Title: Directly observable behavioral effects of lorcaserin in rats

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Abstract

Lorcaserin is approved by the United States Food and Drug Administration for treating obesity and its therapeutic effects are thought to result from agonist activity at serotonin (5-HT)2C receptors. Lorcaserin has affinity for other 5-HT receptor subtypes, although its activity at those subtypes is not fully described. The current study compared the behavioral effects of lorcaserin (0.0032-32.0 mg/kg) to the effects of other 5-HT receptor selective agonists in rats (n=8). The 5-HT2C receptor selective agonist mCPP (0.032 - 1.0 mg/kg) and lorcaserin induced yawning that was attenuated by the 5-HT2C receptor selective antagonist SB 242084 (1.0 mg/kg). The 5-HT2A receptor selective agonist DOM (0.1-3.2 mg/kg) induced head twitching that was attenuated by the 5-HT2A receptor selective antagonist MDL 100907 (0.01 mg/kg), lorcaserin (3.2 mg/kg), and mCPP (3.2 mg/kg). In rats pretreated with SB 242084 (1.0 mg/kg), lorcaserin also induced head twitching. At larger doses, lorcaserin produced forepaw treading that was attenuated by the 5-HT1A receptor selective antagonist WAY 100635 (0.178 mg/kg). While the behavioral effects of lorcaserin in rats are consistent with it having agonist activity at 5-HT2C receptors, these data suggest that, at larger doses, it also has agonist activity at 5-HT2A and possibly 5-HT1A receptors. Mounting evidence suggests that 5-HT2C receptor agonists might be effective for treating drug abuse. A more complete description of the activity of lorcaserin at 5-HT receptor subtypes will facilitate a better understanding of the mechanisms that mediate its therapeutic effects.
Introduction

Lorcaserin (Belviq®; Smith et al., 2008) was recently approved by the United States Food and Drug Administration for treating obesity (Coleman et al., 2012). The therapeutic effects of lorcaserin are thought to be due to agonist activity at serotonin (5-HT)\textsubscript{2C} receptors. Drugs that have agonist activity at 5-HT\textsubscript{2C} receptors decrease food intake in rats (Clifton et al., 2000; Kennett and Curzon, 1991; Vickers et al., 2001a) and they have long been considered for treating obesity (for a review see Bickerdike, 2003). Agonists acting at 5-HT\textsubscript{2C} receptors have other behavioral effects in rats. For example, the prototypical 5-HT\textsubscript{2C} receptor agonist mCPP induces yawning and penile erections (Protais et al., 1995; Kennett and Curzon, 1988). In addition to 5-HT\textsubscript{2C} receptors, lorcaserin also has affinity for other 5-HT receptor subtypes, including 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B}, and 5-HT\textsubscript{1A} (Thomsen et al., 2008). Although lorcaserin has been shown to have efficacy at 5-HT\textsubscript{2A} receptors \textit{in vitro} (Thomsen et al., 2008), it is unclear whether lorcaserin has agonist properties \textit{in vivo} that are mediated by 5-HT\textsubscript{2A} receptors. In humans, drugs with agonist effects at 5-HT\textsubscript{2A} receptors are sometimes abused and can produce hallucinations (Kennett and Clifton, 2010). In rodents, drugs with agonist activity at 5-HT\textsubscript{2A} receptors (e.g., DOI, DOM and LSD) induce a characteristic head twitch responding (Corne et al., 1963; Fantegrossi et al., 2010; Darmani et al., 1992; for a review see Canal and Morgan, 2012). One study compared the behavioral effects of lorcaserin to DOI, a prototypic 5-HT\textsubscript{2A} receptor selective agonist (Thomsen et al., 2008); lorcaserin did not produce behavioral effects like those produced by DOI (e.g., wet dog shakes and back contractions) suggesting that lorcaserin does not have agonist activity at 5-HT\textsubscript{2A} receptors.

Several decades of preclinical research suggest that 5-HT\textsubscript{2C} receptor agonists might be effective for treating substance use disorders (for a review see Howell and Cunningham, 2015). For example, 5-HT\textsubscript{2C} receptor agonists can attenuate the positive reinforcing effects of cocaine, as well as reinstatement of responding by cocaine and cocaine-associated stimuli (Anastasio et al., 2011; Burbassi and Cervo, 2008; Callahan and Cunningham, 1995; Cunningham et al.,
Despite having been approved for treating obesity, the pharmacological profile of lorcaserin has yet to be fully described. This study tested the hypothesis that in rats the behavioral effects of lorcaserin are due to its agonist actions at 5-HT$_{2C}$ receptors by examining directly observable behavior induced by lorcaserin and comparing those effects to behavior induced by prototypic agonists that have selectivity for particular 5-HT receptor subtypes. In order to determine the receptor subtypes mediating the behavioral effects of these drugs, agonists were also examined in combination with 5-HT receptor subtype selective antagonists. Lastly, lorcaserin was also examined in combination with other agonists, in instances when a particular behavior was not observed with lorcaserin alone, to test whether it had antagonist properties at specific 5-HT receptor subtypes.

**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±1°C, 50±10% relative humidity) under a 12:12 hr light/dark cycle (light period 0700–1900 hr). Except during testing, rats had free access to food and water in the home cage. Rats 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).

*Directly observable behavior*

On the day of testing, rats were transferred from a clear plastic home cage to a test cage (the home and test cages were identical with the exception that no food, water, or bedding was
present in the test cage) and allowed to habituate for 15 min. Experiments were conducted at
the same time each test day (14:00 h) by an independent observer blind to the treatment.
Behavior was assessed after injection of vehicle, followed by injection of increasing doses of
drug administered i.p. (except where otherwise noted) every 25 min according to a cumulative
dosing procedure. Behavior was scored either in real time or by video recordings. Beginning 5
min after each injection, the total number of head twitches and yawns observed for 20 min was
recorded. Head twitch was defined as an irregularly occurring horizontal head movement,
resembling a strong pinna reflex (Corne et al., 1963; Li and France, 2008). Yawning was
defined as an opening and closing of the mouth such that the lower incisors were completely
visible (Sevak et al., 2008; Baladi and France, 2009). Presence or absence of forepaw treading,
lower lip retraction, and flat body posture were assessed in 5-s periods every minute during the
20-min observation period following each injection (i.e., maximum possible score = 20).
Forepaw treading was scored as present when repeated flexion and extension of the forepaws
occurred (at least 3 times and involving both forepaws; Colpaert et al., 1989). Lower lip
retraction was scored as present if the lower incisors were visible and flat body posture was
scored as present if the entire ventral surface of the rat was in contact with the cage floor
(Kleven et al., 1997). For tests of antagonism, an injection of one drug (e.g., an antagonist) was
administered immediately after the injection of vehicle.

Data Analyses

Results are expressed as the average (± 1 SEM) number of yawns or head twitches
during a 20-min observation period and plotted as a function of dose. Results are also
expressed as an average (± 1 SEM) forepaw treading score (during a 20-min observation
period) and plotted as a function of dose. For each group, differences between dose-response
curves were analyzed by comparing the following: maximal number for head twitches and
yawns; and maximal score for forepaw treading, lower lip retraction, and flat body posture. A
two-way (dose x test) repeated measures analysis of variance (ANOVA), followed by post-hoc
Bonferroni tests, was used to determine statistical differences between maximal effects for dose-response curves determined in the presence and in the absence of an antagonist. Doses producing the maximum number of yawns, maximum number of head twitches, and the maximum forepaw treading score were also determined for each rat, as well as for each dose-response curve. These doses were log transformed for individual subjects and analyzed using one-way repeated measures ANOVA, followed by a Dunnett’s post-hoc analyses. For all tests, the P-value was less than 0.05.

**Drugs**

Lorcaserin hydrochloride ([1R]-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; MedChem Express, Monmouth Junction, NJ), DOM hydrochloride (2,5-dimethoxy-4-methylamphetamine; NIDA Research Technology Branch, Rockville, Maryland, USA), 8-OH-DPAT (7-[dipropylamino]-5,6,7,8-tetrahydronaphthalen-1-ol; Sigma Aldrich, St. Louis, MO), WAY 100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamid; a gift from Dr. Adrian Newman-Tancredi; Centre de Recherche Pierre Fabre, Castres, France), mCPP (1-[3-chlorophenyl]piperazine; Sigma Aldrich, St. Louis, MO) and ritanserin (Sigma Aldrich, St. Louis, MO) and SB 242084 hydrochloride (6-chloro-5-methyl-N-[6-[(2-methylpyridin-3-yl)oxy]pyridin-3-yl]indoline-1-carboxamide; 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. MDL100907 (R-(+)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol) 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; doses of other drugs are expressed as the salt. Drugs were administered i.p. except for 8-OH-DPAT and WAY 100635 which were administered s.c. All drugs were typically administered in a volume of 1 ml/kg body weight.

**Results**
Yawning

With increasing cumulative doses, mCPP increased then decreased yawning (Fig. 1, left panel) resulting in an inverted U-shaped dose-response curve. Similarly, increasing cumulative doses of lorcaserin also produced an inverted U-shaped dose-response curve for yawning (Fig. 1, right panel). Pretreatment with the 5-HT$_{2C}$ receptor selective antagonist SB 242084 (1.0 mg/kg) significantly attenuated yawning produced by lorcaserin ($F(1,7)=35.48; P=0.006$) or by mCPP ($F(1,7)=21.00; P=0.0025$). Up to a cumulative dose of 3.2 mg/kg, DOM did not increase yawning (data not shown). A smaller dose of SB 242084 (0.1 mg/kg) significantly attenuated lorcaserin-induced yawning (data not shown) in a manner that was not different from antagonism observed with 1.0 mg/kg SB 242084. Pretreatment with the 5-HT$_{2A}$ receptor selective antagonist MDL 100907 (0.01 mg/kg) did not significantly affect lorcaserin-induced yawning (data not shown).

Head Twitching

Cumulative doses of DOM increased, then decreased head twitching resulting in an inverted U-shaped dose-response curve (Fig. 2, left and right panels). In contrast, lorcaserin did not produce head twitching up to a cumulative dose of 32.0 mg/kg (Fig. 2, middle panel, open squares). Pretreatment 0.01 mg/kg of the 5-HT$_{2A}$ receptor selective antagonist MDL 100907 (Fig. 2 left panel) attenuated DOM-induced head twitching ($F(1,7)=21.11; P=0.0025$), as did pretreatment with either 3.2 mg/kg lorcaserin (Fig. 2 right panel, closed diamonds; $F(1,7)=13.24; P=0.0083$) or 3.2 mg/kg mCPP (data not shown). While not producing head twitching when administered alone, lorcaserin significantly increased head twitching in rats pretreated with 1.0 mg/kg of the 5-HT$_{2C}$ receptor selective antagonist SB 242084 (Fig. 2, middle panel; $F(1,7)=5.765; P=0.0474$).

Other Behavioral Effects
Forepaw treading, flat body posture, and lower lip retraction were all induced by 8-OH-DPAT (Fig. 3, left panels, open inverted triangles). Large doses of lorcaserin produced forepaw treading but not flat body posture or lower lip retraction (Fig. 3, right panels, open squares). The maximal effect for 8-OH-DPAT-induced forepaw treading was significantly larger than the maximal effect for lorcaserin-induced forepaw treading (Fig. 3, upper panels; $F(1,7)=175.0$; $P<0.0001$). Pretreatment with 0.178 mg/kg of the 5-HT$_{1A}$ receptor selective antagonist WAY 100635 attenuated forepaw treading produced by 8-OH-DPAT ($F(1,7)=171.5$; $P<0.0001$) or by lorcaserin ($F(1,7)=42.0$; $P=0.0003$; Fig. 3, upper panels). WAY 100635 also attenuated 8-OH-DPAT-induced flat body posture (i.e., maximal effect; $F(1,7)=84.29$; $P<0.0001$) and lower lip retraction (i.e., maximally effective dose; $F(1,7)=91.93$; $P<0.0001$; Fig. 3, middle and lower left panels, respectively). Pretreatment with the nonselective 5-HT$_2$ receptor antagonist ritanserin (0.32 mg/kg) did not significantly impact lorcaserin-induced forepaw treading (Fig. 3, upper right). While not producing flat body posture when administered alone, lorcaserin significantly increased flat body posture in rats pretreated 0.178 mg/kg ritanserin (Fig. 3, middle right panel; $F(1,7)=1980.0$; $P<0.0001$). Lower lip retraction was not observed with lorcaserin alone or in combination with ritanserin (Fig. 3, lower right panel).

**Discussion**

Lorcaserin has highest affinity for 5-HT$_{2C}$ receptors, although it also binds to other 5-HT receptor subtypes and at still higher concentrations to the 5-HT transporter (Thomsen et al., 2008). It is well established that many of the behavioral effects of lorcaserin are mediated by agonist activity at 5-HT$_{2C}$ receptors. For example, lorcaserin decreases food intake in rats and that effect is prevented by the 5-HT$_{2C}$ receptor selective antagonist SB 242084 (Thomsen et al, 2008). In the present study, lorcaserin increased yawning as well as other behavioral effects (e.g., penile erections and grooming, both of which were observed but not recorded) that are
produced by drugs with agonist activity at 5-HT$_{2C}$ receptors (Kennett and Curzon, 1988; Protais et al., 1995). When administered alone, lorcaserin did not produce head twitching; however, lorcaserin significantly increased head twitching in rats that were pretreated with the 5-HT$_{2C}$ receptor selective antagonist SB 242084. Drugs with agonist activity at 5-HT$_{2A}$ receptors increase head twitching (Canal and Morgan, 2012). At doses larger than those producing head twitching, lorcaserin induced forepaw treading, an effect produced by drugs with agonist activity at 5-HT$_{1A}$ receptors (Haberzetti et al., 2013). These results extend an earlier study (Thomsen et al., 2008) by confirming in vivo agonist properties of lorcaserin that appear to be mediated by 5-HT$_{2C}$ receptors and by demonstrating other agonist properties of lorcaserin that appear to be mediated by 5-HT$_{2A}$ and 5-HT$_{1A}$ receptors.

The prototypical 5-HT$_{2C}$ receptor agonist mCPP as well as lorcaserin produced yawning that was attenuated by the 5-HT$_{2C}$ receptor selective antagonist SB 242084, suggesting that yawning induced by both drugs is mediated by agonist activity at 5-HT$_{2C}$ receptors. When administered alone, up to a cumulative dose of 32.0 mg/kg, lorcaserin did not induce head twitching. These data are consistent with a previous report (Thomsen et al., 2008) in which lorcaserin, administered via oral gavage, did not share behavioral effects with the prototypic 5-HT$_{2A}$ receptor selective agonist DOI (e.g., wet dog shakes, back contractions).

Lorcaserin did not produce head twitching when administered alone, although it attenuated head twitching produced by the 5-HT$_{2A}$ receptor selective agonist DOM. The dose-response curve for head twitching produced by DOM or by other 5-HT$_{2A}$ receptor selective agonists (e.g., DOI) is an inverted U-shape, with the ascending limb of the curve being mediated by 5-HT$_{2A}$ receptors and the descending limb by 5-HT$_{2C}$ receptors (Vickers et al., 2001b; Fantegrossi et al., 2010; see Canal and Morgan, 2012 for a review). Thus, it was possible that attenuation of DOM-induced head twitching by lorcaserin could have resulted from agonism at 5-HT$_{2C}$ receptors, from antagonism at 5-HT$_{2A}$ receptors, or from both mechanisms. Similarly,
that lorcaserin did not induce head twitching when administered alone could have occurred
either because it does not have agonist activity at 5-HT_{2A} receptors or because its agonist
activity at 5-HT_{2C} receptors inhibits the expression of (masks) 5-HT_{2A}-receptor mediated head
twitching. When administered in combination with the 5-HT_{2C} receptor selective antagonist SB
242084, lorcaserin significantly increased head twitching. This result suggests that lorcaserin
has agonist activity at both 5-HT_{2C} and 5-HT_{2A} receptors and that its agonist activity at 5-HT_{2C}
receptors can inhibit the expression of a behavior (i.e., head twitching) that is thought to be
mediated by agonist activity at 5-HT_{2A} receptors. The minimally effective dose of lorcaserin to
induce head twitching in rats was 1.78 mg/kg, whereas the therapeutic dose for treating obesity
is 10 mg twice daily (i.e., 0.29 mg/kg for a 70 kg human). Lorcaserin is under evaluation for its
potential in treating substance use disorders (e.g., tobacco smoking, cocaine use disorder) and
it is unclear whether the therapeutic dose of lorcaserin for treating obesity will be effective for
treating substance abuse disorders. Any agonist activity of lorcaserin at other 5-HT receptor
subtypes (e.g., 5-HT_{2A}) might be particularly important when considering its possible use in
treating individuals with a history of substance use disorder.

Indirect-acting 5-HT receptor agonists (e.g., selective 5-HT reuptake inhibitors [SSRIs])
as well as direct-acting 5-HT receptor agonists that are selective for 5-HT_{1A} receptors (e.g., 8-
OH-DPAT) produce a characteristic pattern of behavioral effects in rats that includes forepaw
treating, lower lip retraction, and flat body posture (for a review see Haberzetti et al., 2013). In
the current study, 8-OH-DPAT produced forepaw treading, lower lip retraction, and flat body
posture (see Li and France, 2008 for similar results using i.p. cumulative dosing). In contrast,
lorcaserin produced forepaw treading but not lower lip retraction or flat body posture. Other
results from this study (see above) suggest that lorcaserin has agonist activity at both 5-HT_{2C}
and 5-HT_{2A} receptors and it is possible that activity at those 5-HT receptor subtypes inhibits the
expression of (masks) lower lip retraction and flat body posture. Consistent with this possibility,
both 5-HT\textsubscript{2C} receptor agonists (mCPP) as well as 5-HT\textsubscript{2A} receptor agonists (DOI) attenuate 8-OH-DPAT-induced lower lip retraction (Berendsen et al., 1989). In the present study, pretreatment with the nonselective 5-HT\textsubscript{2} receptor antagonist ritanserin did not significantly impact lorcaserin-induced forepaw treading; however, doses that failed to produce any flat body posture when lorcaserin was administered alone, caused significant, dose-related increases in flat body posture in rats that were pretreated with ritanserin, suggesting that activity of lorcaserin at 5-HT\textsubscript{2} receptors might prevent the expression of a behavior (i.e., flat body posture) that is thought to be mediated by agonist activity at 5-HT\textsubscript{1A} receptors. Lower lip retraction was not observed with lorcaserin alone or in combination with ritanserin.

In summary, these results provide further evidence that lorcaserin has agonist activity at 5-HT\textsubscript{2C} receptors, the site of action that is thought to be important for its therapeutic actions (i.e., treating obesity). However, in addition to agonist activity at 5-HT\textsubscript{2C} receptors, these results also provide evidence that lorcaserin has agonist activity (\textit{in vivo}) at 5-HT\textsubscript{2A} and 5-HT\textsubscript{1A} receptors. Moreover, the rank order potency of lorcaserin for producing yawning (5-HT\textsubscript{2C} receptor mediated), head twitching (5-HT\textsubscript{2A} receptor mediated), forepaw treading and flat body posture (5-HT\textsubscript{1A} receptor mediated) is the same as its rank order binding affinities for these 5-HT receptor subtypes (Thomsen et al., 2008). It is unclear whether actions at these 5-HT receptor subtypes might contribute to the adverse effects that can occur with lorcaserin.

Lorcaserin is a controlled substance (Drug Enforcement Administration Schedule IV) and its adverse effects include hallucinations and euphoria (\texttt{www.belviq.com}; United States Food and Drug Administration, 2012). Overweight patients receiving lorcaserin are also encouraged to diet and exercise. Food restriction decreases sensitivity of rats to some of the behavioral effects of drugs acting on 5-HT receptors (Li and France, 2008; Serafine and France, 2014); it is possible that food restriction and resulting body weight changes might also impact the therapeutic and/or adverse effects of lorcaserin. Finally, lorcaserin is under evaluation for
smoking cessation and for treating cocaine abuse; results of the current study underscore the importance of full characterizing the behavior profile of lorcaserin in order to identify any effects that could be problematic for individuals with a history of substance use disorder (e.g., 5-HT$_{2A}$ agonist activity). A better understanding of the mechanisms of action of lorcaserin at 5-HT receptor subtypes might also facilitate the development of new, improved drugs for treating obesity as well as substance use disorders.

**Authorship Contributions**

Participated in research design: Serafine, France

Conducted experiments: Serafine

Contributed new reagents or analytic tools: Rice

Performed data analysis: Serafine

Wrote or contributed to the writing of the manuscript: Serafine, France

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Footnotes

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Figure Captions

Fig. 1. Average (± 1 SEM) number of yawns observed in a 20-min observation period in rats that received cumulative doses of mCPP (left panel) or lorcaserin (right panel) alone (open symbols) or in combination with 1.0 mg/kg SB 242084 (closed symbols). The average number of yawns (ordinate) is expressed as a change from a saline test (8 saline injections spaced 25 min apart to match the temporal conditions of drug tests) and plotted as a function of dose (abscissae; V = vehicle).
Fig. 2. Average (± 1 SEM) number of head twitches observed in a 20-min observation period in rats that received cumulative doses of DOM (left and right panels, open circles) or lorcaserin (middle panel, open squares). DOM was also studied in combination with 0.01 mg/kg MDL 100907 (left panel, closed circles) and in combination with 3.2 mg/kg lorcaserin (right panel, closed diamonds); lorcaserin was examined in combination with 1.0 mg/kg SB 242084 (middle panel, closed squares). The average number of head twitches (ordinate) is expressed as a change from a saline test (8 saline injections spaced 25 min apart to match the temporal conditions of drug tests) and plotted as a function of dose (abscissae; V = vehicle).

Fig. 3. Average (± 1 SEM) forepaw treading, flat body posture, and lower lip retraction in a 20-min observation period (maximum possible effect = 20) in rats that received cumulative doses of 8-OH-DPAT (left panels, open inverted triangles) or lorcaserin (right panels, open squares) alone, or in combination with 0.0178 mg/kg WAY 100635 (left panels, closed symbols) or 0.32 mg/kg ritanserin (right panels, closed symbols). Average scores (ordinate) are plotted as a function of dose (abscissae; V = vehicle).
Fig 1

- **mCPP** + 1.0 mg/kg
- **SB 242084**

- **lorcaserin** + 1.0 mg/kg
- **SB 242084**

**Yawns / 20 min (change from saline)**

**Dose (mg/kg)**