas shuttleboxes each equipped with a clear Plexiglas door. For conditioning sessions, the boxes were divided into two equal sized compartments by means of a removable partition. One compartment was white with a textured floor. The other was black with a smooth black floor. For test sessions, the wall separating the two compartments was removed and a 2.5 cm × 21.5 cm 'neutral' platform composed of steel mesh and Plexiglas was inserted along the seam separating the two compartments. All sessions were conducted under dim illumination with masking white noise present. Previous studies[16] have shown that under these conditions, Sprague-Dawley rats exhibit no preference for either of the place cues.

Place conditioning was conducted using an unbiased procedure.[16] Sessions were conducted twice each day with 6–8 hr separating each. Prior to each session, rats were wheeled into the room housing the shuttle boxes and allowed to habituate to the testing environment for 10 min. They were then injected with saline and confined to one compartment of the shuttle box for 50 min. Following the administration of the conditioning drug or saline they were confined to the other compartment for 50 min. Treatment compartment and presentation order of all drugs were counterbalanced for each drug dose. Tests of conditioning were conducted 1 day after the last conditioning session and each rat was tested only once. For test sessions, uninjected rats were allowed free access to both compartments of the shuttlebox for 15 min. The time spent in the drug-paired and saline-paired environments were then assessed by visual analysis of the video-recorded test session. The location of the rats was determined by the position of the front paws. Analysis of the videotapes was conducted by an observer blinded to the experimental conditions.

Conditioning scores represent the time spent in the drug-paired place minus the time spent in the saline-paired place and are expressed as means ± SEM. A place preference was defined as a positive conditioning score whereas a place aversion was defined as a negative conditioning score. The Wilcoxon test, in which time spent in the drug-paired place was compared to that spent in the saline-paired place, was used to determine whether an individual dose produced significant place conditioning. A one-way random-effects model factorial analysis of variance was used to determine the dose-response relationship for the various drugs.

### *Cocaine-Conditioned Motoric Activity (CCMA)*

#### *Overview of CCMA*

The conditioned drug effect paradigm attempts to identify potential pharmacotherapeutic interventions using the conditioned locomotor effects of cocaine as the dependent variable. The paradigm pairs repeated administration of cocaine with the locomotor activity monitor. Following repeated administration of the drug in the activity monitor, saline is administered on the test day to determine the presence or absence of conditioned locomotor activation. Non-activating/depressing (subthreshold) doses of potential therapeutic compounds (*i.e.*, doses not resulting in altered baseline activity) are tested in order to determine their ability to alter the behavioral response (locomotor activity) to stimuli associated with cocaine administration. Experimental groups are shown in TABLE 1. Comparison of groups A and B determines if repeated administration of cocaine results in conditioned locomotor activity. Comparison of

TABLE 1. Experimental Design of Cocaine-Conditioned Motoric Activity Assay

| | | | | Test | Day 4 |
|---|---|---|---|---|---|
| Condition | Day 1 | Day 2 | Day 3 | Pretreatment | Test |
| **A** | saline | saline | saline | saline | saline |
| **B** | cocaine 10 | cocaine 10 | cocaine 10 | saline | saline |
| **C** | cocaine 10 | cocaine 10 | cocaine 10 | FEN | saline |
| **D** | cocaine 10 | cocaine 10 | cocaine 10 | PHEN | saline |
| **E** | cocaine 10 | cocaine 10 | cocaine 10 | FEN/PHEN | saline |

Note: The experimental design of the CCMA experiments is outlined above. See Methods for a more detailed explanation.

groups B–E determines whether or not administration of FEN, PHEN or the combination (FEN/PHEN) significantly alters the conditioned locomotor activating effects of cocaine.

*Subjects*

Adult male Swiss Webster mice (Harlan Sprague-Dawley), 60–120 days old and weighing approximately 21–26 g at the start of the experiment were used. All animals were experimentally naive, housed in groups of 6 in a temperature-controlled room (26°C) with a 12-hr light-dark cycle (0700–1900 lights on), and given free access to Purina Laboratory Chow and tap water during the entire experimental procedure.

*Conditioning*

Subjects were randomly divided into five groups (see TABLE 1). All subjects received three conditioning sessions. Conditioning sessions were run once per day across three consecutive days. On each conditioning day, mice were given saline or cocaine (10 mg/kg) immediately prior to being placed in the locomotor activity monitor for 60 min. Saline and cocaine were administered i.p. in a volume of 0.01 ml/g body weight.

*Testing*

Pretreatment doses of FEN, PHEN and FEN/PHEN were determined in separate experiments. Dose-effect curves for FEN and PHEN were determined by administering either drug alone immediately prior to the mouse being placed in the locomotor activity monitor. Subthreshold doses for stimulation of locomotor activity were defined as the dose one quarter log less than a dose resulting in a significant change in locomotor behavior. Pretreatment of the combination of FEN and PHEN at their respective subthreshold doses was determined in the same manner as FEN and PHEN alone. Saline, FEN, PHEN and FEN/PHEN were administered i.p. in a volume of 0.01 ml/g body weight.

All subjects received 2 injections on the test day. Subjects received saline, FEN (0.1 mg/kg), PHEN (4.6 mg/kg) or FEN/PHEN (0.1 and 4.6 mg/kg, respectively) 20 min prior to being placed in the locomotor activity monitor. In addition, all groups re-

ceived a saline injection immediately prior to being placed in the locomotor activity monitor for 60 min

Locomotor activity was monitored in an Omnitech Activity Monitor (Omnitech Electronics Inc., Columbus, OH). Animals were placed in a rectangular Plexiglas retainer (46 cm long × 24 cm wide × 19 cm high). Activity in the monitor was recorded by photobeam interruptions. Distance traveled (cm) and time spent in stereotypy-like behavior were recorded as the dependent measure. Distance traveled is determined by photocell breaks in conjunction with the Pythagorean theorem to monitor location and distance traveled. Stereotypy-like behavior is defined by movement within 0.1-sec intervals. If movement during the 0.1-sec interval did not exceed 2.4 cm yet broke the photocell beam repeatedly the interval would be counted as stereotypic time. Data were collected in 10-min intervals. All activity measurements were conducted in a soundproof isolation chamber under red light.

### *Statistical Analysis*

Activity measurements were collected in 10-min intervals across the 60-min session. A two-way analysis of variance (group × time) was performed across groups with a repeated measures factor of session time. A one-way ANOVA with a least significant difference (LSD) post-hoc test was used to determine differences across groups.

## RESULTS

### *In Vivo Microdialysis Experiments*

The first series of experiments examined the effect of PHEN (FIG. 1A), FEN (FIG. 1B) and an equimolar combination of the two drugs (FIG. 1C) on extracellular DA (ECDA) and extracellular 5-HT (EC5-HT) in the n. accumbens of awake rats. When administered through the microdialysis probe, PHEN modestly and preferentially increased ECDA relative to EC5-HT in a dose-dependent manner. Only at probe concentrations of 100 μM did PHEN substantially increase EC5-HT. In contrast, FEN selectively and robustly increased EC5-HT in a dose-dependent manner. The combination of PHEN and FEN increased both ECDA and EC5-HT in a dose-dependent manner. Similar results were obtained when the medications were administered i.p. As shown in FIGURE 2, 1 mg/kg PHEN increased ECDA without significantly increasing EC5-HT, FEN increased EC5-HT without significantly increasing ECDA, and the combination of the two medications increased both neurotransmitters.

Because of the established role of mesolimbic DA as a mediator of cocaine reinforcement,[17] we hypothesized that PHEN might attenuate the effects of cocaine on DA transmission. The results,[18] reproduced here (FIG. 3A), demonstrated that PHEN substantially reduced the ability of cocaine to elevate ECDA. The fact that PHEN-pretreatment did not alter cocaine-induced increases in EC5-HT demonstrates the specificity of this effect (FIG. 3B).

### *Cocaine-Conditioned Motoric Activity*

In these experiments, cocaine administration is paired with a specific contextual environment (the locomotor activity chamber) for 3 consecutive days. On the fourth day of the test sequence, the mouse is placed back in the locomotor activity chamber, but

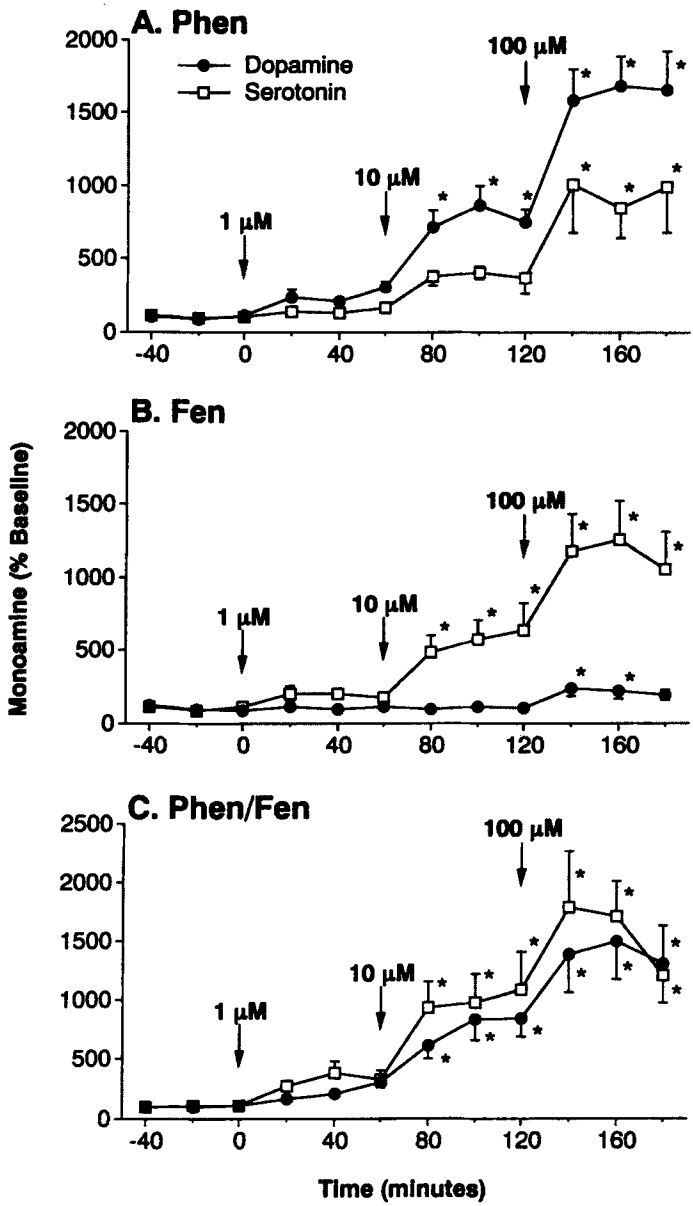



FIGURE 1. Effect of (A) PHEN, (B) FEN, and (C) PHEN/FEN on extracellular DA and 5-HT in the n. accumbens. All drugs were administered via the microdialysis probe at the indicated concentrations. Each point is the mean ± SEM ($n$ = 5–6 rats).

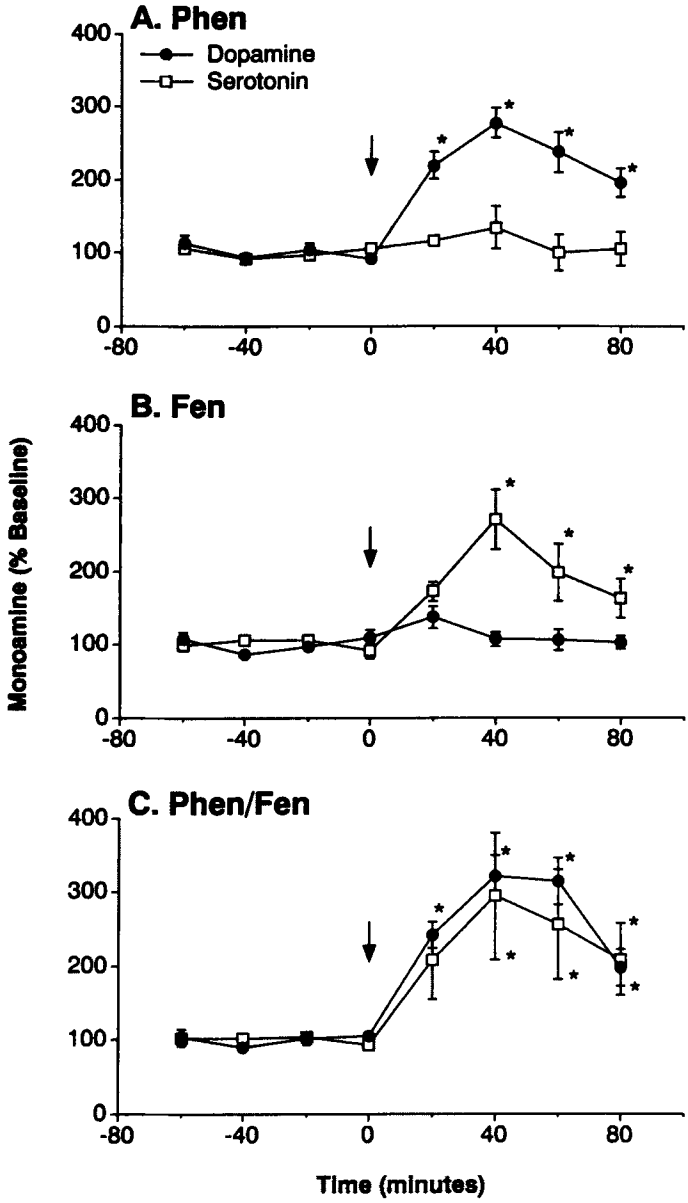



**FIGURE 2.** Effect of **(A)** PHEN, **(B)** FEN, and **(C)** PHEN/FEN on extracellular DA and 5-HT in the n. accumbens. All drugs were administered i.p. at 1 mg/kg. Each point is the mean ± SEM ($n$ = 5–6 rats). (Data from Soabib *et al.*[27])

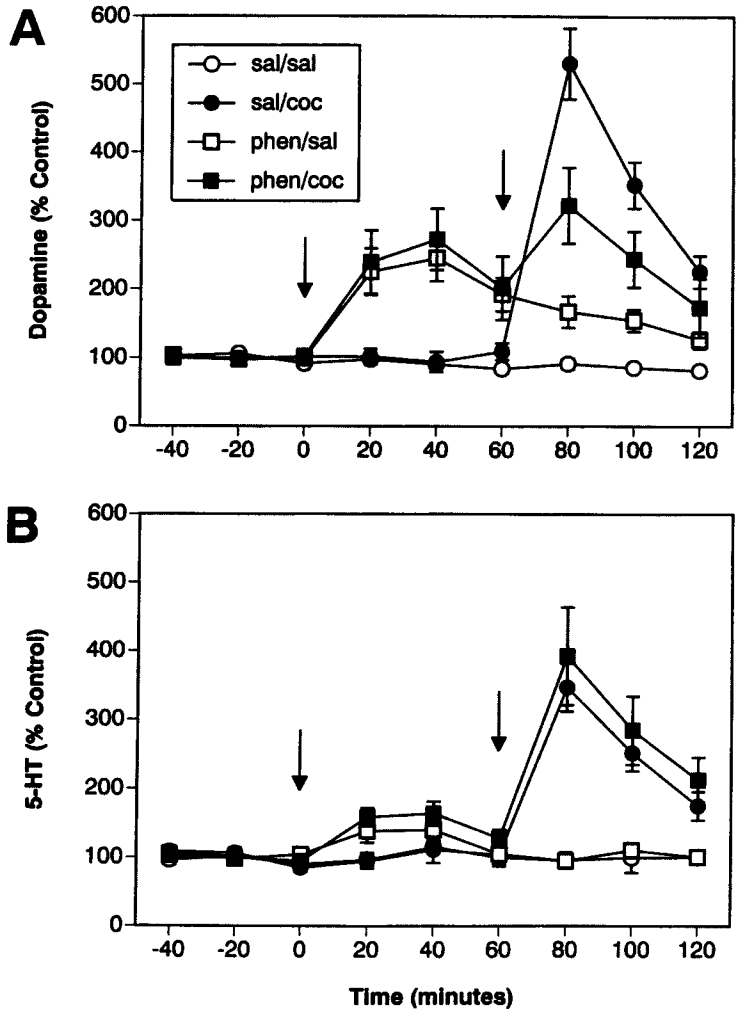



**FIGURE 3.** The effect of PHEN pretreatment on cocaine-induced increases in extracellular **(A)** DA and **(B)** 5-HT in the n. accumbens. Rats received either saline or PHEN (1.0 mg/kg, i.v.) at time zero, followed by challenge injection of saline or cocaine (3.0 mg/kg, i.v.) 60 min later. Data are mean ± SEM expressed as % baseline determined from the 3 samples immediately preceding pretreatment injection. $n = 7$ rats/group. $^{*}p < 0.05$ compared to corresponding saline-pretreated group. (From Rothman *et al.*[18])

not administered any drug. Mice treated in this manner demonstrate, on the fourth day, increased motoric activity. This is termed 'conditioned motoric activity' or CMA. The increased motoric activity increases both horizontal locomotor activity and stereotypic movement. Conditioned behaviors resulting from chronic drug exposure may be an integral and potentially independent component of the addiction process.[19] In par-

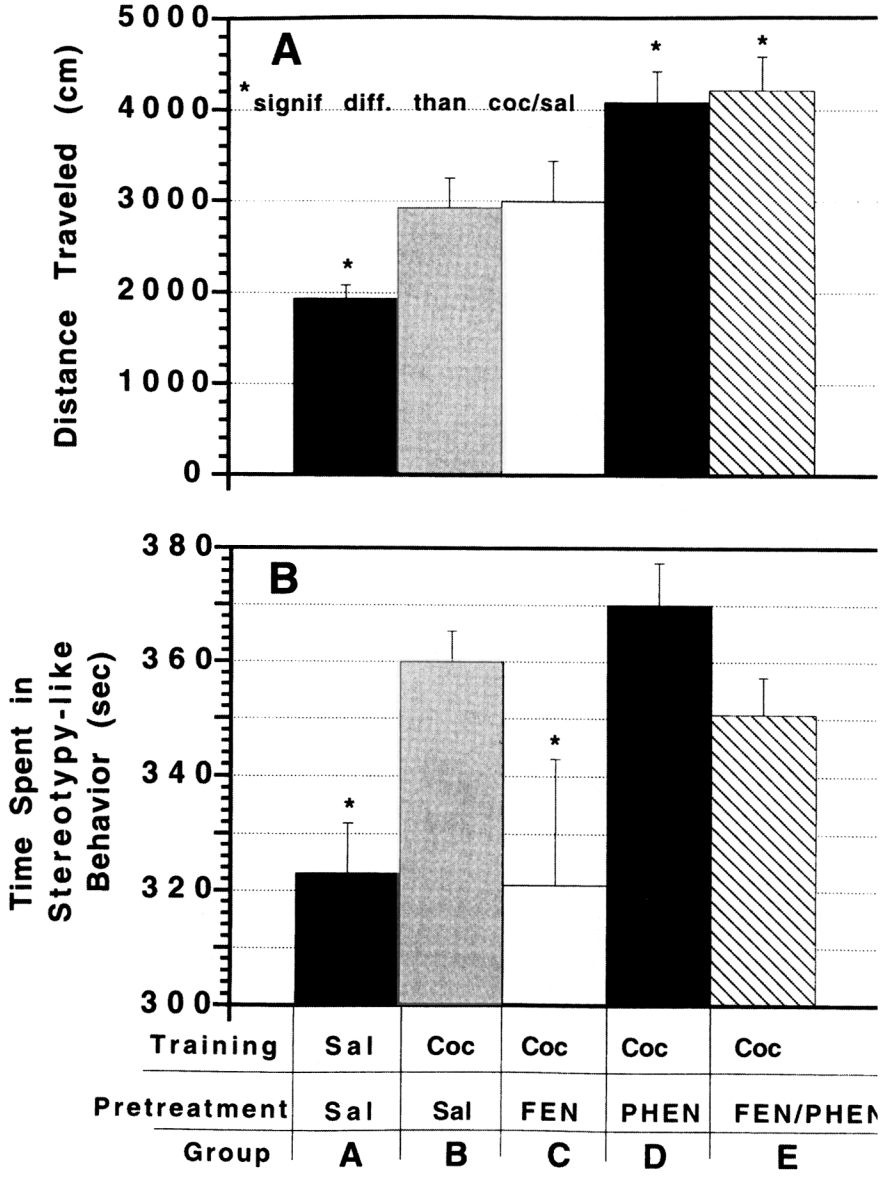



**FIGURE 4.** Effect of PHEN and FEN on cocaine-conditioned motoric activity in mice: results **(A)** on horizontal locomotor activity and **(B)** on stereotypy-like movement.

ticular, individual differences in baseline locomotor activity and conditioned motoric activity have been proposed to be predictive of vulnerability to drug use. To this end, pharmacological alterations in CCMA may prove useful in assessing potential pharmacotherapeutics.

Subthreshold doses for stimulation of locomotor activity were defined as the dose one quarter log less than a dose resulting in a significant change in locomotor behavior. Subthreshold doses for FEN and PHEN were determined to be 0.1 mg/kg and 4.6 mg/kg, respectively. Administration of doses 1/4 log unit higher resulted in a significant increase in distance traveled and stereotypy-like behavior. The combined administration of FEN/PHEN (0.1 and 4.6 mg/kg, respectively) did not significantly increase either dependent measure.

FIGURE 4 shows distance traveled (panel A) and stereotypy-like behavior (panel B) as a function of experimental group collapsed across time. There was a significant overall effect of experimental group and time for distance traveled and stereotypy-like behavior [*distance traveled:* $F$ (group) = 6.1, df = 4,620; $p < 0.0001$; $F$ (time) = 11.6, df = 5,620; $p < 0.0001$; *stereotypy:* $F$ (group) = 8.9, df = 4,620; $p < 0.0001$; $F$ (time) = 3.0, df = 5,620; $p < 0.01$]. There was no significant interaction across group and time. In general, distance traveled and stereotypy-like behavior decreased across time in a parallel manner across all groups.

Repeated administration of cocaine resulted in a significant conditioned increase in distance traveled and stereotypy-like behavior (group A vs B). FEN pretreatment alone (group B vs C) had no effect on distance traveled yet significantly decreased conditioned stereotypy-like behavior ($p < 0.05$). Conversely, PHEN pretreatment alone (group B vs D) had no effect on stereotypy-like behavior yet significantly enhanced conditioned increases in distance traveled ($p < 0.05$). The FEN/PHEN combination (group B vs E) significantly enhanced conditioned increases in distance traveled ($p < 0.05$) yet had no net effect on conditioned stereotypy-like behavior.

### *Conditioned Place Preference (CPP)*

PHEN alone produced a significant preference for an environment previously associated with its administration. However, the magnitude of this effect was markedly less then that observed in response to amphetamine or morphine (data not shown). FEN, in contrast, produced significant aversions for the drug-associated place. As reported in FIGURE 5, a subeffective dose of FEN eliminated the PHEN-induced CPP. Thus, the combination of PHEN/FEN, in contrast to either drug alone, was devoid of motivational effects. These results are similar to those observed in humans administered PHEN, FEN or PHEN/FEN under double-blind placebo-controlled conditions.[20]

### *Cocaine Self-Administration*

Cocaine is avidly self-administered by Rhesus monkeys. Using behavioral parameters described in detail elsewhere,[21] Glowa *et al.* determined the effect of PHEN, FEN or PHEN/FEN on cocaine self-administration.[22] The results, reproduced in FIGURE 6A, showed that PHEN, infused i.v. over 15 min, suppressed cocaine self-administration without altering responding for the alternate reinforcer, food. FEN alone had no effect. Coadministration of FEN with 1 mg/kg PHEN appeared to decrease the rate-suppressing effect of PHEN (FIG. 6B).

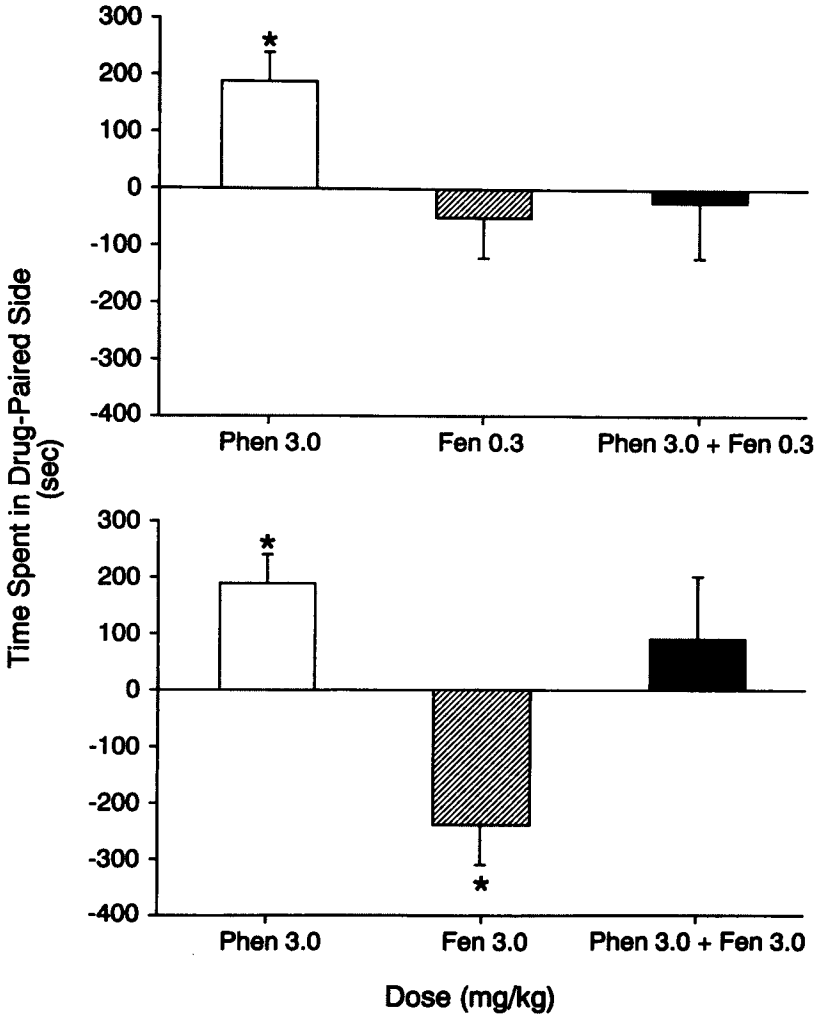



**FIGURE 5.** Effect of PHEN, FEN and PHEN/FEN on conditioned place preference.

## DISCUSSION

Although considerable data support the hypothesis that mesolimbic DA plays a key role in mediating the reinforcing effects of drugs of abuse as well as the rewarding effects of ingestive behaviors,[23-25] converging lines of evidence indicate that prolonged withdrawal from cocaine and alcohol results in synaptic deficits of both DA and 5-HT.[1-5] The dual deficit model accounts for the affective syndrome accompanying drug withdrawal, including anhedonia, which may result from a DA deficit, as well as poor impulse control and depression, which may result from lower synaptic 5-HT. The dual

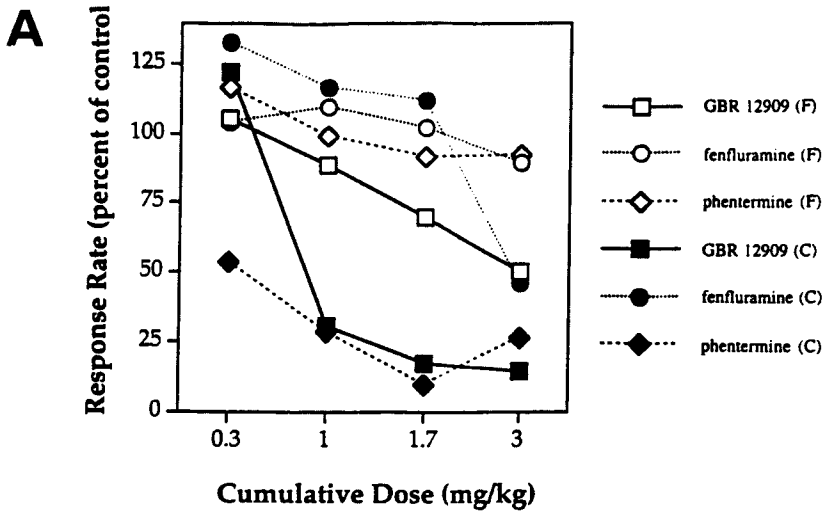
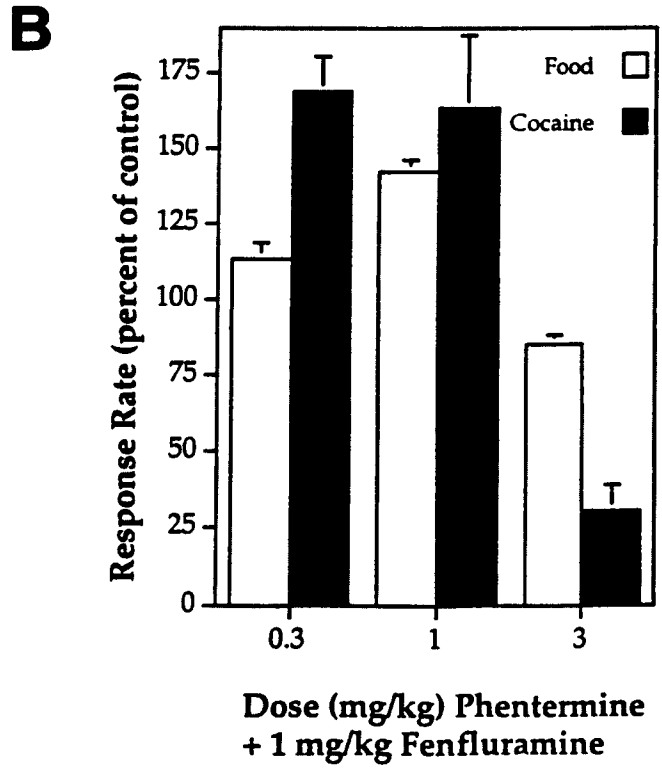



**FIGURE 6.** Effect of PHEN on cocaine self-administration. **(A)** The effects of cumulative doses of GBR12909, FEN and PHEN on responding maintained by food *(open symbols)* or cocaine *(filled symbols)* in Rhesus monkeys ($n = 8$). Effects are reported as the mean percentage of individual control rates of responding. **(B)** The effects of FEN (1 mg/kg) and PHEN (0.3, 1 or 3 mg/kg) on responding maintained by food *(open symbols)* or cocaine *(filled symbols)* in Rhesus monkeys. Error bars indicate the SEM. (From Glowa *et al.*[22])

deficit model also accounts for the failure to identify medications which effectively treat cocaine addiction.[26] Clinical trials to-date have used single agents, which effect either the DA system or the 5-HT system. The dual deficit model predicts that monosystem therapy will have little therapeutic value.

The dual deficit model predicts that agents which increase dopaminergic and serotonergic tone may be useful in treating cocaine and alcohol withdrawal. As noted in the introduction, open-label clinical studies support this hypothesis.[10-13] The purpose of the studies reviewed here was to examine the effect of two such agents, PHEN and FEN, in animal models of cocaine addiction.

PHEN is an old medication which has not been studied with modern neurochemical methods. The *in vivo* microdialysis results reviewed here demonstrate that PHEN, which is structurally similar to amphetamine, preferentially increases ECDA. The mechanism of this effect is likely similar to that of amphetamine, *i.e.*, resulting from DA release rather than from inhibition of DA uptake. FEN, on the other hand, is a selective releaser of 5-HT. The PHEN/FEN combination increases both DA and 5-HT. We did not measure the effect of PHEN on norepinephrine (NE). It is likely that PHEN releases NE both in the central nervous system (CNS) and from peripheral sympathetic nerves. This effect may contribute to its anorectic actions as well as its cardiovascular side effects. Pretreatment with PHEN substantially reduces the ability of cocaine to increase ECDA. The fact that PHEN did not alter cocaine-induced increases in EC5-HT indicates that this effect of PHEN is specific for DA. Patients treated with PHEN and FEN report blunted subjective effects of cocaine.[10,13] The present findings suggest,




therefore, that PHEN may diminish the subjective effects of cocaine in humans via a dopaminergic mechanism.

PHEN is also active in the CCMA model. Low doses of PHEN enhanced the horizontal CCMA and had no effect on the stereotypic CCMA. The enhancement of CCMA by PHEN is consistent with the dopaminergic effects of this drug and the common DA-related interoceptive cues shared by PHEN and cocaine.[27] The interpretation of this finding is unclear. Until the predictive ability of the CCMA assay is validated by clinical studies, it is impossible to know apriori if an efficacious treatment medication would increase or decrease CCMA.

The finding that FEN inhibited stereotypic CCMA is of interest for several reasons. These data demonstrate an anti-cocaine effect of FEN in an animal model of conditioned cocaine effects. In contrast, FEN has little effect in more established models of cocaine addiction such as drug discrimination[27] and cocaine self-administration.[22] The reasons for this are likely complex in nature, but may relate to the fact that the cocaine drug discrimination and the cocaine self-administration assays are dopaminergically driven. FEN, being an indirect serotonergic agonist, would predictably be inactive in these assays.

Whereas horizontal motor behavior is mediated by the n. accumbens, stereotypy is mediated by the caudate nucleus.[28] Recent studies of obsessive compulsive disorder (OCD) in humans, which is characterized by obsessive thoughts and repetitive type be-

haviors, demonstrate both low CNS serotonergic tone[29] and differences in the caudate nuclei of patients vs controls.[30–33] Cocaine addiction is also characterized by repetitive behaviors, such as compulsive foraging.[34] Agents which increase serotonin effectively treat OCD.[29] The observation that FEN, an indirect 5-HT agonist, inhibits stereotypic CCMA, may provide a mechanism to explain the clinical impression that FEN contributes to the PHEN/FEN mixture by decreasing obsessive thoughts of drug use.[13]

The fact that PHEN produces a positive CPP and FEN produces a negative CPP is not unexpected in view of the place conditioning produced by other drugs which alter DA or 5-HT neurotransmission.[35–36] Perhaps the most interesting finding from the CPP experiments is that a subeffective dose of FEN combined with an effective dose of PHEN acted as a reward-neutral agent. This is consistent with the results Brauer *et al.*[20] observed in humans and also supports the observation, reported above, that coadministration of FEN (1 mg/kg) with PHEN appeared to decrease the rate-suppressing effect of PHEN (FIG. 6B) on cocaine self-administration. These data suggest that the FEN contributes to the PHEN/FEN combination by lowering the abuse liability of PHEN. As a reward-neutral agent, the PHEN/FEN combination, or its neurochemical equivalent (see below), would be a suitable substitution-type medication for cocaine dependence.

Although this paper emphasizes studies of PHEN/FEN in models of cocaine addiction, other studies demonstrate an effect of similar medications (amphetamine plus FEN) on alcohol consumption by rats.[37,38] Open-label studies with PHEN/FEN support these preclinical observations.[12] Viewed in the context of the results presented here, the preclinical data obtained with PHEN/FEN in various models of drug provide a strong rationale for pursuing controlled conceal trials in humans. However, recent reports of valvular heart damage associated with the use of FEN,[39] which prompted the withdrawal of FEN from the market place, obviously rule out this particular approach. The results point to the need to develop a single molecular entity that possess the neurochemical profile of the PHEN/FEN mixture but that lacks the significant drawbacks of FEN: pulmonary hypertension,[40] neurotoxicity[40] and valvular heart damage.[39]

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