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Self-administration of mixtures of fenfluramine and amphetamine by rhesus monkeys

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Abstract

Previous research with psychostimulants has suggested a negative relationship between both potency and efficacy as a reinforcer and serotonergic potency, particularly relative to dopaminergic potency. The present experiment was designed to examine the relationship between the serotonergic activity and efficacy as a reinforcer by allowing rhesus monkeys ($n=5$) to self-administer amphetamine mixed with a serotonin releaser, fenfluramine. Additionally, the role of 5-HT_2 receptors in the interaction between amphetamine and fenfluramine was investigated using ketanserin, a selective 5-HT_2 receptor antagonist. Amphetamine and fenfluramine were combined in ratios of, respectively, 1:1 to 1:10 on a mg/kg basis and made available for self-administration under a progressive-ratio schedule of reinforcement. Amphetamine (0.0056–0.1 mg/kg/injection) functioned as a positive reinforcer with sigmoidal or biphasic dose–response functions. The addition of fenfluramine to amphetamine decreased the maximum responding, at least at the highest dose ratio (1:10, amphetamine/fenfluramine), in all monkeys. When measured after the pretreatment of ketanserin (1.0–3.0 mg/kg, i.m.), the self-administration of the mixture of amphetamine and fenfluramine at a ratio of 1:10 decreased in three monkeys and was unaffected in the fourth. These results support the notion of a negative influence of increased serotonergic neurotransmission on reinforcing efficacy of drugs that act via monoamine systems. However, the involvement of 5-HT_2 receptors in the interaction between the serotonergic system and the reinforcing efficacy still remains equivocal.
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Among the three monoamine neurotransmitters that are affected by psychostimulants, increased dopamine (DA) neurotransmission has been strongly implicated in the reinforcing effect of psychostimulants (Wise, 1978; Ritz et al., 1987; Woolverton and Johnson, 1992; Koob, 1992). On the other hand, several studies have suggested that increased serotonin (5-HT) negatively modulates the reinforcing effect of psychostimulants. A negative correlation between potency as a reinforcer and binding affinity at the 5-HT transporter (SERT) among amphetamine analogs (Ritz and Kuhar, 1989) was previously reported. Reinforcing efficacy among a series of cocaine analogs was shown to be negatively related to the potency at the SERT relative to DAT (Roberts et al., 1999). Further, an increased potency in releasing 5-HT among a series of amphetamine analogs was associated with the decreased reinforcing efficacy and potency in rhesus monkeys (Wee et al., 2005).

The present experiment was designed to further examine the relationship between serotonergic neurotransmission and the reinforcing efficacy of psychostimulants using a drug interaction approach. Monkeys were allowed to self-administer various mixtures of D-amphetamine and a selective 5-HT releaser, D,L-fenfluramine. Our goal was to systematically add 5-HT release to the effects of amphetamine and our hypothesis was that, as the proportion of 5-HT/DA increased, self-administration would decrease. Additionally, it has been suggested that 5-HT_2 receptor subtypes mediate the effect of D-fenfluramine to decrease the self-administration of heroin (Wang et al., 1995). In other studies, the stimulation or antagonism of 5-HT_{2C} receptor subtypes was found to, respectively, decrease or increase

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cocaine-maintained responding in rats under a fixed-ratio schedule of reinforcement (Grottick et al., 2000; Fletcher et al., 2002). Further, Ro 60-0175, 5-HT_{2C} receptor agonist, reduced in a dose-dependent manner the breaking point, the maximum responding, for cocaine self-administration under a PR schedule by rats, indicating the decreased reinforcing efficacy of cocaine by the stimulation of 5-HT_{2C} receptor subtypes (Grottick et al., 2000). These findings prompted us to question whether 5-HT_2 receptors might be involved in the negative action of the increased 5-HT on the reinforcing efficacy of psychostimulants. The present study, thus, also investigated the role of 5-HT_2 receptors in the action of fenfluramine on the reinforcing effect of amphetamine using ketanserin, a selective 5-HT_2 receptor antagonist.

1. Materials and methods

All animal use procedures were approved by the University of Mississippi Medical Center's Animal Care and Use Committee, and they were in accordance with the National Institutes of Health guidelines (NIH Publication No. 85-23, revised 1996).

1.1. Animals and apparatus

The subjects were five male rhesus monkeys (*Macaca mulatta*; AV88, L463, L500, M1389, M341) weighing between 9.0 and 11 kg at the beginning of the study. All the monkeys had histories of self-administration of cocaine and other stimulants, most recently as described by Wee et al. (2004, 2005). All monkeys were provided with sufficient food to maintain stable body weight (120–180 g/day, Teklad 25% Monkey Diet, Herlan/Teklad, Madison, WI) and had unlimited access to water. Fresh fruit and a vitamin supplement were provided daily and three times a week, respectively. Lighting was cycled to maintain 16 h of light and 8 h of darkness, with light on at 06:00 a.m.

The monkeys were individually housed in experimental cubicles (1.0 m^3, Plaslabs, Lansing, MI; details in Wee et al., 2004). Each monkey was fitted with a stainless-steel harness attached by a tether to the rear wall of the cubicle. Drug injections were delivered by a peristaltic infusion pump (Cole-Parmer Co., Chicago, IL). A Macintosh computer with custom interface and software controlled all events in an experimental session.

1.2. Procedure

Monkeys were implanted with a silastic catheter (0.26 cm OD × 0.076 cm ID; Cole-Parmer Co., Chicago, IL) into the jugular (internal or external), femoral or brachial vein under isoflurane anesthesia as previously described (Wee et al., 2004). In the event of catheter failure, surgery was repeated using another vein, after the veterinarian confirmed the health of the monkey.

Experimental sessions began at noon each day and were conducted 7 days a week. About 30 min before each session started, catheters were filled with drugs for the sessions without infusing the drugs into monkeys. At the start of a session, the white lights were illuminated above both levers and pressing the right lever resulted in the delivery of a drug injection for 10 s. During the injection, the white lights were extinguished and the red lights were illuminated. Pressing the left lever was counted but had no other programmed consequence. After the session, catheters were filled with 0.9% saline containing heparin (40 units/ml).

Drugs were available under a progressive-ratio (PR) schedule of reinforcement (see Wilcox et al., 2000). The PR schedule consisted of five components, with four trials available in each component, for a total of 20 trials/day available. The response requirement began at 100 responses/injection and doubled in each successive component. A subject had 30 min to complete a trial (limited hold 30 min: LH 30′). A trial ended with a 10-s drug injection or the expiration of the LH. There was a 30-min timeout (TO 30′) after each trial. If the response requirement was not completed for two consecutive trials (i.e., the LH expired), or the animal self-administered all 20 injections, the session ended.

In baseline sessions, the baseline dose (0.3 mg/kg/injection) of cocaine or saline (0.9%) was available for injection. Cocaine or saline was initially available under a double-alternation sequence, i.e., two consecutive daily cocaine sessions were followed by two consecutive daily saline sessions. When responding was stable (±2 injections from a previous session without trend) for at least two consecutive double-alternation sequences of cocaine and saline (i.e., eight sessions), test sessions were inserted between two saline or two cocaine baseline sessions. To prevent monkeys from learning this session sequence, a randomly determined saline or cocaine baseline session was inserted after every other test session. Thus, the daily sequence of sessions was C, S, T, S, C, T, R, C, S, T, S, C, T, R, where "C", "S", "R" and "T" represent a cocaine baseline, a saline, a randomly determined cocaine/saline and a test session, respectively.

In test sessions, one of various doses of (+)-amphetamine alone or the mixture of (+)-amphetamine with (±)-fenfluramine at various ratios (1:1 to 1:10, respectively) was available for monkeys under conditions identical to baseline sessions. The drugs were tested twice, once after a cocaine baseline session and once after a saline session, and in a counterbalanced order across monkeys. At the end of the study, ketanserin was examined for its effect on the self-administration of the mixture of amphetamine/fenfluramine at a ratio of 1:10. In ketanserin test sessions, a dose of ketanserin (1.0–3.0 mg/kg) or vehicle (5% DMSO) was intramuscularly injected to monkeys 30 min before a test session. Doses of ketanserin were selected because the dose range of 0.1 to 1.7 mg/kg (i.m.) has been shown to have behavioral effects in rhesus monkeys (Fantegrossi et al., 2002; Taffe et al., 2002). A dose of amphetamine that maintained the maximum self-administration in each monkey was mixed with fenfluramine at a ratio of 1:10, respectively, and was made available for monkeys in ketanserin test sessions. The mixed ratio of 1:10 was chosen to evaluate the antagonizing

effect of ketanserin on a fenfluramine action because the self-administration of amphetamine and fenfluramine at the ratio was reduced in all the monkeys.

1.3. Data analysis

We have previously presented break point data, i.e. the maximum responses/injection achieved, as well as the maximum number of injections in a paper (Rowlett et al., 1996) and found no difference between two measures as an index of relative reinforcing efficacy under a PR schedule. Thus, we used only the number of injections as a variable in this study. The mean number of injections per session was calculated from the two test sessions as a function of dose in individual monkeys. The range of injections served as a measure of variability in individual subjects. A dose of a drug was considered to function as a reinforcer if the mean number of injections was above levels seen with saline and the ranges did not overlap.

For the group mean dose–response function for amphetamine and the mixture of amphetamine and fenfluramine, the dose–response function of amphetamine in each monkey collapsed across monkeys in a way that the peaks of the dose–response functions of individual monkeys aligned at the same *x*-axis regardless of doses. The dose–response function of the mixture of amphetamine and fenfluramine in individual monkeys collapsed across monkeys according to the position of the dose–response function of amphetamine of the individual monkeys. This was done because each drug maintained qualitatively comparable dose–response functions across the monkeys but with the maximum responding at a different dose because of different sensitivity in individual monkeys. Statistical analysis was done with these groups' mean dose–response functions. That is, the group mean maximum number of injections for amphetamine was calculated by averaging the individual maximum mean injections. Then, for a comparison, the group mean number of injections for the mixture of amphetamine and fenfluramine at each mixed ratio was obtained by averaging the individual mean number of injections at the dose of the maximum injections of amphetamine (e.g., Woolverton and Wang, 2004). Repeated measures one-way analysis of variance with the Student–Newman–Keuls as a post hoc test

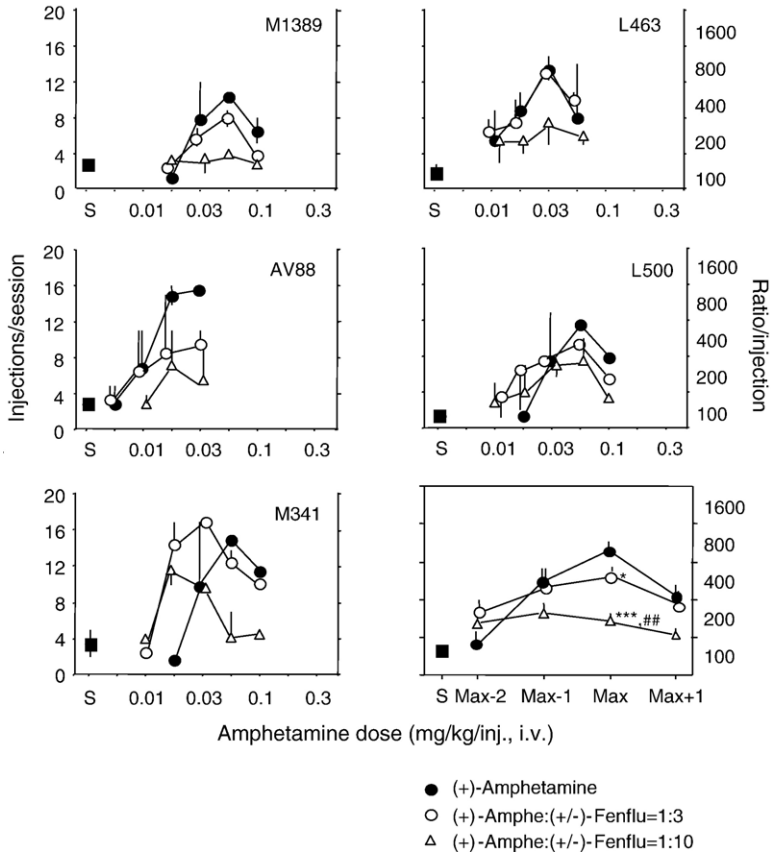

Fig. 1. Self-administration of D-amphetamine and the mixture of amphetamine and fenfluramine by individual monkeys under a PR schedule of reinforcement. Each data point represents the mean injections/session from two test sessions and vertical bars represent the range of the two determinations. The point above S represents self-administration of saline in test sessions. The graph on the bottom right-hand corner depicts the group mean data (±S.E.M). The dose–response functions (amphetamine, amphe+fenflu at 1:3, amphe+fenflu at 1:10) in each monkey collapsed across the monkeys as to the dose of the peak of amphetamine dose–response function. This resulted in the group mean values at Max+1 from four monkeys without monkey AV88. Max: the dose of the maximum injections of amphetamine in each animal. Max+1: quarter-log dose higher than Max. Max−1: quarter-log dose lower than Max. Max−2: half-log dose lower than Max. *$p<0.05$, ***$p<0.001$ compared with amphetamine at the dose of Max. $^{\#\#}p<0.01$ compared with the mixture of D-amphetamine and fenfluramine at a ratio of 1:3, respectively, at the dose of Max.

was then used to assess statistically significant differences among those group mean injections for amphetamine and the mixture of amphetamine and fenfluramine (GraphPad Prism 4.0, San Diego, CA).

For the reinforcing potency of amphetamine, the ED_{50} value was calculated for each animal in which the drug served as a reinforcer using the ascending limb of a dose–response function and non-linear regression analysis (GraphPad Prism 4.0). The mean ED_{50} value of amphetamine was calculated by averaging the log (geometric) ED_{50} doses in all monkeys in which the drug functioned as a reinforcer and taking the antilog of that value. The variability of the mean ED_{50} value was expressed as 95% confidence interval (CI) by taking the antilog of geometric 95% CI because, under log and exponential transformation, variances do not transform correctly whereas percentiles do.

1.4. Drugs

(−)-Cocaine hydrochloride and D-amphetamine sulfate were provided by the National Institute on Drug Abuse (Rockville, MD). (±)-Fenfluramine hydrochloride and ketanserin were purchased from Sigma-Aldrich (St Louis, MO). Amphetamine and the mixture of amphetamine and fenfluramine were dissolved in 0.9% saline. Ketanserin was dissolved in 5% DMSO. Doses were expressed as the salt forms of the drugs except ketanserin. The dose of ketanserin was expressed as a base.

2. Results

In baseline sessions, saline maintained an average of 2.6 (M1389) to 3.4 (AV88) injections/session (Fig. 1). The baseline dose of cocaine (0.3 mg/kg/injection) functioned as a positive reinforcer in all monkeys with an average of 14.2 (M1389) to 18.6 (M341) injections/session (data not shown). In test sessions, amphetamine functioned as a positive reinforcer with a sigmoidal or biphasic dose–response function in all monkeys (Fig. 1). The maximum self-administration of amphetamine ranged between 15.5 (AV88) and 10.5 (M1389) under the present condition. The mean ED_{50} dose of amphetamine was 0.02 mg/kg/injection (95% CI: 0.012–0.039).

The addition of fenfluramine to amphetamine decreased the maximum self-administration by all the monkeys at a ratio of 1:10 (amphetamine/fenfluramine) and at a ratio of 1:3 in some monkeys. There was no consistent change in the potency of amphetamine as a reinforcer with the addition of fenfluramine. In monkey M341, the addition of fenfluramine shifted the dose–response function of amphetamine to the left. The dose–response function of amphetamine alone was redetermined after the mixture had been tested, and it was unchanged from the original. Fenfluramine alone did not maintain self-administration above saline level when tested in that monkey (data not shown). A similar trend was noted in monkey L500. Again, the doses of fenfluramine in them did not function as a positive reinforcer when tested in monkey L500. Fenfluramine alone was not tested in the other three monkeys. When compared as a group mean, the addition of fenfluramine significantly decreased the maximum self-administration of amphetamine in a ratio-dependent manner [Fig. 1, the bottom right-hand graph; $F(2,8)=2.04$, $p<0.001$].

Pretreatment with ketanserin further reduced self-administration of the mixture of amphetamine and fenfluramine at a ratio of 1:10 in three of four monkeys (Fig. 2). There was no effect in M1389. L463 did not respond after the pretreatment with 3 mg/kg of ketanserin. When compared as a group mean, there was no significant effect of ketanserin on the self-administration of the mixture of amphetamine and fenfluramine at a ratio of 1:10 [$F(3,9)=1.98$, $p=0.18$].

3. Discussion

Under the present PR schedule of reinforcement, amphetamine functioned as a positive reinforcer with a biphasic or sigmoidal dose–response function in all monkeys. The maximum self-administration and the ED_{50} dose of amphetamine were compatible with those reported in a previous study using the same paradigm (Wee et al., 2005). A full dose–response function of cocaine was not determined in this study. However, the data in studies that examined cocaine under identical conditions indicate that amphetamine was a more potent reinforcer than cocaine, which was predicted by their potencies on the dopaminergic system (see Wilcox et al., 2000: Woolverton and Wang, 2004).

The addition of fenfluramine to amphetamine for co-self-administration decreased the maximum responding at least at the highest ratio of fenfluramine in all monkeys. Similar observations were previously noted in that pretreatment with fenfluramine dose-dependently decreased the self-administration of methamphetamine under a fixed-ratio schedule (Munzar et al., 1999). The PR schedule, by increasing response requirement for successive injections, measures the maximum behavioral output maintained by a drug. The

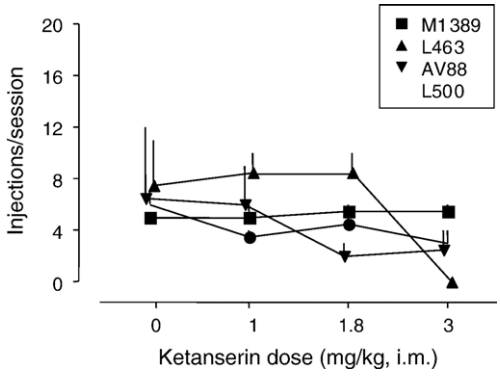

Fig. 2. Effect of ketanserin on the self-administration of the mixture of amphetamine and fenfluramine mixed at a ratio of 1:10, respectively. A dose of ketanserin was intramuscularly injected 30 min before a session. Then, the mixture of amphetamine and fenfluramine at a ratio of 1:10 was made available for self-administration under a PR schedule of reinforcement. Each data point represents the mean injections/session from two test sessions and vertical bars represent the range of the two determinations.

maximum responding maintained by a drug is often used as an index of the maximum reinforcing effect, or reinforcing efficacy, of the drug (Depoortere et al., 1993; Griffiths et al., 1978; Risner and Silcox, 1981; Woolverton, 1995). The decreased self-administration for the mixture of amphetamine and fenfluramine under the present PR schedule suggests reduced reinforcing efficacy of amphetamine by the addition of fenfluramine. (±)-Fenfluramine, a substituted amphetamine derivative, is an appetite-suppressant mainly acting at the serotonergic system (Garattini et al., 1986; Garattini, 1995). Specifically, it is a potent 5-HT releaser when measured in vivo and in vitro (Rothman et al., 1998; Rothman and Baumann, 2002, respectively), and it has direct agonist activity at 5-HT_2 receptors as well (Fitzgerald et al., 2000; Rothman and Baumann, 2002). Several studies have proposed a negative relationship between the reinforcing effect of psychostimulants and the serotonergic activity of the drugs (Loh and Roberts, 1990; Roberts et al., 1999; Wee et al., 2005). It is, therefore, reasonable to expect that the addition of fenfluramine to amphetamine weakened the reinforcing efficacy of amphetamine via enhanced serotonergic neurotransmission.

Fenfluramine and its metabolite, norfenfluramine, are moderately potent NE releasers in vitro (Rothman et al., 2003; Rothman and Baumann, 2002). Therefore, one might speculate that the increased NE by fenfluramine influenced the reinforcing effect of the mixture of amphetamine and fenfluramine. Nevertheless, the fact that no convincing evidence in the influence of NE on the reinforcing effect of psychostimulants has been found to date argues against this suggestion. For instance, it was found in our laboratory that co-self-administration of DMI with cocaine did not alter self-administration of cocaine under a PR schedule (Wee et al., 2006). The pretreatment with adrenergic receptor antagonists, such as prazosin, phentolamine and phenoxybenzamine, did not attenuate the reinforcing effect of amphetamine or cocaine under a PR schedule in rats or rhesus monkeys (Wilson and Schuster, 1974; Woolverton, 1987; Yokel and Wise, 1976). Similarly, the pre-session treatment with an α-adrenergic receptor agonist, or selective NET inhibitors did not affect amphetamine or cocaine self-administration under a PR schedule in rats whereas dopamine receptor agonists and a selective DAT inhibitor did so (Tella, 1995; Yokel and Wise, 1978).

Another factor that may reduce self-administration is a non-specific disruption of lever pressing caused by fenfluramine + amphetamine, especially at a high mixed ratio of fenfluramine. The present PR schedule, by allowing a TO of 30 min and a limited hold of 30 min for responding, after each injection, is designed to minimize the influence of a non-specific effect of a drug on responding. The test doses of fenfluramine in the present study ranged from 0.056 to 1 mg/kg/injection approximating less than 5 mg/kg of the accumulated dose over several hours of a session. It was reported that the half-life of a single dose of 2 mg/kg of oral D-fenfluramine was 2 to 3 hours in baboon and rhesus monkeys indicating a shorter half-life of the dose of intravenous fenfluramine (Caccia et al., 1995). Moreover, Glowa et al. (1997) reported little change in the rate of food-maintained responding after the pretreatment of up to a single dose of 3 mg/kg of fenfluramine (i.v.) in rhesus monkeys. Although these points argue against a non-specific effect of fenfluramine on lever pressing, it is possible that the drugs were synergistic in their non-specific effects on lever pressing.

An additional mechanism that could account for the decreased self-administration of amphetamine by the increased serotonergic neurotransmission could be a punishing effect on responding. It was demonstrated that the addition of histamine to an injection of cocaine could punish cocaine self-administration (Woolverton, 2003). Similarly, response contingent histamine injection (i.v.) was shown to punish food-maintained responding (Katz and Goldberg, 1986; Woolverton, 2003). Delivery of response contingent electric shock also decreased self-administration of cocaine (Bergman and Johanson, 1981). Therefore, in considering unpleasant subjective effects of serotonergic drugs in humans (Birmes et al., 2003; Finfgeld, 2004; Sternbach, 1991), it is plausible that the increased 5-HT by fenfluramine may suppress self-administration via a punishment mechanism.

Several studies provided evidence suggesting that 5-HT_2 receptors mediate the negative action of the serotonergic system on the reinforcing effect of drugs of abuse (Fletcher et al., 2002; Grottick et al., 2000; Wang et al., 1995). Likewise, a positive modulation of cocaine self-administration by a selective 5-$HT_{2A/C}$ receptor antagonist, ketanserin, was proposed in squirrel monkeys (Howell and Byrd, 1995). Here, we hypothesized that the activation of 5-HT_2 receptors mediated the mechanism of fenfluramine in decreasing self-administration of amphetamine. And, the blockade of 5-HT_2 receptors would increase self-administration of the mixture of amphetamine and fenfluramine. The present results, however, showed that the pretreatment of ketanserin did not significantly alter the self-administration of amphetamine and fenfluramine in general. This lack of an overall effect of ketanserin might put in question the pretreatment time of ketanserin (30 min) in the present study. In a study by Fantegrossi et al. (2002), ketanserin (i.m.) that was administered 15 min before a session (0.1 and 0.3 mg/kg) attenuated responding for 3,4-methylenedioxymethamphetamine, not for cocaine, in rhesus monkeys. Moreover, a half-life of ketanserin (i.v.) was reported to be 14.3 h in healthy humans and 2–5 h in rats (Heykants et al., 1986; Michiels et al., 1988) ruling out the pretreatment time as a contributing factor. Another possibility that the doses of ketanserin tested might be below a behaviorally effective range was raised. Using positron emission tomography, it was shown that 1.5 mg/kg of ketanserin (i.v.) significantly displaced a selective 5-HT_{2A} receptor radioligand in cynomolgus monkey brain (Lundkvist et al., 1996). Furthermore, the finding by Fantegrossi et al. (2002) mentioned above argues against this possibility. Consequently, the data do not appear to support the hypothesis that 5-HT_2 receptors mediated the negative influence of fenfluramine on self-administration of amphetamine.

Taken together, the present finding supports the hypothesis that increased serotonergic neurotransmission is associated with decreased reinforcing efficacy of psychostimulants. However, the involvement of 5-HT_2 receptors in the interaction between the serotonergic system and the reinforcing efficacy still remains equivocal.

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