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CHARACTERIZATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF LORCASERIN IN RATS

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Abstract

Lorcaserin is approved by the Food and Drug Administration for treating obesity and is under consideration for treating substance use disorders; it has agonist properties at serotonin (5-HT)_{2C} receptors and might also have agonist properties at other 5-HT receptor subtypes. This study used drug discrimination to investigate the mechanism(s) of action of lorcaserin. Male Sprague-Dawley rats discriminated 0.56 mg/kg i.p. lorcaserin from saline while responding under a fixed-ratio 5 schedule for food. Lorcaserin (0.178–1.0 mg/kg) dose-dependently increased lorcaserin-lever responding. The 5-HT_{2C} receptor agonist mCPP and the 5-HT_{2A} receptor agonist DOM each occasioned greater than 90% lorcaserin-lever responding in seven of eight rats. The 5-HT_{1A} receptor agonist 8-OH-DPAT occasioned greater than 90% lorcaserin-lever responding in four of seven rats. The 5-HT_{2C} receptor selective antagonist SB 242084 attenuated lorcaserin-lever responding in all eight rats and the 5-HT_{2A} receptor selective antagonist MDL 100907 attenuated lorcaserin-lever responding in six of seven rats. These results suggest that, in addition to agonist properties at 5-HT_{2C} receptors, lorcaserin also has agonist properties at 5-HT_{2A} and 5-HT_{1A} receptors. Because some drugs with 5-HT_{2A} receptor agonist properties are abused, it is important to fully understand the behavioral effects of lorcaserin while considering its potential for treating substance use disorders.

Keywords

serotonin receptor; lorcaserin; drug discrimination; lever press; rat

Preclinical evidence from several different laboratories suggests that drugs with agonist properties at serotonin (5-HT)_{2C} receptors might be effective for treating substance use disorders (for a review, see Howell & Cunningham, 2015). In rats, 5-HT_{2C} receptor agonists

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decrease the positive reinforcing effects of cocaine as well as reinstatement of responding by cocaine and cocaine-associated stimuli (Anastasio et al., 2011; Burbassi & Cervo, 2008; Callahan & Cunningham, 1995; Cunningham et al., 2011; Harvey-Lewis, Li, Higgins, & Fletcher, 2016; Navarra, Comery, Graf, Rosenzweig-Lipson, & Day, 2008). Lorcaserin is approved by the United States Food and Drug Administration (FDA) for treating obesity and has well-documented agonist properties at 5-HT_{2C} receptors that are thought to account for its ability to decrease feeding in rats (Thomsen et al., 2008). Lorcaserin also attenuates nicotine self-administration (Higgins et al., 2012) which, in part, prompted clinical investigations on the potential utility of lorcaserin for smoking cessation (<http://www.clinicaltrials.gov>). Clinical trials are also being planned to examine lorcaserin for treating cocaine use disorder, consistent with the finding that lorcaserin attenuates cocaine self-administration in rats (Harvey-Lewis et al., 2016) and monkeys (Collins, Gerak, Javors, & France, 2016).

Despite having been approved by the FDA for treating obesity, the pharmacological profile of lorcaserin is not fully described, with relatively few studies having investigated the pharmacological mechanism(s) of action of lorcaserin *in vivo*. Although *in vitro* binding assays demonstrate high selectivity for 5-HT_{2C} receptors ($K_i = 15$ nM) over other 5-HT receptor subtypes, lorcaserin has affinity for 5-HT_{2A} ($K_i = 112$ nM) and 5-HT_{1A} ($K_i = 700$ nM) receptors (see Thomsen et al., 2008). When administered alone, lorcaserin induces directly observable behavioral effects that are consistent with agonist properties at 5-HT_{2C} receptors (e.g., decreases in food consumption: Thomsen et al., 2008; and increases in yawning: Serafine, Rice, & France, 2015). However, at larger doses, lorcaserin induces forepaw treading, a behavior commonly produced by drugs such as 8-OH-DPAT that have agonist properties at 5-HT_{1A} receptors (Serafine et al., 2015). When combined with a selective 5-HT_{2C} receptor antagonist (SB 242084), lorcaserin also induces head twitching (Serafine et al., 2015), a behavior commonly produced by drugs with agonist properties at 5-HT_{2A} receptors (e.g., LSD). Thus, it is possible that some actions of lorcaserin (e.g., 5-HT_{2C} receptor agonism) might inhibit other actions of lorcaserin (e.g., 5-HT_{2A} receptor agonism). For example, the dose–response function for head twitching induced by 5-HT₂ receptor agonists is an inverted U-shape (Fantegrossi et al., 2010; see Canal & Morgan, 2012, for a review). From experiments using antagonists that are selective for different 5-HT receptor subtypes, it appears as though 5-HT_{2A} receptors mediate the ascending limb (e.g., the initiation of head twitching) of the inverted U-shaped dose–response function while 5-HT_{2C} receptors mediate the descending limb (e.g., the inhibition of head twitching; see Fantegrossi et al., 2010). That lorcaserin produces head twitching only when administered in combination with a 5-HT_{2C} receptor antagonist supports the notion that actions at one 5-HT receptor subtype preclude the expression of actions at another 5-HT receptor subtype.

Given the apparent therapeutic potential of lorcaserin for treating substance use disorders, it is important to fully characterize the pharmacological profile of this drug. Drug discrimination (Glennon, Rosecrans, & Young, 1983) is an assay with high pharmacological selectivity, and as a measure of the stimulus effects of drugs, allows for the empirical study of mechanism(s) of action through the use of selective pharmacological agonists and antagonists. Subjects are trained to respond on one of two levers for a reinforcer after receiving an injection of drug and to respond on the other lever after receiving an injection

of vehicle. Once stimulus control is established (i.e., subjects reliably respond on the lever appropriate for the injection received before the session) different doses of the training drug or different drugs can be assessed for their similarity to the training drug (i.e., stimulus generalization). Information about the mechanism of action of the training drug can be determined by testing drugs with known mechanisms of action (e.g., substitution tests) and by testing known pharmacologically selective antagonists in combination with the training drug (e.g., antagonism tests). The present study used drug discrimination to investigate the behavioral pharmacology of lorcaserin.

Methods

Subjects

Eight male Sprague Dawley rats (Harlan, Indianapolis, IN, USA), weighing 250–300 g upon arrival, were housed individually in an environmentally controlled room ($24\pm1^{\circ}\text{C}$, $50\pm10\%$ relative humidity) under a 12:12 hr light/dark cycle (light period 0700–1900 hr). All rats had restricted access to food and water in the home cage except as indicated below. Animals were maintained and experiments were conducted in accordance with the Institutional Animal Care and Use Committee, the University of Texas Health Science Center at San Antonio, and with the 2011 Guide for Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, the National Research Council, and the National Academy of Sciences). Approximately 8 months into the experiment, rat #4 died from causes unrelated to this experiment. As such, the total number of rats tested varied between 7 and 8 as indicated below.

Apparatus

Experiments were conducted in commercially available operant conditioning chambers ($26 \times 32 \times 21.5$ cm high) enclosed within sound-attenuating cubicles. Each chamber was equipped with a house light, two response levers, two stimulus lights, a pellet trough, a pellet dispenser, and a fan for ventilation (MED Associates, Inc., St. Albans, VT). An interface connected the chambers to a computer that controlled the experimental events and recorded data using Med-PC software (MED Associates, Inc., St. Albans, VT).

Procedure

Rats ($n = 8$) were trained to discriminate 0.56 mg/kg lorcaserin from saline (vehicle) while responding under a fixed-ratio 5 schedule of food presentation. This training dose was selected based on the doses producing directly observable behavioral effects in a previous study (Serafine et al., 2015) and based on the effects of lorcaserin on response rate in the current study. Sessions were 45 min in duration, each consisting of a 25-min pretreatment period (during which the chamber was dark and responding had no programmed consequence) followed by a maximum 20-min response period that was signaled by the illumination of stimulus lights above the levers. During the response period, five consecutive responses on the lever designated correct (based on the injection administered immediately prior to the pretreatment period) resulted in the delivery of a food pellet. The lever (right or left) that was designated correct after an injection of lorcaserin was counterbalanced across

rats. The session ended and lights were extinguished (i.e., responding had no programmed consequence) after either the delivery of 50 food pellets or 20 min, whichever occurred first.

Rats received an injection at the beginning of each session. When saline was administered before a training session, only responding on the saline-associated lever delivered food (e.g., on these days the saline-associated lever was designated as the correct lever); responding on the lorcaserin-associated lever reset the response requirement on the saline-associated lever. When lorcaserin was administered before a training session, only responding on the lorcaserin-associated lever delivered food (e.g., on these days, the lorcaserin-associated lever was designated as the correct lever); responding on the saline-associated lever reset the response requirement on the lorcaserin-associated lever. In general, a double-alternation injection schedule (drug, drug, saline, saline...) across training sessions was used during training. Testing began when the following criteria were satisfied for five consecutive or six of seven training sessions: at least 90% of the total responses in each session occurred on the correct lever; and fewer than five responses occurred on the incorrect lever prior to the delivery of the first food pellet. Once these criteria were satisfied, test sessions occurred no more often than every third day and only so long as the above criteria were satisfied during two consecutive training sessions.

Test sessions were identical to training sessions except that five consecutive responses on either lever delivered food and different doses of lorcaserin or other drugs were administered prior to cycles. Several different types of tests were conducted. First, dose–response curves were determined for lorcaserin by administering different doses on different days. The order of testing different doses varied among subjects; however, when a dose produced at least 90% lorcaserin-lever responding, larger doses were not studied in that subject. Similarly, when a dose decreased response rate (e.g., calculated from the total number of responses on both levers during the response period and expressed as responses per s) to less than 20% of the control rate, larger doses were not studied in that subject. During the course of this study, dose–response curves for lorcaserin were determined twice in each subject, once at the beginning of the study and again near the end of the study (i.e., 7–12 months later). After the first dose–response curve of lorcaserin was determined, the time course of lorcaserin was determined by varying the time between administration of drug and the beginning of the response period, with the maximum duration of the response period remaining 20 min. Following assessment of time course, other drugs were examined alone or in combination with lorcaserin to determine the pharmacological selectivity of the lorcaserin discriminative stimulus. For drug combination studies, an antagonist was administered 25 min prior to the administration of lorcaserin while rats were in their home cages. The order in which different doses and drugs were studied was randomized across subjects such that no two subjects received tests in the same order.

Drugs

Lorcaserin hydrochloride (MedChem Express, Monmouth Junction, NJ), 2,5-dimethoxy-4-methylamphetamine (DOM hydrochloride; NIDA Research Technology Branch, Rockville, MD), (+)-8-hydroxy-2-(dipropylamino) tetralin hydrobromide (8-OH-DPAT; Sigma Aldrich, St. Louis, MO), and m-chlorophenylpiperazine (mCPP; Sigma Aldrich) were dissolved in

sterile 0.9% saline. 6-Chloro-5-methyl-N-(6-[(2-methylpyridin-3-yl)oxy]pyridin-3-yl)indoline-1-carboxamide (SB 242084 hydrochloride; ABCAM, Cambridge, MA) was dissolved in a mixture of saline (0.9%) containing hydroxypropyl- β -cyclodextrin (8% by weight) plus citric acid (25 mM). Sodium hydrochloride was then added to achieve a more basic pH. R-(1)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol] (MDL 100907) was synthesized by Kenner Rice (Ullrich and Rice, 2000) and dissolved in 20% dimethylsulfoxide (v/v). Doses of SB 242084 are expressed as the base, and doses of other drugs are expressed as the salt. Drugs were administered i.p., typically in a volume of 1 ml/kg body weight.

Data Analyses

Control response rates were determined during training sessions in which rats received saline injections and satisfied the testing criteria. For individual rats, control rates were averaged across 10 training sessions (mean $\pm$ 1 SEM). Group mean response rates were determined by averaging among rats. The percentage of responses on the lorcaserin-associated lever and response rates (in responses per s) are plotted as a function of dose or time since drug administration. Discrimination data for an individual rat were not included in the data analysis when response rate was less than 20% of control for that subject.

Results were compared by simultaneously fitting straight lines to the dose–effect curves for individual rats using GraphPad Prism version 6 for Mac (GraphPad Software, San Diego, CA). Straight lines were fitted to the linear portion of the dose–effect curves which included at least two data points with one data point below 25% and one above 75%. To determine the simplest model that best fitted the data, slopes of those lines were compared using an *F*-ratio test. Slopes that were significantly different indicated that the test compound altered the dose–effect curve and that a more complex model was required to fit the data; when slopes were not different, a simpler model with a common slope was used. Dose–effect curves were further compared by determining whether the data were best fitted by a common intercept. Significance was set at $p < .05$.

Results

Reliable stimulus control with lorcaserin was established in all eight rats and was maintained throughout the experiment. The average ($\pm$ 1 SEM) number of training sessions needed to establish reliable stimulus control with lorcaserin (i.e., satisfy the testing criteria) was 47 ± 2 . Lorcaserin (0.178–1.0 mg/kg; Fig. 1) dose-dependently increased responding on the drug-associated lever with greater than 80% drug-lever responding occurring with doses of 0.56 and 1.0 mg/kg. The two lorcaserin dose-response curves for discriminative stimulus effects were not significantly different. Doses of lorcaserin larger than 0.56 mg/kg slightly decreased rate of responding (lower panel, Fig. 1).

Figure 2 shows the time course for the effects of lorcaserin determined by varying the time between drug administration and the response period. Partial (less than 40%) drug-lever responding was observed when lorcaserin was administered 6.25 or 12.5 min prior to the response period. With a 25-min pretreatment (i.e., the condition used for training), rats responded more than 90% on the lorcaserin-associated lever. With longer pretreatment times

(50 and 100 min), less drug-lever responding was observed. Rate of responding was slightly decreased with a 25-min pretreatment but otherwise not markedly affected (lower panel, Fig. 2). When saline was administered 12.5 or 25 min prior to the response period, rats responded predominantly on the saline-associated lever.

Figure 3 shows discrimination and response rate data for individual rats in tests with drugs that have agonist properties at different 5-HT receptor subtypes (Fig. 3). The 5-HT_{2C} receptor agonist mCPP occasioned greater than 90% lorcaserin-lever responding in seven of eight rats (left panel), as did the 5-HT_{2A} receptor agonist DOM (middle panel). The 5-HT_{1A} receptor agonist 8-OH-DPAT occasioned greater than 90% lorcaserin-lever responding in only four of seven rats. In contrast to the very similar potency among rats of lorcaserin to occasion drug-lever responding (Fig. 1 and left panel Fig. 4), doses of mCPP, DOM and 8-OH-DPAT that occasioned lorcaserin-lever responding varied markedly among rats (Fig. 3; see also Table 1). For example, the dose of mCPP occasioning at least 90% responding on the lorcaserin lever varied from 0.056 (rat 6) to 1.0 (rat 8) mg/kg.

Figure 4 shows data for individual rats in tests with lorcaserin, fluoxetine, cocaine, and morphine. Whereas all rats responded on the drug-associated lever after receiving 0.32 or 1.0 mg/kg lorcaserin, all rats responding predominantly on the saline-associated lever after receiving fluoxetine or morphine up to doses that markedly decreased rate of responding. One rat responded on the lorcaserin lever after receiving one dose (5.6 mg/kg) of cocaine; otherwise rats responded predominantly on the saline-associated lever after receiving cocaine (see Table 1).

The discriminative stimulus effects of lorcaserin were attenuated by pretreatment with a 5-HT receptor antagonist. Specifically, the 5-HT_{2C} receptor selective antagonist SB 242084 attenuated lorcaserin-lever responding in all eight rats (left panel, Fig. 5); however, the potency of SB 242084 varied among rats, with effective doses ranging from 0.001 (rat 1) to 0.1 (rats 2,3, 5, and 8) mg/kg. The 5-HT_{2A} receptor selective antagonist MDL 100907 attenuated lorcaserin-lever responding in six of seven rats; whereas a dose of 0.0001 mg/kg MDL 100907 fully antagonized lorcaserin in rat 1, a $\sqrt{1000}$ -fold larger dose of MDL 100907 was ineffective in rat 7 (right panel, Fig. 5).

Discussion

Lorcaserin is approved by the FDA for treating obesity and it is currently being evaluated for smoking cessation and for treating other substance use disorders. This study trained rats to discriminate between saline and 0.56 mg/kg lorcaserin in order to examine the pharmacological mechanism(s) that might be important in its therapeutic use. Rats in this study were under adequate stimulus control for testing after an average of 47 ± 2 training sessions. Others have trained rats to discrimination compounds with 5-HT_{2C} receptor agonist properties; for example, rats were trained to discriminate 1 mg/kg mCPP in an average of 25 sessions and to discriminate 0.8 mg/kg mCPP in an average of 27 sessions (Callahan & Cunningham, 1994; Winter & Rabin, 1993). Lorcaserin and mCPP have similar *in vitro* selectivity for 5-HT_{2C} over 5-HT_{2A} receptors (see Thomsen et al., 2008; Kimura et al., 2004) as well as similar potency in producing other behavioral effects that are mediated

by 5-HT_{2C} receptors (Serafine et al., 2015); thus, the slightly larger training doses of mCPP used in previous studies might account for the relatively fewer training sessions that were required to establish stimulus control in those studies (Stolerman, Childs, Ford, & Grant, 2011). The lorcaserin discriminative stimulus was stable as evidenced by the striking similarity in dose–response curves determined at the beginning and end of the current study. Moreover, the discriminative stimulus effects of lorcaserin in this study were not accompanied by marked effects on rate of responding for food and the duration of action of the training dose was less than 1 hr.

Although lorcaserin has highest affinity at 5-HT_{2C} receptors it also binds to other 5-HT receptor subtypes including 5-HT_{2A} and 5-HT_{1A} receptors (Thomsen et al., 2008). A previous study demonstrated that some doses of lorcaserin produced behavioral effects that were consistent with agonist properties at 5-HT_{2A} and 5-HT_{1A} receptors (Serafine et al., 2015). In the current study, other direct-acting 5-HT receptor agonists were studied for their ability to occasion responding on the lorcaserin-associated lever. mCPP, which also has high affinity for 5-HT_{2C} receptors, occasioned more than 90% lorcaserin-lever responding in seven of eight rats. Moreover, DOM, which has well-documented agonist properties at 5-HT_{2A} receptors, also occasioned more than 90% lorcaserin-lever responding in seven of eight rats. Finally, 8-OH-DPAT which has agonist properties at 5-HT_{1A} receptors, occasioned more than 90% lorcaserin-lever responding in four of seven rats tested. Consistent with results of the current study, compounds with agonist properties at 5-HT_{2A} receptors, but not 8-OH-DPAT (5-HT_{1A}), also occasioned predominantly drug-appropriate responding in rats discriminating mCPP from saline (Callahan & Cunningham, 1994).

Drugs that do not act directly at 5-HT receptors did not reliably occasion responding on the lorcaserin-associated lever up to doses that decreased responding. For example, the indirect-acting 5-HT receptor agonist and selective 5-HT reuptake inhibitor fluoxetine occasioned responding predominantly on the saline-associated lever. This finding is in contrast to a previous report in which rats discriminating mCPP responded nearly 40% on the drug-associated lever after receiving fluoxetine (Callahan & Cunningham, 1994). Other drugs with primary mechanisms of action at other targets also did not occasion responding on the lorcaserin-associated lever. The nonselective monoamine reuptake inhibitor cocaine occasioned drug-lever responding at one dose in one rat and the *mu* opioid receptor agonist morphine occasioned nearly exclusive saline-lever responding in all rats. Thus, based on substitution studies with direct- and indirect-acting 5-HT receptor agonists as well as pharmacologically unrelated drugs, it appears as though the lorcaserin discriminative stimulus (when trained at a dose of 0.56 mg/kg) is selective for agonist activity at 5-HT receptors. Moreover, it appears as though more than one subtype of 5-HT receptor contributes to the discriminative stimulus effects of this dose of lorcaserin.

Further evidence in support of the notion that the discriminative stimulus effects of lorcaserin are mediated by 5-HT receptors was obtained from studies with 5-HT receptor selective antagonists. The smallest dose of lorcaserin to produce at least 90% lorcaserin-lever responding in individual rats (0.32 or 0.56 mg/kg) was combined with the 5-HT_{2C} receptor selective antagonist SB 242084 and the 5-HT_{2A} receptor selective antagonist MDL 100907. Pretreatment with SB 242084 fully attenuated the discriminative stimulus effects of

lorcaserin in all rats. However, the effective dose of SB 242084 varied 100-fold among the eight rats. Pretreatment with MDL 100907 also attenuated the discriminative stimulus effects of lorcaserin in six of the seven rats, with the effective doses of MDL 100907 also varying markedly among rats. Taken together, these results support the view that more than one subtype of 5-HT receptor contributes to the discriminative stimulus effects of this dose of lorcaserin and further suggest that the contribution of different receptor subtypes might vary markedly among subjects.

The apparent contribution of multiple 5-HT receptor subtypes to the discriminative stimulus effects of lorcaserin in the current study is likely related to the particular dose that was used to establish stimulus control. For example, smaller doses of lorcaserin (e.g., 0.1 mg/kg) have been shown to produce unconditioned behavioral effects (e.g., yawning) that are thought to be mediated by 5-HT_{2C} receptors (Serafine et al., 2015). When administered alone a dose of 0.56 mg/kg lorcaserin has no apparent direct (unconditioned) behavioral effects; however, when administered in combination with the 5-HT_{2C} receptor selective antagonist SB 242084, lorcaserin produced head twitching, an effect that is thought to be mediated by 5-HT_{2A} receptors (Serafine et al., 2015). That 5-HT_{2A} receptors might contribute to the discriminative stimulus effects of lorcaserin is consistent with results from other studies that examined directly observable behavioral effects in rats. At doses larger than those producing effects that are mediated by 5-HT_{2C} or 5-HT_{2A} receptors, lorcaserin had behavioral effects that are commonly observed with drugs that have agonist properties at 5-HT_{1A} receptors. That is, lorcaserin produced forepaw treading which is a characteristic behavioral effect of drugs acting at 5-HT_{1A} receptors. Moreover, lorcaserin-induced forepaw treading was attenuated by the 5-HT_{1A} receptor selective antagonist WAY 100635 (Serafine et al., 2015). While the 5-HT receptor agonists used in this study were selected because of their reported selectivity for receptor subtypes, higher concentrations of these agonists also bind to 5-HT_{2C} receptors. For example, although DOM has highest affinity for 5-HT_{2A} receptors, it also binds to 5-HT_{2C} receptors (Eshleman et al., 2014). Similarly, 8-OH-DPAT is highly selective for 5-HT_{1A} receptors, but at least one study reported affinity for 5-HT_{2C} receptors (Knight et al., 2004). Thus, the possibility that these agonists share discriminative stimulus effects with lorcaserin because of actions at 5-HT_{2C} receptors cannot be dismissed. Further, it is possible that training with a smaller dose of lorcaserin would have generated a discriminative stimulus that is predominantly or exclusively due to actions at 5-HT_{2C} receptors.

Although lorcaserin is approved for treating obesity, it is currently being evaluated for smoking cessation and planning is underway to examine lorcaserin for treating cocaine use disorder. Some drugs with agonist properties at 5-HT_{2A} receptors (e.g., LSD) are abused. Lorcaserin is a Schedule IV controlled substance (Drug Enforcement Administration) and was reported to produce adverse effects in humans that might be consistent with actions at 5-HT_{2A} receptors, including hallucinations and euphoria (US Food and Drug Administration, 2012). Individuals that have a history of substance use disorders might be particularly vulnerable to any abuse-related effects of lorcaserin (e.g., as a function of actions at 5-HT_{2A} receptors). A more thorough understanding of the mechanism(s) of action of lorcaserin at 5-HT and other receptors might help facilitate the development of new, improved drugs for the treatment of obesity, as well as substance use disorders.

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Fig. 1.

Mean (± 1 SEM) percent responding on the lorcaserin-associated lever (upper panel) and mean (± 1 SEM) rate of responding in responses per s (lower panel) during test sessions preceded by saline (vehicle, "V") or lorcaserin at the beginning (closed diamonds, $n = 8$;) and at the end (open diamonds, $n = 7$) of the study, plotted as a function of dose of lorcaserin (in mg/kg body weight).

Fig. 2.

Mean (± 1 SEM) percent responding on the lorcaserin-associated lever (upper panel) and mean (± 1 SEM) rate of responding in responses per s (lower panel) in test sessions when the pretreatment time was varied for the training dose of lorcaserin (closed diamonds) or saline (open diamonds), plotted as a function of dose of lorcaserin (in mg/kg body weight). Data presented are from only the first 5 min of the response period ($n = 8$).

Fig. 3. Percent responding on the lorcaserin-associated lever (upper panel) and rate of responding in responses per s (lower panel) for individual subjects that received mCPP ($n = 8$), DOM ($n = 8$), or 8-OH-DPAT ($n = 7$), plotted as a function of dose (in mg/kg body weight).

Fig. 4.

Percent responding on the lorcaserin-associated lever (upper panel) and rate of responding in responses per s (lower panel) for individual subjects that received lorcaserin ($n = 8$), fluoxetine ($n = 7$), cocaine ($n = 7$), or morphine ($n = 7$), plotted as a function of dose (in mg/kg body weight).

Fig. 5.

Percent responding on the lorcaserin-associated lever (upper panel) and rate of responding in responses per s (lower panel) for individual subjects after an injection of the smallest dose of lorcaserin to produce at least 90% responding on the lorcaserin-associated lever administered alone (“L”) and in combination with SB 242084 ($n = 8$) or MDL 100907 ($n = 7$), plotted as a function of antagonist dose (in mg/kg body weight). The dose of lorcaserin used in antagonism experiments was 0.32 mg/kg for rats 2, 6, and 8 while the dose of lorcaserin was 0.56 mg/kg for rats 1, 3, 5 and 7.

Table 1

Minimum doses (mg/kg) to produce >90% lorcaserin-lever responding

Rat	1	2	3	4	5	6	7	8	Group Mean	(SEM)
Lorcaserin	0.56	0.32	0.32	0.32	0.56	0.32	0.56	0.32	0.41	0.04
mCPP	0.1	0.178	n/a	0.56	0.32	0.056	0.1	1.0	0.33	0.13
DOM	n/a	0.32	0.32	0.32	0.32	0.178	0.56	0.178	0.31	0.05
8-OH-DPAT	0.056	0.056	n/a	x	0.32	n/a	0.1	n/a	0.133	0.06
Cocaine	n/a	n/a	n/a	x	5.6	n/a	n/a	n/a	n/a	

n/a = no dose produced >90% lorcaserin-lever responding

x = not tested