**Neuropsychopharmacology (2012) 37,** 1177–1191

**www.neuropsychopharmacology.org**

# The 5-$HT_{2C}$ Receptor Agonist Lorcaserin Reduces Nicotine Self-Administration, Discrimination, and Reinstatement: Relationship to Feeding Behavior and Impulse Control

**Guy A Higgins*[,1,2], Leo B Silenieks[1], Anne Roßmann[1], Zoe Rizos[3], Kevin Noble[3], Ashlie D Soko[3] and Paul J Fletcher[3,4]**

*[1]InterVivo Solutions Inc., Toronto, ON, Canada; [2]Department Pharmacology, University of Toronto, Toronto, ON, Canada; [3]Section of Biopsychology, Clarke Division, Centre for Addiction and Mental Health, Toronto, ON, Canada; [4]Department Psychiatry & Psychology, University of Toronto, Toronto, ON, Canada*

Lorcaserin ((1R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl) is a selective 5-$HT_{2C}$ receptor agonist with clinical efficacy in phase-III obesity trials. Based on evidence that this drug class also affects behaviors motivated by drug reinforcement, we compared the effect of lorcaserin on behavior maintained by food and nicotine reinforcement, as well as the stimulant and discriminative stimulus properties of nicotine in the rat. Acutely administered lorcaserin (0.3–3 mg/kg, subcutaneous (SC)) dose dependently reduced feeding induced by 22-h food deprivation or palatability. Effects up to 1 mg/kg were consistent with a specific effect on feeding motivation. Lorcaserin (0.6–1 mg/kg, SC) reduced operant responding for food on progressive and fixed ratio schedules of reinforcement. In this dose range lorcaserin also reversed the motor stimulant effect of nicotine, reduced intravenous self-administration of nicotine, and attenuated the nicotine cue in rats trained to discriminate nicotine from saline. Lorcaserin also reduced the reinstatement of nicotine-seeking behavior elicited by a compound cue comprising a nicotine prime and conditioned stimulus previously paired with nicotine reinforcement. Lorcaserin did not reinstate nicotine-seeking behavior or substitute for a nicotine cue. Finally, lorcaserin (0.3–1 mg/kg) reduced nicotine-induced increases in anticipatory responding, a measure of impulsive action, in rats performing the five-choice serial reaction time task. Importantly, these results indicate that lorcaserin, and likely other selective 5-$HT_{2C}$ receptor agonists, similarly affect both food- and nicotine-motivated behaviors, and nicotine-induced impulsivity. Collectively, these findings highlight a therapeutic potential for 5-$HT_{2C}$ agonists such as lorcaserin beyond obesity into addictive behaviors, such as nicotine dependence.
*Neuropsychopharmacology* (2012) **37,** 1177–1191; doi:10.1038/npp.2011.303; published online 21 December 2011

**Keywords:** reward; obesity; nicotine dependence; impulsivity; addiction; 5-$HT_{2C}$ receptor

## INTRODUCTION

The indirect 5-HT agonist dexfenfluramine (Redux) provided clinical proof of concept that pharmacological strategies that elevate 5-HT tone are an effective means to treat obesity (Guy-Grand *et al*, 1989; Halford *et al*, 2007). Unfortunately its subsequent withdrawal owing to cardiac valvulopathy and pulmonary hypertension (Connolly *et al*, 1997) highlighted clinical complications associated with the indiscriminate activation of this neurotransmitter system. The 5-HT system comprises 14 distinct receptor subtypes organized into seven subclasses based on sequence homology, signal transduction mechanisms, and pharmacology (Hoyer *et al*, 2002). The 5-$HT_2$ subclass consists of three receptor subtypes, the 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ subtypes, each sharing similar sequence homology and a preferential coupling to $G_{q/11}$ to increase intracellular inositol phosphate and [$Ca^{2+}$] levels (Hoyer *et al*, 2002).

Interest in the 5-$HT_{2C}$ receptor as a potential target for treating obesity initially came from observations that selective 5-$HT_{2C}$ receptor antagonists, such as SB-242084 (6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbomyl] indoline) (Kennett *et al*, 1997), block the

Part of this work was previously presented in abstract format at the 40th Annual Society for Neuroscience meeting held in San Diego, CA, 13–17 November 2010 (Higgins GA, Silenieks LB, Rizos Z, Noble K, Fletcher PJ (2010). The selective 5-$HT_{2C}$ receptor agonist, lorcaserin, reduces indices of nicotine reward as well as food intake in the rat. Abstract 168.19, Society for Neuroscience: Washington, DC). During the course of manuscript review, Levin *et al* reported that lorcaserin reduced nicotine self-administration in female Sprague–Dawley rats (Levin ED, Johnson JE, Slade S, Wells C, Cauley M, Petro A, Rose JE (2011). Lorcaserin, a 5-$HT_{2C}$ agonist, decreases nicotine self-administration in female rats. *J Pharmacol Exp Ther* **338**: 890–896).

*Correspondence: Dr GA Higgins, InterVivo Solutions Inc., 120 Carlton Street, Toronto, Canada, ON M5A 4K2, Tel: +647 724 5094, Fax: +416 920 1876, E-mail: guyh@intervivo.com

Received 16 July 2011; revised 31 October 2011; accepted 3 November 2011

anorectic effects of dexfenfluramine in rodents (Clifton *et al*, 2000; Vickers *et al*, 2001) and that 5-HT$_{2C}$ receptor-deficient mice show an attenuated response to dexfenfluramine (Vickers *et al*, 1999). The cardiac valvulopathy associated with dexfenfluramine has since been attributed to activation of the 5-HT$_{2B}$ receptor (Fitzgerald *et al*, 2000), which unlike the 5-HT$_{2C}$ subtype is highly localized in cardiac tissue (Elangbam *et al*, 2005). Because some hallucinogens, such as LSD, are 5-HT$_{2A}$ receptor agonists, the identification of functionally selective 5-HT$_{2C}$ agonists is of critical importance and a significant pharmaceutical challenge because of homology within the 5-HT$_2$ receptor subclass (Nilsson, 2006; Wacker and Miller, 2008).

Lorcaserin ((1R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl) has emerged as the most advanced drug of this class (Thomsen *et al*, 2008; Smith *et al*, 2008). In functional assays using HEK-293 cells transiently expressing either h5-HT$_{2A}$, h5-HT$_{2B}$, or h5-HT$_{2C}$ receptors, lorcaserin has agonist properties at each subtype, but importantly 100-fold functional selectivity for h2C *vs* h2B, and 15-fold functional selectivity for h2C *vs* h2A receptor subtypes (Thomsen *et al*, 2008). Lorcaserin reduces weight gain, food intake, and body fat mass in rats (Smith *et al*, 2008; Thomsen *et al*, 2008), and the anorectic effect of lorcaserin is absent in 5-HT$_{2C}$ receptor-knockout (KO) mice (Fletcher *et al*, 2009b). Clinical efficacy of lorcaserin to reduce body weight has been demonstrated in phase-II and III trials, with no evidence of cardiovascular signs indicative of valvulopathy or pulmonary hypertension compared with placebo (Smith *et al*, 2009, 2010; Fidler *et al*, 2011). Furthermore, at therapeutic doses lorcaserin appears well tolerated, with no report of hallucinogenic activity or abuse liability (Shram *et al*, 2011; Smith *et al*, 2009, 2010).

In addition to reducing feeding and body weight gain, 5-HT$_{2C}$ receptor agonists also consistently reduce behaviors related to drug abuse. Thus compounds such as Ro 60-0175, MK212, and WAY-163909 reduce self-administration of cocaine, ethanol, and nicotine (Grottick *et al*, 2000, 2001; Higgins and Fletcher, 2003; Cunningham *et al*, 2011), and reinstatement of cocaine seeking after a period of abstinence (Grottick *et al*, 2000; Fletcher *et al*, 2008; Niesewander and Acosta, 2007; Burbassi and Cervo, 2008; Cunningham *et al*, 2011). There are several commonalities between obesity and drug addiction: similar CNS circuitries mediate each behavior, both are outcomes of learned habits, which persist despite negative consequence, and both are heavily influenced by environmental stimuli (Volkow and Wise, 2005; Kenny, 2011). Indeed it has been proposed that obesity, or at least the behavior that may cause it, be recognized as a mental disorder and included in the upcoming DSM-V, with diagnostic criteria modeled on those identified for substance abuse (Volkow and O'Brien, 2007).

Nicotine dependence poses a significant global health burden, and identification of new pharmacotherapies to treat this condition is considered a major medical need particularly given the extremely favorable benefit-to-risk ratio after smoking cessation (Henningfield *et al*, 2009). Accordingly, given the clinical efficacy of lorcaserin in obesity and the observation that Ro 60-0175 reduces nicotine self-administration (Grottick *et al*, 2001), we investigated the effects of lorcaserin on nicotine self-administration and reinstatement of nicotine-seeking after extinction. These experiments were complemented by an assessment of the effects of lorcaserin on nicotine-induced hyperactivity, and on the subjective effects of nicotine measured in a drug discrimination procedure. Also because of positive associations between nicotine dependence and behavioral disinhibition, a process, which may promote continued nicotine seeking (Bickel *et al*, 1999; Fields *et al*, 2009), we examined the effect of lorcaserin on impulsive behavior induced by nicotine in the five-choice serial reaction time task (5-CSRTT; Robbins, 2002).

However, as lorcaserin has been developed to treat obesity, and preclinical information on this drug is limited, we first established its effects on food-motivated behaviors. This was achieved by examining the effects of lorcaserin on feeding induced by deprivation and palatability. The palatability test included a measurement of the behavioral satiety sequence (BSS) to examine the behavioral specificity of lorcaserin's effect on feeding (see Rodgers *et al*, 2010 for a recent review). Additional tests examined the effect of lorcaserin on operant responding for food under an identical schedule of reinforcement to that used for nicotine. Together these experiments represent a comparison between the effect of lorcaserin against nicotine and food-motivated behaviors.

## MATERIALS AND METHODS

Experiments were conducted at the InterVivo Solutions test facility, except the nicotine self-administration, reinstatement and five-choice serial reaction time experiments, which were conducted at the Centre for Addiction and Mental Health, Toronto, Canada. All experiments complied with the appropriate local and CCAC guidelines relating to animal experimentation.

### Animals and Housing

Adult male Sprague–Dawley rats were used in all studies, except nicotine self-administration, reinstatement, and 5-CSRTT experiments, which used adult male Long–Evans rats (source: Charles River, St Constant, QC, Canada). Animals were housed in polycarbonate cages with sawdust bedding. Water was freely available; food availability varied as described below. Housing was maintained at a constant temperature of $22 \pm 2\,^{\circ}C$, under a 12-h light–dark cycle (lights on at 0600–1800 hours; InterVivo Solutions; 0700–1900 hours; CAMH). All testing was conducted during the light phase of the light/dark cycle except self-administration studies, which were run during the dark phase.

### Drugs and Injections

Lorcaserin (source NPS Pharmaceuticals, Toronto, Canada) was prepared in 0.9% saline solution and administered subcutaneously. SB-242084 (source Sigma-Aldrich, Oakville, Canada) was prepared in 0.9% saline solution containing 8% hydroxypropyl-$\beta$-cyclodextrin and 25 mM citric acid. SB-242084 was injected by the intraperitoneal (IP) route. Nicotine bitartrate dihydrate (source: Toronto Research

Chemicals) was dissolved in 0.9% saline. All doses are expressed as that of base, dose volume 1 ml/kg. For self-administration studies nicotine solutions (nicotine bitartrate; Sigma-Aldrich) were prepared fresh each day, dissolved in sterile saline, adjusted to pH 7, and filtered prior to use.

### Tests of Food Intake

The effect of lorcaserin was examined in two separate groups of rats: one trained to consume their food within a 2-h period each day, that is, deprivation assay, and a second non-food-deprived group trained to consume a sweetened wet mash in 1 h each day.

In the deprivation cohort, 12 rats consumed their daily food ration in their home cage in 2 h. During this period, each rat had access to approximately 40 g of chow, and intakes stabilized after 14 days. In the palatability-induced feeding cohort, 12 rats had *ad-lib* access to standard lab chow and water, but in addition were given access to food in a sweetened mash form (100 g chow + 100 ml water + 3 g sugar) in a distinct test chamber for 1 h each day. Food intakes stabilized in a subgroup of nine rats after 21 days. The effect of lorcaserin (0.3–3 mg/kg, SC) on food consumed was assessed using a repeated-measures design with 2–3 days between each treatment cycle. Intakes were corrected for spillage.

In the palatability-induced feeding cohort, on test days the animals were behaviorally assessed every 30 s over the 1-h test. The animals were monitored remotely by a video camera and behavior was scored by the observer for the occurrence of one of four mutually exclusive behaviors (eating/drinking, grooming, active, resting). Behavior was scored in $12 \times 5$-min time bins and the frequency of each behavior within each bin was calculated to determine a temporal frequency of each measure (Rodgers *et al*, 2010).

### Food Maintained Responding

Twenty-four singly housed male Sprague–Dawley rats were initially food-restricted by presentation of 18–20 g of food at the end of the day. After a 2- to 3-day acclimatization to the food restriction, they were trained daily to lever press for food (45 mg Bioserve pellet) in standard operant conditioning chambers controlled by the Med-PC software over a period of 1 week (Med. Associates, St. Albans, VT). The rats received 18 g of food in their home cage at the end of the day.

After acquisition of the lever press response, 12 rats were trained to lever press for food, with schedule requirements gradually increased from FR1 to FR5, with a 20-s time-out period after each reinforcement, during which lever presses were recorded but had no programmed consequences, that is, FR5TO20s. A 20-s light and 2-s tone combination accompanied the delivery of each food pellet. Session duration was 60 min. Once the animals reached asymptotic levels of performance (approximately 3 weeks daily training), drug testing began. Number of food pellets earned, both active and inactive lever presses, and timeout responses were recorded.

The second group of 12 rats were trained to respond for food on a single lever under a progressive ratio (PR) schedule in which the number of responses required to obtain a food pellet increased for successive reinforcers (progression 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178 etc. derived from the equation: Ratio = $(5 \times e^{(0.2 \times \text{reinforcer no.})} - 5)$). The breakpoint was reached when the rat failed to earn a food pellet in 20 min. Drug testing began once individual breakpoints did not vary by $>15\%$ over three consecutive sessions, which required approximately 4 weeks daily training. The number of food pellets earned was the primary measure of breakpoint.

For both experiments, all rats received a vehicle or lorcaserin (0.3–1 mg/kg, SC), or lorcaserin (1 mg/kg) + SB-242084 (0.5 mg/kg, IP), according to a randomized design. A 2- to 3-day interval was used between each cycle, during which the animals continued to be run daily.

### Locomotor Activity and Rotorod Testing

The methods were essentially as described by Grottick *et al* (2001). In an initial experiment (Experiment 3), a group of eight rats were first administered sham vehicle injections and two habituation sessions to the test apparatus (17″ W × 17″ L × 12″ H) before testing the effect of lorcaserin (0.1–3 mg/kg, SC; 10-min pretreatment) on locomotor activity for 90 min. A repeated-measures design was used, with a washout period of 2–3 days between each treatment cycle. Total distance travelled and rearing counts were the primary dependent variables, which were measured by beam breaks.

To examine the interaction between lorcaserin and nicotine on motor activity, two separate groups of rats (Experiments 4a and b) were first sensitized to nicotine by 10 consecutive daily nicotine injections (0.4 mg/kg, SC) administered in the home cage. Rats were habituated to the test chambers on two occasions prior to testing and continued to receive nicotine injections between treatment days, which were at 2- to 3-day intervals.

After habituation and nicotine sensitization, the effects of lorcaserin (0.1–1 mg/kg, SC) against nicotine (0.4 mg/kg, SC)-induced hyperactivity were assessed in 12 rats (Experiment 4a). Rats were administered vehicle or combinations of nicotine and lorcaserin in a pseudo-random design. Lorcaserin or vehicle was administered 5 min before nicotine, which was administered 10 min before test. In Experiment 4b, 13 nicotine-sensitized rats received combinations of nicotine (0.4 mg/kg, SC) and lorcaserin (0.6 mg/kg, SC), and/or SB-242084 (0.5 mg/kg, IP), in a four-cycle design. Two vehicle only treatment cycles were included prior to (V1) and after (V2) the four-cycle study to determine vehicle baseline activity at the start and completion of this study.

The rotorod methods were similar to Grottick *et al* (2000) except an accelerating (4–40 r.p.m.) condition was included. The cut-off time for the fixed-speed condition was 120 s.

### Nicotine Self-Administration and Reinstatement Procedures

Testing was conducted in standard operant conditioning chambers (Med. Associates) as described by Fletcher *et al* (2008).

Rats were maintained at ~85% of free feeding body weight. After a brief period of food magazine training, a catheter was implanted into the right jugular vein of each rat while under ketamine and xylazine anesthesia. Initially rats were trained to self-administer nicotine (0.03 mg/kg per infusion) on an FR1 schedule. Each infusion (2-s duration) was accompanied by a compound conditioned stimulus (CS) consisting of a 2-s tone and 20-s stimulus light/20-s offset house-light. After 5 days on the FR1 schedule, schedule requirements were increased to FR2 (4 days) and then FR5 until stable responding was reached (29 days).

Twelve rats were used to test the effect of varying doses of lorcaserin on nicotine self-administration according to a repeated-measures design, with each animal receiving each dose and the vehicle in a counterbalanced sequence, with 2–4 days between cycles (Experiment 5a). After a washout period of 1 week, the same rats entered a second experiment where they received combinations of vehicle or lorcaserin (1 mg/kg, SC) and vehicle or SB-242084 (0.5 mg/kg, IP) in a $2 \times 2$ design (Experiment 5b), with identical washout interval.

For tests of nicotine reinstatement, 12 rats were trained to self-administer nicotine under identical conditions as above. These rats had 5 sessions at FR1, 4 sessions at FR2, and 18 sessions at FR5. Subsequently extinction sessions occurred, with responding on the previously active lever having no programmed consequence. After 18 sessions responding was less than 15 on the previously active lever. Reinstatement testing then began. During reinstatement sessions rats received both a non-response-contingent, experimenter-administered injection of nicotine (0.15 mg/kg, SC) and a response-contingent delivery of the previously associated nicotine-paired conditioned stimulus (ie, light + tone CS) on an FR1 schedule. In an initial experiment (Experiment 6a) each animal received each lorcaserin dose and vehicle in a counterbalanced sequence, with a 2- to 4-day interval between each cycle. After a washout period of 1 week, the same rats entered a second experiment where they received combinations of vehicle or lorcaserin (1 mg/kg, SC) and vehicle or SB-242084 (0.5 mg/kg, IP) in a four-cycle $2 \times 2$ design (Experiment 6b) with identical washout interval.

After a further week washout, in eight of these animals, the ability of lorcaserin (1 mg/kg, SC) to reinstate nicotine self-administration behavior was examined. Three test conditions were run in a counterbalanced sequence with a 2- to 4-day interval between each: lorcaserin (1 mg/kg, SC), saline, and exposure to the nicotine prime and response-contingent light + tone CS (Experiment 7).

### Nicotine Drug Discrimination Procedures

Twelve male Sprague–Dawley rats were food-restricted, following which they were trained to lever press for food to an FR10 value as described previously (see food responding procedure). Subsequently discrimination training began to a nicotine training dose of 0.3 mg/kg using standard techniques, for example, Recker and Higgins (2002). Training sessions lasted 30 min or until the delivery of 50 pellets and continued until the animals attained appropriate stimulus control (defined as six consecutive sessions where animals made no more than 16 lever presses before the delivery of the first reward and at least 95% total responses on the appropriate lever).

Drug testing was conducted on Tuesdays and Fridays, subject to appropriate performance on intervening days. On test days, both levers were designated active, that is, every tenth response on either lever resulted in delivery of a food pellet. Test sessions continued until 50 pellets had been obtained or 60 min had elapsed. During these sessions response rate was also measured.

### Five-Choice Serial Reaction Time Test Procedure

Ten male, adult Long–Evans rats were maintained on 18–20 g lab chow per day and trained on the five-choice serial reaction time test using procedures described in detail previously (Fletcher *et al*, 2007). Rats were trained until they were responding at 80% accuracy ((correct/correct + incorrect)*100%), with fewer than 20% omissions to final test conditions of stimulus duration 1 s, limited hold 5 s, and inter-trial interval 5 s. Incorrect responses, or failures to respond within 5 s, were followed by a 5-s time-out period before the next trial started. Responses (premature) occurring during the inter-trial interval led to a 5-s time-out period. Sessions lasted for 100 trials, or 30 min maximum. At asymptote, rats received five daily injections of nicotine (0.4 mg/kg, SC) in the home cage several hours after completion of that day's session. The effects of lorcaserin and nicotine were examined in a fully repeated-measures design, with all rats tested under every combination of lorcaserin (vehicle, 0.3 mg/kg, 1 mg/kg) and nicotine (vehicle, 0.3 mg/kg nicotine) administered in a counterbalanced order at 72-h intervals.

### Statistical Analysis

All operant, food intake, and locomotor activity data were analyzed by one- or two-way, repeated-measures ANOVA (Statistica). In the event of a significant main effect, *post hoc* comparisons were performed with Tukey's test. BSS expression was measured over time and analyzed by dividing the 1-h continuous behavioral data into $4 \times 15$-min time bins and applying a two-factor, repeated-measures ANOVA (condition $\times$ time). BSS profiles were plotted using data from each 5-min time bin. The fixed-speed rotorod scores were analyzed by using the Kruskal–Wallis test for non-parametric data. In the event of a significant main effect, *post hoc* comparisons between drug and vehicle groups was made using Mann–Whitney *U*-test. In all cases the accepted level of significance was taken at $P < 0.05$.

## RESULTS

### Experiment 1: Effects of Lorcaserin on Deprivation- and Palatability-Induced Feeding

Lorcaserin (0.3–3 mg/kg, SC) produced a dose-related decrease in deprivation-induced ($F3, 33 = 66.0$; $P < 0.01$) and palatability-induced ($F3, 24 = 17.9$; $P < 0.01$) food intake. *Post hoc* testing showed that the threshold dose of lorcaserin to significantly reduce intakes in both tests was 1 mg/kg (see Figure 1a). There was no obvious difference in

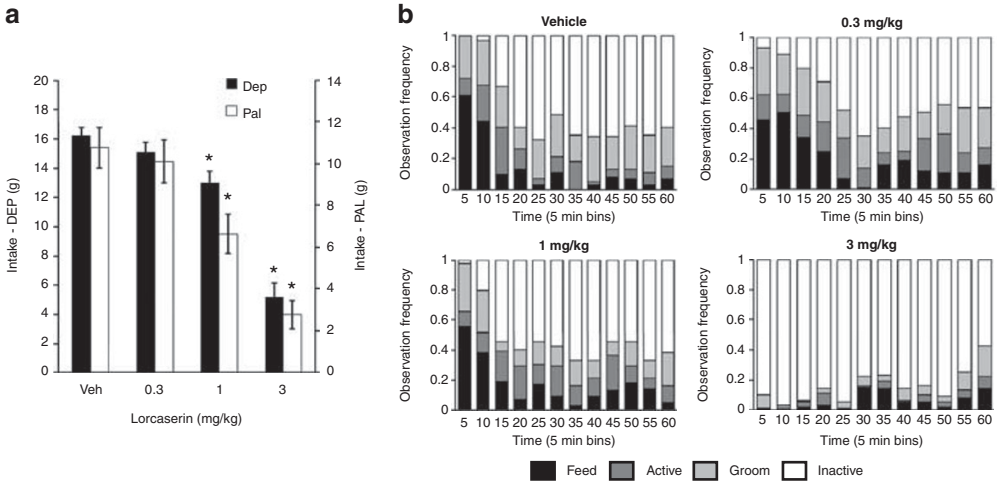


**Figure 1** (a) Amount of food consumed (measured in gram) after lorcaserin (0.3–3 mg/kg, SC) compared with vehicle pretreatment in rats trained to consume food over a limited access period under conditions of 22-h food deprivation, or palatability-induced feeding in non-deprived rats. $n = 9$ (palatability) to 12 (deprivation) rats per study. *$P < 0.05$ *vs* vehicle pretreatment (Tukey's test). Note the different *y*-axis scales to accommodate the different baseline intakes between tests. (b) Effect of lorcaserin (0.3–3 mg/kg) on the BSS measured during the palatability-induced feeding experiment. Note in the vehicle controls and the lorcaserin (0.3–1 mg/kg) groups, the predominant behaviors are feeding and active/grooming over the first 15–20 min, before 'inactive' predominates from 20–25 min onwards. At these doses, lorcaserin is therefore reducing food intake, with minimal effect on the BSS.

the magnitude of change in food intake produced by lorcaserin dose between each schedule.

The behaviors recorded during the palatability-induced feeding test are summarized in Figure 1b. In the vehicle-treated animals and animals treated with 0.3–1 mg/kg lorcaserin, both feeding and 'active' behaviors predominated during the early part of the test session before gradually transitioning 15–20 min into the session to 'inactive,' which became the primary behavior. Thus, at these doses of lorcaserin, the behavioral sequence was similar to the vehicle controls. At 3 mg/kg, lorcaserin completely suppressed both feeding and active behaviors throughout the test session, with 'inactive' predominant. Thus there was a main effect of treatment and a treatment × time interaction for both eating (treatment: $F3, 24 = 8.9$, $P < 0.01$; treatment × time: $F9, 72 = 4.6$, $P < 0.01$) and resting (treatment: $F3, 24 = 21.8$, $P < 0.01$; treatment × time: $F9, 72 = 4.6$, $P < 0.01$).

## Experiments 2a and b: Effects of Lorcaserin and SB-242084 on Operant Responding for Food

In rats trained to the FR5TO20s schedule, the animals typically received approximately 140 pellets, with an average of 1800 lever presses, including time-out responses. Lorcaserin (0.3–1 mg/kg, SC) produced a dose-related decline in responding and pellets earned, with the threshold for significance at 0.6 mg/kg ($F4, 44 = 7.1$, $P < 0.01$) (see Figure 2a). For the lever press measure, a main effect of treatment ($F4, 44 = 13.8$, $P < 0.01$) and the treatment × lever interaction ($F4, 44 = 14.4$, $P < 0.01$) reflected that lorcaserin selectively reduced the number of active lever presses. A separate analysis of time-out responses found a main effect of treatment ($F4, 44 = 10.9$, $P < 0.01$), with *post hoc* tests showing that lorcaserin (0.6–1 mg/kg) reduced this measure compared with the vehicle control (see Table 1). The effect of lorcaserin (1 mg/kg, SC) on all measures was blocked by pretreatment with SB-242084 (0.5 mg/kg, IP). In a separate experiment, SB-242084 (0.5 mg/kg, IP) had no effect on the number of food rewards earned compared with the vehicle control (vehicle: 140.6 ± 7.4 rewards; SB, 0.5: 132.7 ± 10.4 rewards, NS).

In animals trained to respond for food under a PR schedule, lorcaserin (0.3–1 mg/kg, SC) produced a dose-related decline in lever presses ($F4, 44 = 18.2$, $P < 0.01$) and breakpoint ($F4, 44 = 21.5$, $P < 0.01$). The threshold lorcaserin dose for significance was 0.6 mg/kg, SC (see Figure 2b and Table 1). The effect of lorcaserin (1 mg/kg, SC) on both measures was reversed by SB-242084 (0.5 mg/kg, IP). In a separate experiment, SB-242084 (0.5 mg/kg, IP) had no effect on breakpoint or lever presses compared with the vehicle control when tested alone (eg, breakpoint: vehicle, 11.2 ± 0.8; SB, 0.5: 10.6 ± 0.9, NS).

## Experiments 3a and b: Effects of Lorcaserin on Locomotor Activity and Rotorod Performance

Lorcaserin (0.1–3 mg/kg, SC) produced a dose-related decrease in total distance travelled ($F5, 35 = 8.4$, $P < 0.01$) and rearing counts ($F5, 35 = 4.3$, $P < 0.01$). *Post hoc* testing showed that the threshold dose of lorcaserin to reduce these measures was 1 and 3 mg/kg, respectively (see Table 2). The data were also collected into 10-min time bins. For the distance travelled measure there was a main effect of treatment ($F5, 35 = 8.4$, $P < 0.01$), time ($F8, 56 = 26.7$, $P < 0.01$), and a treatment × time interaction ($F40, 280 = 3.3$, $P < 0.01$), which generally reflected that lorcaserin reduced activity primarily at the earlier time points when vehicle baseline activity was highest (data not shown).

In animals previously trained to perform the rotorod test, lorcaserin (0.3–1 mg/kg) had no effect on performance when tested under two speeds in a fixed-speed paradigm,

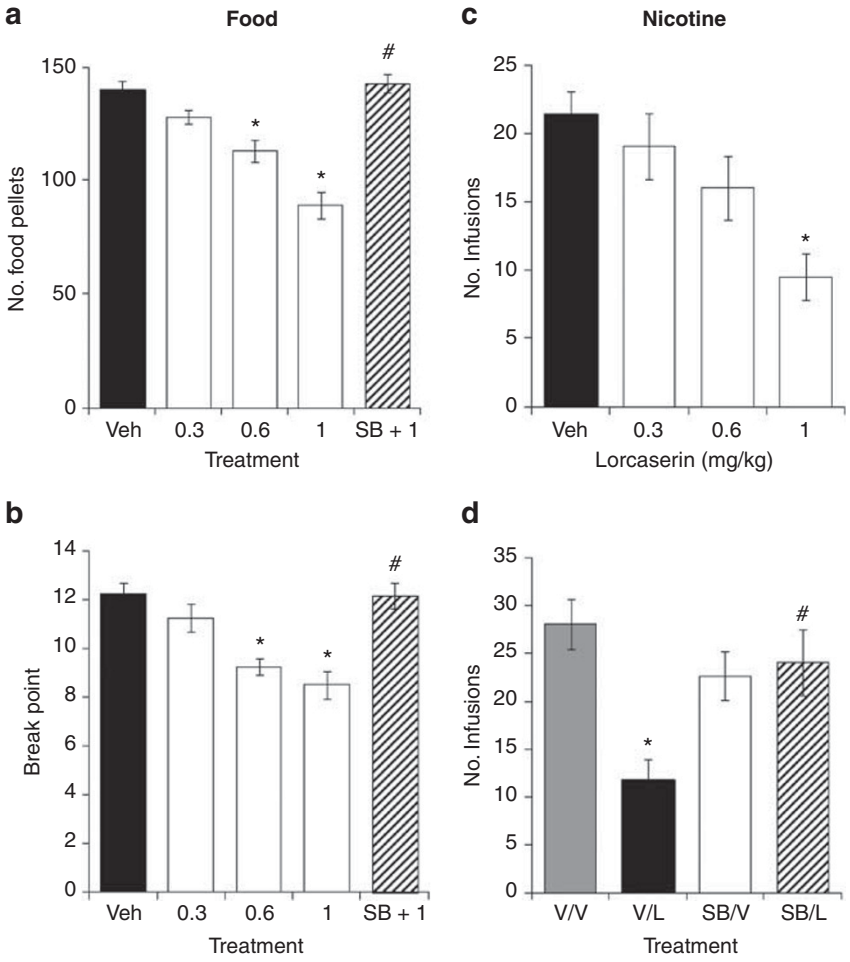


**Figure 2** Effect of lorcaserin (0.3–1 mg/kg, SC) pretreatment on behaviors motivated by food (a, b) or nicotine (c, d) reinforcement. In rats trained to respond for food (45 mg Bioserve pellet) under an FR5TO20s schedule, lorcaserin (0.3–1 mg/kg, SC) produced a dose-related decrease in (a) the number of food pellets; the effect of 1 mg/kg lorcaserin was blocked by SB-242084 (0.5 mg/kg). $n = 12$ rats. (b) Equivalent doses of lorcaserin (0.3–1 mg/kg, SC) reduced breakpoint for food under a PR schedule of reinforcement. $n = 12$ rats. In rats trained to respond for nicotine (0.03 mg/infusion) under an FR5TO20s schedule, lorcaserin (0.3–1 mg/kg, SC) produced a dose-related decrease in (c) the number of nicotine infusions. $n = 12$ rats. (d) The effect of 1 mg/kg lorcaserin on nicotine self-administration was blocked by SB-242084 (0.5 mg/kg). In each study all rats received all treatments according to a randomized design. $^{*}P < 0.05$ *vs* vehicle pretreatment; $^{\#}P < 0.05$ *vs* lorcaserin pretreatment (Tukey's test).

**Table 1** Effect of Lorcaserin on Lever Press Measures in Rats Trained to Respond for Food or Nicotine Reinforcement

| | Lorcaserin (mg/kg, SC) | | | | |
|---|---|---|---|---|---|
| | **Vehicle** | **0.3** | **0.6** | **1** | **SB+1** |
| *Food maintained responding* | | | | | |
| Total active lever responses (FR5TO20s) | 1727 ± 206 | 1206 ± 131 | 930 ± 111* | 678 ± 102* | 2024 ± 301$^{\#}$ |
| Total inactive lever responses (FR5TO20s) | 22 ± 9 | 19 ± 5 | 10 ± 4 | 12 ± 8 | 33 ± 13 |
| Time-out responses (FR5TO20s) | 1025 ± 192 | 568 ± 124 | 367 ± 91* | 232 ± 77* | 1313 ± 289$^{\#}$ |
| Total lever presses (PR schedule) | 371 ± 35 | 296 ± 41 | 147 ± 13* | 144 ± 23* | 396 ± 56$^{\#}$ |
| *Nicotine maintained responding* | | | | | |
| Total active lever responses | 121 ± 12 | 112 ± 14 | 92 ± 12 | 55 ± 9* | NT |
| Total inactive lever responses | 15 ± 4 | 13 ± 4 | 8 ± 2 | 6 ± 2 | NT |

Responses are expressed as means ± SEM. $^{*}P < 0.05$ *vs* vehicle; $^{\#}P < 0.05$ *vs* lorcaserin 1 mg/kg (Tukey's test). NT, not tested. SB, SB-242084 (0.5 mg/kg). Food was made available under either an FR5TO20s or PR schedule. Nicotine was available under an FR5TO20s schedule, that is, identical to the equivalent food schedule (see Materials and Methods for more detail).

**Table 2** Effect of Lorcaserin on Measures of Locomotor Activity and Rotorod Performance

| | Lorcaserin (mg/kg, SC) | | | | | |
|---|---|---|---|---|---|---|
| | **Vehicle** | **0.1** | **0.3** | **0.6** | **1** | **3** |
| *Locomotor activity* | | | | | | |
| Distance travelled | 3260 ± 677 | 3490 ± 757 | 2342 ± 446 | 1930 ± 544 | 1609 ± 334* | 759 ± 211* |
| Rearing | 107 ± 24 | 111 ± 27 | 70 ± 16 | 63 ± 15 | 56 ± 12 | 35 ± 14* |
| Ambulatory episodes | 159 ± 28 | 167 ± 32 | 120 ± 21 | 101 ± 28 | 87 ± 18 | 41 ± 11* |
| *Rotorod* | | | | | | |
| Fixed (8 r.p.m.) | 120 (120–120) | NT | 120 (120–120) | 120 (120–120) | 120 (120–120) | 72 (21–120) |
| Fixed (16 r.p.m.) | 120 (120–120) | NT | 120 (96–120) | 120 (120–120) | 120 (99–120) | 23 (9–33)* |
| Accelerating (4–40 r.p.m.) | 136 ± 16 | NT | 129 ± 6 | 164 ± 25 | 113 ± 12 | 30 ± 11* |

Distance travelled is in units of centimeter. Eight rats, with each animal receiving each treatment in a randomized schedule. Rotorod measures are in seconds. Both fixed-speed tests had a maximal cut-off time of 120 s; the accelerating speed test had no cut-off time. NT, not tested. Data are presented as mean ± SEM, except fixed-speed rotorod where data are presented as median and interquartile range. *$P<0.05$ compared with vehicle treatment (Tukey's test), except fixed-speed rotorod (Mann–Whitney *U*-test).

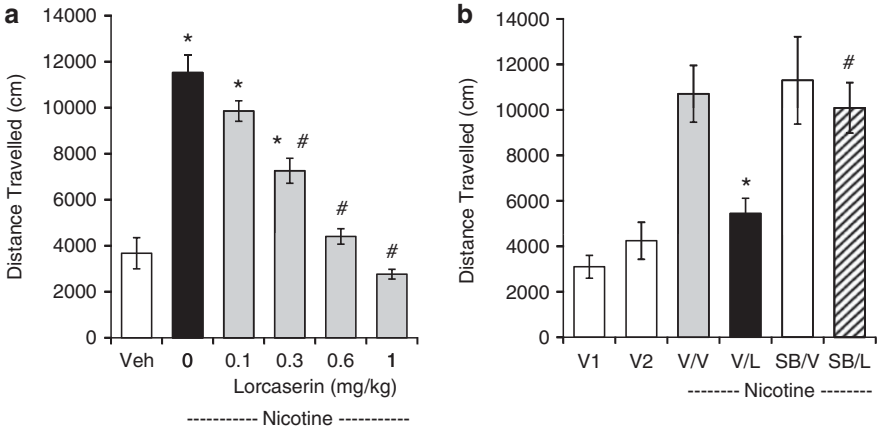


**Figure 3** (a) Effect of lorcaserin (0.1–1 mg/kg, SC) pretreatment against a nicotine (0.4 mg/kg, SC)-induced hyperactivity. Twelve rats, with each rat receiving all treatments according to a randomized design. *$P<0.05$ *vs* vehicle/vehicle; $^{\#}P<0.05$ *vs* vehicle/nicotine (Tukey's test). (b) Effect of SB-242084 (0.5 mg/kg, IP) against the suppressant effect of lorcaserin (0.6 mg/kg, SC) against a nicotine (0.4 mg/kg, SC)-induced hyperactivity. Thirteen rats, with each rat receiving all treatments according to a randomized design. *$P<0.05$ *vs* vehicle/cocaine treatment; $^{\#}P<0.05$ *vs* lorcaserin 1 mg/kg/nicotine treatment (Tukey's test). V1 and V2 represent vehicle-only (no nicotine) pretreatment, V1 prior to main experimental study and V2 immediately after study.

and also under an accelerating speed design (see Table 2). A decline in performance was evident at the 3-mg/kg dose.

### Experiments 4a and b: Effects of Lorcaserin and SB-242084 on Nicotine-Induced Increase in Locomotor Activity

Lorcaserin (0.1–1 mg/kg) produced a dose-related inhibition of nicotine-induced hyperactivity (see Figure 3a). *Post hoc* analysis after significant one-way ANOVA ($F5, 55 = 25.9$, $P<0.01$) revealed that nicotine (0.4 mg/kg, SC) significantly increased total locomotor counts over the 90-min test session compared with the vehicle-pretreated controls. Lorcaserin produced a dose-related inhibition of nicotine-induced hyperactivity, with a threshold dose of 0.3 mg/kg, SC.

In Experiment 4b, analysis of the lorcaserin/SB/nicotine interaction data revealed a main effect of lorcaserin ($F1, 12 = 10.9$, $P<0.01$), SB-242084 ($F1, 12 = 6.2$, $P<0.05$), and a significant lorcaserin × SB interaction ($F1, 12 = 6.2$, $P<0.05$). Thus the inhibition of nicotine hyperactivity produced by lorcaserin (0.6 mg/kg) was completely blocked by SB-242084 (0.5 mg/kg). SB-242084 alone had no effect on the nicotine-induced hyperactivity (see Figure 3b). Comparison of vehicle-only pretreatment assessed prior to and after the lorcaserin/SB-242084 interaction experiment failed to show any difference ($t(12) = 2.1$, NS), indicating that no significant baseline change in locomotor activity developed during the course of this study.

### Experiments 5a and b: Effects of Lorcaserin and SB-242084 on Nicotine Self-Administration

Lorcaserin (0.3–1 mg/kg, SC) produced a dose-related suppression of the number of responses made ($F3, 33 = 7.5$, $P<0.01$) and the number of nicotine infusions earned

($F3, 33 = 9.0$, $P < 0.01$) under an FR5TO20s schedule. Significant reductions in nicotine infusions were recorded at the 1 mg/kg dose compared with the vehicle control (see Figure 2c). The effect of lorcaserin on the total number of active and inactive lever presses is presented in Table 2. In Experiment 5b, again a significant main effect of lorcaserin was found ($F1, 7 = 7.5$, $P < 0.05$) and a significant lorcaserin/SB-242084 interaction ($F1, 7 = 9.0$, $P < 0.05$), reflecting the fact that SB-242084 (0.5 mg/kg) pretreatment blocked the suppressant effect of lorcaserin (1 mg/kg, SC) on the number of nicotine infusions earned (see Figure 2d). SB-242084 alone had no effect on nicotine self-administration.

### Experiments 6a and b: Effects of Lorcaserin and SB-242084 on Reinstatement of Nicotine Seeking

During the self-administration phase, responding on the active lever was significantly higher than on the inactive lever ($F1, 7 = 56.8$, $P < 0.001$) and increased over sessions with increasing response ratio ($F27, 189 = 9.3$, $P < 0.001$). Rats took on average $476.4 \pm 43.6$ infusions across the whole self-administration phase (total 27 sessions); the average daily number of infusions for the last 7 days of self-administration was $17.4 \pm 2.3$ infusions. During the extinction phase (18 sessions) responding rapidly declined over sessions ($F17, 136 = 12.5$, $P < 0.001$) and was consistently below 15 responses per session on average before reinstatement testing started.

After extinction, reinstatement of nicotine-seeking behavior was reliably induced by presentation of a compound cue comprising a nicotine prime injection (0.15 mg/kg) and the response-contingent presentation of the light + tone CS previously paired with nicotine infusion. Thus lever pressing on the nicotine-associated lever increased from approximately $12 \pm 2$ responses to $74 \pm 9$ responses, with minimal change on the inactive lever (Figure 4a). In Experiment 6a, the effect of lorcaserin was examined against the nicotine prime and cue-induced reinstatement. A significant main effect of treatment (0.3–1 mg/kg) on the number of active lever presses ($F2, 16 = 21.6$, $P < 0.01$) showed that lorcaserin reduced this measure at both doses.

In an experiment investigating the interaction between lorcaserin and SB-242084, a significant main effect of lorcaserin ($F1, 8 = 28.7$, $P < 0.01$) and a significant lorcaserin × SB-242084 interaction ($F1, 8 = 11.4$, $P < 0.01$) showed that SB-242084 pretreatment prevented the lorcaserin decrease in the reinstatement of nicotine seeking (Figure 4b).

### Experiment 7: Effects of Lorcaserin to Reinstate Responding for Nicotine

After a further washout period of 1 week, an acute administration of either saline or lorcaserin (1 mg/kg, SC) failed to reinstate nicotine seeking (Figure 4c). In the same experiment the effect of the nicotine prime plus CS cue to reinstate responding was also measured. Presentation of nicotine plus the CS increased responding from $13 \pm 2$ to $61 \pm 5$ lever presses, confirming that nicotine-seeking behavior could still be elicited in these animals. The magnitude of this increase was similar to that seen in Experiments 6a and b, suggesting that there was no decline in the reinstatement of nicotine-seeking behavior over the course of these studies.

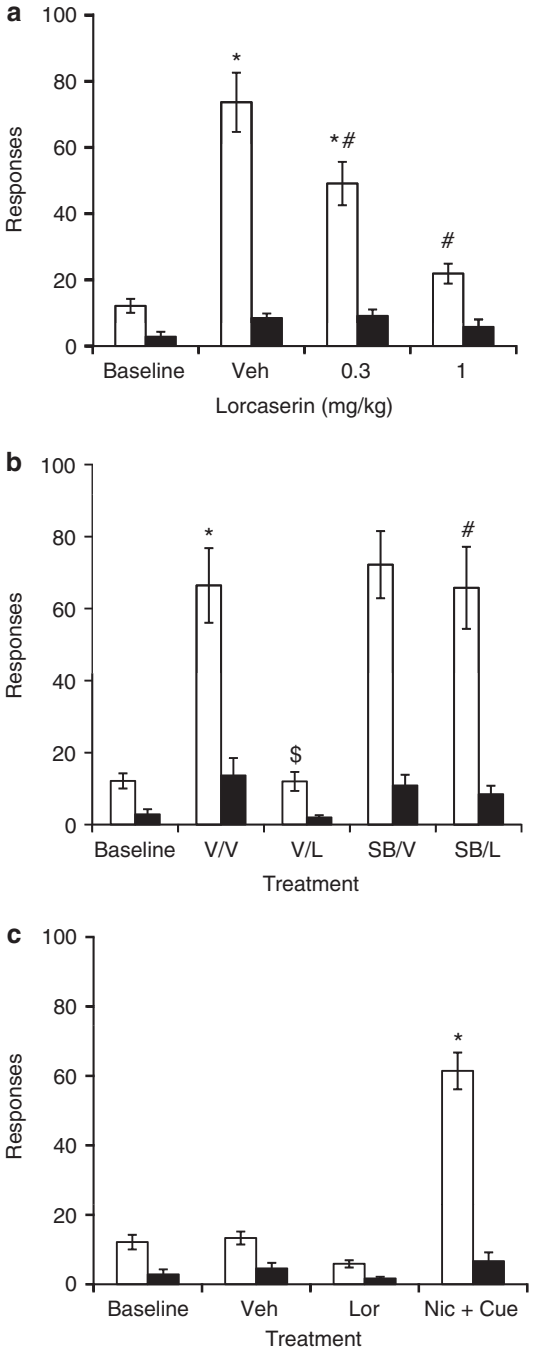


**Figure 4** (a) Effect of lorcaserin (0.3–1 mg/kg, SC) on reinstatement of nicotine-seeking behavior after a period of extinction training (see Materials and Methods for further detail). Twelve rats, with each receiving all treatments according to a randomized design. $^{*}P < 0.05$ *vs* baseline, that is, reinstatement; $^{\#}P < 0.05$ *vs* vehicle (Tukey's test). (b) Interaction between SB-242084 (0.5 mg/kg, IP) and lorcaserin (1 mg/kg, SC) against nicotine-induced reinstatement. Twelve rats, with each rat receiving all treatments according to a randomized design. $^{*}P < 0.05$ *vs* baseline; $^{\$}P < 0.05$ *vs* vehicle/vehicle pretreatment; $^{\#}P < 0.05$ *vs* vehicle/lorcaserin 1-mg/kg treatment (Tukey's test). (c) Effect of lorcaserin (1 mg/kg, SC) to reinstate nicotine-seeking behavior. Eight rats, with each receiving all treatments according to a randomized design. $^{*}P < 0.05$ *vs* baseline (Tukey's test).

### Experiment 8: Generalization Test of Lorcaserin to a Nicotine Discrimination

Appropriate stimulus control was attained with all rats treated with nicotine (0.3 mg/kg, SC) by approximately 25–30 training sessions. At a 0.3-mg/kg SC dose, nicotine evoked 95.7 ± 2.5% responding to the nicotine-associated lever, with minimal effect on response rate relative to the vehicle control (see Figure 5a). Lorcaserin (0.3–3 mg/kg, SC) administered 10 min prior to testing elicited predominantly (>85%) vehicle lever responding, that is, ⩽15% nicotine appropriate responding. Lorcaserin did reduce response rate ($F4, 35 = 18.5$, $P < 0.01$), with a significant decline relative to the vehicle at doses of 0.6 mg/kg and above (see Figure 5b).

### Experiment 9: Effect of Lorcaserin on Nicotine Discrimination

Based on results from Experiment 8, lorcaserin doses of 0.3 and 0.6 mg/kg were selected to study the interaction with the nicotine discriminative stimulus. Nicotine produced a dose-related generalization over the dose range 0.03–0.3 mg/kg (Figure 5c). Lorcaserin at 0.3, and notably at 0.6 mg/kg, produced an inhibition of the nicotine stimulus. For example, at the 0.6-mg/kg dose, lorcaserin reduced the nicotine (0.3 mg/kg, SC) stimulus from 98.3 ± 0.6 to 44.1 ± 13.2% ($P < 0.01$) (see Figure 5c). Nicotine had no overall effect on response rate, although lorcaserin significantly reduced this measure ($F2, 81 = 34.9$, $P < 0.01$). There was no lorcaserin × nicotine interaction on rate of response ($F6, 81 = 0.2$, NS) (Figure 5d).

### Experiment 10: Effect of Lorcaserin and Nicotine on Five-Choice Serial Reaction Time Test Performance

Ten rats entered the study but one rat pretreated with lorcaserin (1 mg/kg) completed 12 or fewer trials under both the vehicle and the nicotine condition, and so was removed from all analyses. A summary of trials completed,

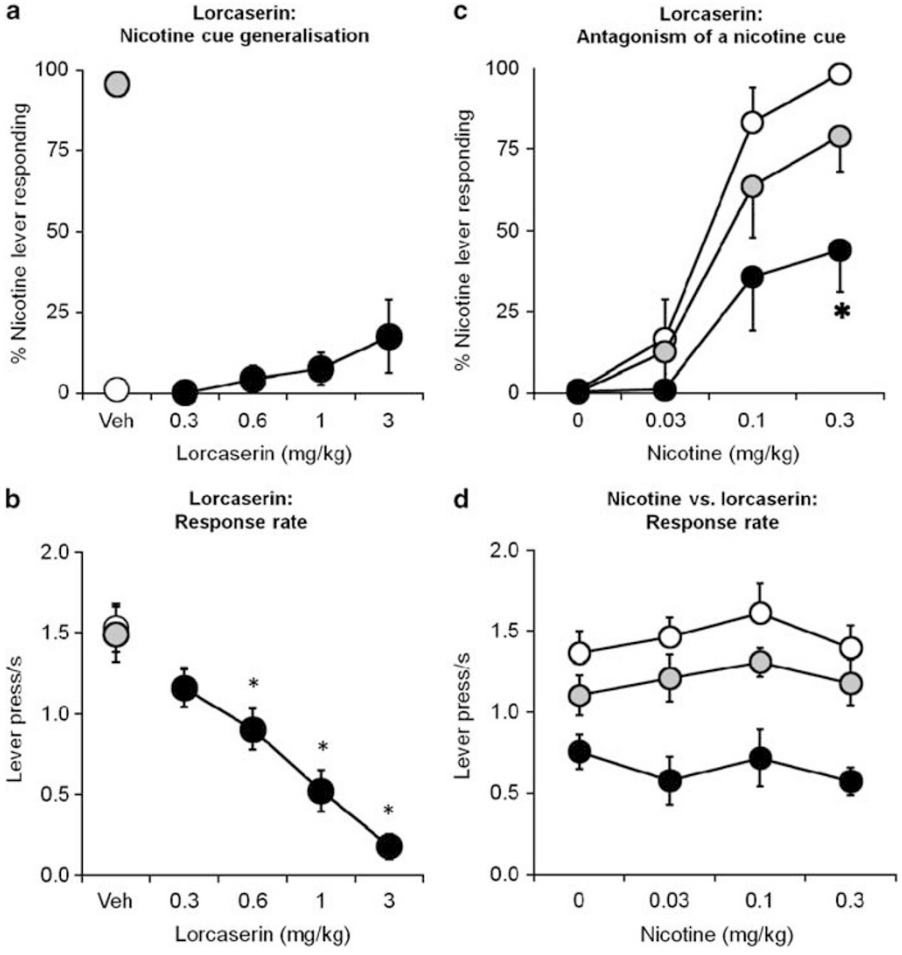


**Figure 5** (a) Effect of lorcaserin to substitute for a nicotine (0.3 mg/kg, SC) cue in a two-lever food reinforced discrimination procedure. In this experiment, rats treated with nicotine (0.3 mg/kg, SC) (●) responded with 95.7 ± 2.5% generalization and vehicle (○) with 1.1 ± 0.8% generalization. Data are presented as % nicotine lever responding. (b) Effect of lorcaserin on response rate from same study as in panel a. Data are expressed as number of responses(s). *$P < 0.05$ *vs* the vehicle group (Tukey's test). (c) Effect of lorcaserin at a dose of 0.3 mg/kg (●), 0.6 mg/kg (◐), or vehicle (○) pretreatment prior to nicotine (0.03–0.3 mg/kg, SC). Data are presented as % nicotine lever responding. *$P < 0.05$ *vs* vehicle/nicotine (Tukey's test). (d) Effect of lorcaserin and nicotine combinations on response rate from same study as in panel c. Data are expressed as number of responses(s). Both lorcaserin/nicotine groups were significantly different to vehicle/nicotine (see relevant results section). All data are presented as means ± SEM.

accuracy, response latencies, and anticipatory responses for the remaining nine rats is presented in Figure 6 and Table 3.

The main effects of lorcaserin on omissions ($F2, 16 = 12.4$, $P < 0.01$), correct latency ($F2, 16 = 12.1$, $P < 0.01$), and magazine latency ($F2, 16 = 10.5$, $P < 0.01$), but not percent correct ($F2, 16 = 2.6$, NS), reflected that lorcaserin (1 mg/kg) slowed response speed and increased the proportion of missed trials without affecting accuracy. No main effect of nicotine or nicotine × lorcaserin interaction was seen on these measures. In contrast on premature responding, both a main effect of nicotine ($F1, 8 = 8.3$, $P < 0.05$), lorcaserin ($F2, 16 = 31.2$, $P < 0.01$), and a borderline nicotine × lorcaserin interaction ($F2, 16 = 3.5$, $P = 0.056$) reflected that lorcaserin (0.3–1 mg/kg) reduced this measure relative to vehicle baseline. *Post hoc* tests confirmed that both doses blocked the nicotine-induced increase in premature responses (see Figure 6).

## DISCUSSION

The primary finding of these studies is that the selective 5-HT$_{2C}$ receptor agonist lorcaserin reduced the stimulant, discriminative stimulus, and reinforcing properties of nicotine, as well as reinstatement of nicotine seeking, at doses that affected feeding behavior. Lorcaserin also reduced a measure of nicotine-induced impulsive action. While the effects on feeding behavior are consistent with the development of this drug as a treatment for obesity (Smith *et al*, 2009, 2010; Fidler *et al*, 2011), the effects on nicotine-related behaviors indicate an additional therapeutic potential for treating nicotine dependence. The primary pharmacological property of lorcaserin is 5-HT$_{2C}$ receptor activation (Thomsen *et al*, 2008; Fletcher *et al*, 2009a, b), and the demonstration that its effects on food- and nicotine-related behaviors were blocked by the selective 5-HT$_{2C}$ antagonist SB-242084 (Kennett *et al*, 1997) confirms this mechanism of action.

Despite its clinical status, there have been relatively few preclinical reports detailing the effect of lorcaserin in feeding tests, these being essentially limited to a study of cumulative food intake measured over 24 h, and 28-day studies in normal and DIO Levin rats (Smith *et al*, 2008; Thomsen *et al*, 2008). The present studies extend this work by showing that lorcaserin reduced schedule-controlled responding for food under both PR and FR5 schedules, as well as feeding induced by palatability and 22 h food deprivation. The effective dose range of lorcaserin in the present studies was consistent across all of these test situations and considerably lower than described in previous reports. This is likely reflective of the route of drug administration (SC *vs* oral) and the duration of the test period: 1–2 h in the present studies compared with 24-h intake in prior studies, which necessitate a longer period of receptor occupancy. Thus the current feeding studies were important for comparison with the effects of lorcaserin on nicotine discrimination, reinforcement, and reinstatement, which were run over similarly short test periods.

The outcomes from the feeding experiments suggest a behaviorally specific anorectic action of lorcaserin. For example, the motivation to work for food reinforcement assessed by breakpoint on a PR schedule of availability, or

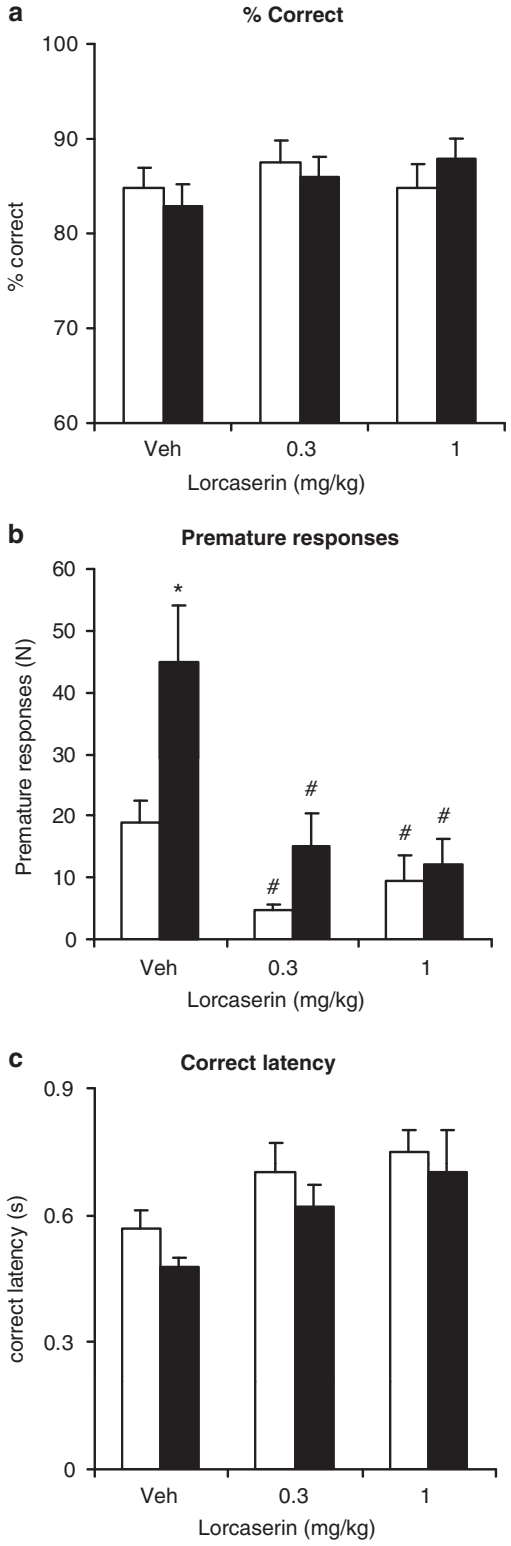


**Figure 6** Interaction between nicotine and lorcaserin on performance of rats in the 5-CSRTT. (□) Vehicle, (■) nicotine 0.3 mg/kg, SC. (a) Percent correct, (b) number of premature responses, (c) correct latency. Data are presented as means ± SEM. $n = 9$ rats. $^{*}P < 0.05$ *vs* vehicle control; $^{\#}P < 0.05$ *vs* the respective vehicle/vehicle or vehicle/nicotine control group (Tukey's test).

**Table 3** Effect of Lorcaserin and Nicotine on Various Performance Measures from the 5-CSRTT

| | | No. trials | No. omissions | % omissions | No. correct | No. incorrect | Magazine latency |
|---|---|---|---|---|---|---|---|
| Vehicle | Vehicle | 100 ± 0 | 2.2 ± 0.6 | 2.2 ± 0.6 | 82.8 ± 2.5 | 15.0 ± 2.1 | 1.81 ± 0.16 |
| Vehicle | Nicotine (0.3 mg/kg) | 96.7 ± 3.3 | 2.3 ± 0.7 | 2.4 ± 0.7 | 78.1 ± 3.7 | 16.2 ± 2.4 | 1.57 ± 0.12 |
| Lorcaserin (0.3 mg/kg) | Vehicle | 99.4 ± 0.6 | 6.4 ± 1.5 | 6.5 ± 1.5 | 78.9 ± 3.4 | 14.1 ± 2.3 | 2.17 ± 0.28 |
| Lorcaserin (0.3 mg/kg) | Nicotine (0.3 mg/kg) | 100 ± 0 | 1.6 ± 0.5 | 1.6 ± 0.5 | 84.3 ± 2.0 | 14.1 ± 1.9 | 1.92 ± 0.21 |
| Lorcaserin (1 mg/kg) | Vehicle | 82.2 ± 9.2 | 13.3 ± 2.9* | 19.1 ± 4.6* | 59.8 ± 8.6 | 9.1 ± 2.0 | 3.27 ± 0.66* |
| Lorcaserin (1 mg/kg) | Nicotine (0.3 mg/kg) | 82.1 ± 10.6 | 5.7 ± 1.6 | 12.7 ± 6.7 | 67.4 ± 10.1 | 9.0 ± 2.2 | 2.81 ± 0.53 |

Nine rats treated with each treatment combination. *$P < 0.05$ *vs* the respective vehicle/vehicle or vehicle/nicotine group (Tukey's test).

under the FR5 schedule, was reduced at lorcaserin doses with no significant effects on rotorod performance. Also the reduction in palatability-induced feeding at 1 mg/kg lorcaserin was associated with advancement of the BSS, further indicating a specificity to its anorectic effect (Rodgers *et al*, 2010). Similar findings have been reported for the 5-HT$_{2C}$ agonists Ro 60-0175 (Clifton *et al*, 2000; Hewitt *et al*, 2002) and VER23779 (Somerville *et al*, 2007). At 3 mg/kg, lorcaserin produced a more pronounced decrease in food intake, accompanied by an obvious disruption of the BSS, significant hypolocomotion, and impaired rotorod performance. This likely reflects the more generalized motor disruption that can be produced by 5-HT$_{2C}$ receptor agonists at higher doses (eg, Grottick *et al*, 2000).

Having established doses that reliably affected feeding behavior, the primary objective of this study was to examine the effect of equivalent doses of lorcaserin on nicotine-induced behaviors. Both nicotine-induced hyperactivity and self-administration were reduced by lorcaserin (0.3–1 mg/kg, SC) in an SB-242084 reversible manner. A notable feature of the results of experiments involving food and nicotine reinforcement was that lorcaserin elicited similar reductions in responding for both reinforcers despite markedly differing response rates. For example the response rate for food was approximately 10–15 times higher than the response rates for nicotine, yet at the 1-mg/kg dose lorcaserin reduced the number of reinforcers earned compared with the vehicle control by 36 ± 5% for food and 54 ± 7% for nicotine.

It is generally accepted that activation of nicotinic receptors, predominantly (but not exclusively) of the $\alpha_4\beta_2$ subtype, localized on multiple cell types within the VTA, is necessary for the stimulant and reinforcing effects of nicotine (eg, Reavill and Stolerman, 1990; Clarke *et al*, 1988; Corrigall *et al*, 1992, 1994), each being a result of nicotine eliciting a net shift toward excitation of the mesolimbic DA reward system (Mansvelder *et al*, 2002; Keath *et al*, 2007). Recent mapping studies detail a close overlap between nAchR and 5-HT$_{2C}$ receptors within VTA subregions (Zhao-Shea *et al*, 2011; Bubar and Cunningham, 2007) consistent with a potent inhibitory effect of systemically applied 5-HT$_{2C}$ agonists on nicotine-induced increases in VTA cell firing and terminal DA release (Pierucci *et al*, 2004; Di Matteo *et al*, 2004). Consequently the property of lorcaserin to attenuate both the stimulant and reinforcing effects of nicotine likely arises from activation of 5-HT$_{2C}$ receptors localized within the VTA. It has also been proposed that the nicotinic $\alpha_4\beta_2$ partial agonist varenicline (CHANTIX) reduces nicotine self-administration through a functional dampening of nicotine's stimulatory effects on mesolimbic DA function at the level of the VTA (Rollema *et al*, 2007).

An additional action of nicotine that was affected by lorcaserin was its discriminative stimulus property. Although lorcaserin did not engender nicotine appropriate responding, it did diminish the discriminative stimulus property of nicotine. Similar findings have been reported for other 5-HT$_{2C}$ receptor agonists, Ro 60-0175 and WAY-163909 (Quarta *et al*, 2007; Zaniewska *et al*, 2007), confirming that 5-HT$_{2C}$ receptor activation weakens the nicotine cue. In contrast to the stimulant and reinforcing effects, the contribution of DA mechanisms to the discriminative stimulus effects of nicotine is less clear (Corrigall and Coen, 1994; Desai *et al*, 2003; Smith and Stolerman, 2009), and neuroanatomically sites distinct to the mesolimbic DA pathway appear to contribute to the cue, with nicotine infusions into the prefrontal cortex producing the most reliable generalization of the sites examined (Miyata *et al*, 2002; Smith and Stolerman, 2009). Consequently these findings are of interest from two perspectives. First, they suggest an additional site beyond the VTA through which 5-HT$_{2C}$ agonists may influence the behavioral effects of nicotine, and there is accumulating evidence that 5-HT$_{2C}$ receptors localized within the frontal cortex may exert control over behaviors guided by other drugs of abuse (Filip and Cunningham, 2003; Pentkowski *et al*, 2011). Second, because drug discrimination is measured as a percentage of drug *vs* non-drug responding, it represents a rate-free measure. Thus the effect of lorcaserin (and other 5-HT$_{2C}$ agonists) to attenuate a nicotine cue is not confounded by the effect of these drugs on response rate.

While the stimulant, discriminative stimulus, and reinforcing effects of nicotine likely contribute to the clinical state of nicotine dependence, assessment of potential treatment effects ideally should also include some measure of relapse prevention (Henningfield *et al*, 2009). Nicotine dependence (tobacco smoking) is associated with high rates of relapse. For example, it is estimated that only 20% of patients attempting to quit will remain abstinent for over a month, decreasing to 3% for over a year (Hughes *et al*, 2004; Henningfield *et al*, 2009). The reinstatement model of drug relapse is a frequently used animal model of this condition, notwithstanding debate about its construct validity (Epstein *et al*, 2006; Shaham *et al*, 2003). Two main types of trigger for relapse in humans, and reinstatement in animals, are re-exposure to the drug and to cues associated

with drug-taking (Shaham *et al*, 2003). Given these two types of trigger and the multifactorial nature of cues associated with clinical nicotine dependence (Rose and Levin, 1991), we chose to use a compound cue in the present studies, comprising a nicotine prime and light–tone CS previously paired with nicotine infusion. Presentation of the nicotine prime plus cue stimulus reliably reinstated nicotine-seeking behavior, and lorcaserin significantly reduced this reinstatement at both the 0.3- and 1-mg/kg doses, in an SB-242084 reversible manner. Interestingly, varenicline has been recently reported to reduce reinstatement to a nicotine cue and prime similar to that used in the present study (O'Connor *et al*, 2010), and clinically it has proven efficacious both in the context of smoking cessation and relapse prevention (Gonzales *et al*, 2006; Tonstad *et al*, 2006).

Clinical studies support a strong positive association between nicotine dependence and impulsive behavior (eg, Bickel *et al*, 1999; Fields *et al*, 2009), although the relationship between these two features, that is, cause or consequence, seems presently unclear. Nevertheless, a deficit of inhibitory control can promote a vulnerability to continued drug usage and likelihood to relapse (Pattij and Vanderschuren, 2008; Winstanley *et al*, 2010). Like many abused substances, nicotine will promote indices of impulsive action and choice in rodents (Popke *et al*, 2000; Kolokotroni *et al*, 2011). For example, nicotine increases anticipatory (premature) responding in the 5-CSRTT (Stolerman *et al*, 2000; Grottick and Higgins, 2000), a measure of impulsive action, and conversely drug-naïve rats identified as 'impulsive' based on high premature response rates, subsequently showed enhanced motivation to self-administer nicotine compared with their 'less impulsive' counterparts (Diergaarde *et al*, 2008). In the present study, nicotine reliably increased premature responding and lorcaserin (0.3–1 mg/kg) significantly reduced this measure to baseline levels, without significantly disrupting a principal measure of choice accuracy (see also Quarta *et al*, 2007 with respect to Ro 60-0175). A feature of all 5-HT$_{2C}$ agonists tested to date is that premature responding as measured in the 5-CSRTT is particularly sensitive to modulation by this class (Quarta *et al*, 2007; Fletcher *et al*, 2007; Navarra *et al*, 2008; present study). The small effects of lorcaserin (1 mg/kg) to increase omissions and response latencies may be partially attributable to its anorectic effects as they are qualitatively similar to those seen after pre-feeding rats prior to the task (eg, Grottick and Higgins, 2000). Overall, the primary observation from this experiment is that lorcaserin reduced a measure of motor impulsivity elicited by nicotine, which in the context of the present studies, further supports its potential to treat nicotine dependence.

A potential complicating issue when interpreting the effects of selective 5-HT$_{2C}$ receptor agonists, for example, lorcaserin (present study), CP-809101 (Siuciak *et al*, 2007), and WAY-161505 (Hayes *et al*, 2009), on behavior is their inhibitory effects on motor function (Fletcher *et al*, 2009a, b; Halberstadt *et al*, 2009), coupled with the anorectic effect of these drugs when using food reinforced operant procedures. Therefore, a major issue in interpreting the effects on operant responding for food or nicotine, or in tests of reinstatement, is whether these just reflect motor impairment or sedation. Our results provide multiple examples that this is unlikely, at least over the effective dose range 0.3–1 mg/kg. First, lorcaserin-treated rats were not impaired on a forced motor task, the rotorod. Second, in the food-reinforced operant conditioning tasks, the response rates of lorcaserin-treated rats were 10 to 15-fold higher than in rats responding for nicotine. Therefore, an impaired capability to lever press cannot account for reduced responding in the self-administration and reinstatement experiments. Third, lorcaserin-treated rats performed consistently and accurately on the five-choice serial reaction time test, which involves a sustained series of rapid coordinated motor responses and cognitive processes (Robbins, 2002). On average, rats tested with lorcaserin responded to the light stimulus only marginally slower than under control conditions. Similarly the normal BSS was also retained in the palatability feeding test. Fourth, on the drug discrimination test, the effect of lorcaserin to alter the discriminative stimulus properties of nicotine was independent of changes in response rate. Finally, and most significantly, clinical experience with lorcaserin suggests it to be well tolerated at efficacious doses in phase II/III obesity trials, with no increased incidence in detrimental motor signs such as sedation compared with placebo (Smith *et al*, 2009, 2010; Fidler *et al*, 2011; Shram *et al* 2011). The similarity in dose (and likely plasma exposure) seen in the preclinical feeding- and nicotine-based studies would support that an equivalent dosage is necessary to evaluate lorcaserin in smoking cessation trials as that used in obesity trials. Taken together, with careful dose selection, the sedative effects of lorcaserin do not appear to be an issue in the clinic and do not provide a reasonable explanation for the findings described in the present report—at least up to doses of 1 mg/kg. Interestingly, at supratherapeutic doses of lorcaserin (40–60 mg), clinical measures of dislike (eg, headache, nausea) are frequently reported by study subjects (Shram *et al*, 2011) and this may be reflected by the behavioral disruption seen in the present study after a subcutaneous (SC) dose of 3 mg/kg.

A prominent hypothesis for the anorectic properties of 5-HT$_{2C}$ agonists and (dex)fenfluramine is that these agents activate 5-HT$_{2C}$ receptors localized on pro-opioid melanocortin (POMC) neurones located within the arcuate nucleus of the hypothalamus. As these cells are also responsive to a variety of peripheral metabolic signals such as leptin and insulin, 5-HT$_{2C}$ agonists directly modulate this circuitry important in the regulation of energy balance (Heisler *et al*, 2002; Cone, 2005). However, given the effects of 5-HT$_{2C}$ receptor agonists on motivated behaviors that are driven by a wide range of reinforcers (eg, Higgins and Fletcher, 2003; Cunningham *et al*, 2011), and the observation that the anorectic effects of fenfluramine and the non-selective 5-HT$_{2C}$ agonist TFMPP remain evident in rats with hypothalamic lesions (Fletcher *et al*, 1993), a second plausible locus is through 5-HT$_{2C}$-mediated regulation of forebrain systems, including the DA mesolimbic pathway. Given the complexity and redundancy of mechanisms that directly control ingestive behavior, such a dual mechanism of action could be advantageous when considering this drug class as treatments for obesity. Indeed the observation that lorcaserin appears to similarly affect feeding induced by deprivation (likely driven by metabolic signals in response

to energy demand) and palatability (likely driven by reward related processes) is consistent with such a dual hypothesis. Similarly the property of lorcaserin to reduce the stimulant, cueing, and reinforcing effects of nicotine, and the reinstatement of nicotine-seeking behavior, suggests the therapeutic potential of lorcaserin, and 5-HT$_{2C}$ agonists, in general, might further extend into the treatment of addictive behaviors such as nicotine dependence (Fletcher *et al*, 2009a).

## ACKNOWLEDGEMENTS

We acknowledge Sandy Thevarkunnel (InterVivo Solutions) for conducting some of the statistical analyses.

## DISCLOSURE

The authors declare that this work was partially funded by InterVivo Solutions and by an operating grant from the Canadian Institutes of Health Research (CIHR) to PJF. The authors declare no conflict of interest.

## REFERENCES

Bickel WK, Odum AL, Madden GJ (1999). Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology* **146**: 447–454.

Bubar MJ, Cunningham KA (2007). Distribution of serotonin 5-HT$_{2C}$ receptors in the ventral tegmental area. *Neuroscience* **146**: 286–297.

Burbassi S, Cervo L (2008). Stimulation of serotonin2C receptors influences cocaine-seeking behaviour in response to drug-associated stimuli in rats. *Psychopharmacology* **196**: 15–27.

Clarke PBS, Fu DS, Jakubovic A, Fibiger HC (1988). Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats. *J Pharmacol Exp Ther* **246**: 701–708.

Clifton PG, Lee MD, Dourish CT (2000). Similarities in the action of Ro 60-0175, a 5-HT$_{2C}$ receptor agonist and d-fenfluramine on feeding patterns in the rat. *Psychopharmacology* **152**: 256–267.

Cone RD (2005). Anatomy and regulation of the central melanocortin system. *Nature Neuroscience* **8**: 571–578.

Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD *et al* (1997). Valvular heart disease associated with fenfluramine–phentermine. *N Engl J Med* **337**: 581–588.

Corrigall WA, Coen KM (1994). Dopamine mechanisms play at best a small role in the nicotine discriminative stimulus. *Pharmacol Biochem Behav* **48**: 817–820.

Corrigall WA, Coen KM, Adamson L (1994). Self administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Res* **653**: 278–284.

Corrigall WA, Franklin KB, Coen KM, Clarke PBS (1992). The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology* **107**: 285–289.

Cunningham KA, Fox RG, Anastasio NC, Bubar MJ, Stutz SJ, Moeller FG *et al* (2011). Selective serotonin 5-HT$_{2C}$ receptor activation suppresses the reinforcing efficacy of cocaine and sucrose but differentially affects the incentive-salience value of cocaine *vs* sucrose-associated cues. *Neuropharmacology* **61**: 513–523.

Desai RI, Barber DJ, Terry P (2003). Dopaminergic and cholinergic involvement in the discriminative stimulus effects of nicotine and cocaine in rats. *Psychopharmacology* **167**: 335–343.

Di Matteo V, Pierucci M, Esposito E (2004). Selective stimulation of serotonin2c receptors blocks the enhancement of striatal and accumbal dopamine release induced by nicotine administration. *J Neurochem* **89**: 418–429.

Diergaarde L, Pattil T, Poortvleit I, Hogenboom F, de Vries W, Schoffelmeer ANM *et al* (2008). Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. *Biol Psychiatry* **63**: 301–308.

Elangbam CS, Lightfoot RM, Yoon LW, Creech DR, Geske RS, Crumbley CW *et al* (2005). 5-Hydroxytryptamine (5HT) receptors in the heart valves of cynomolgus monkeys and Sprague–Dawley rats. *J Histochem Cytochem* **53**: 671–677.

Epstein DH, Preston KL, Stewart J, Shaham Y (2006). Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology* **189**: 1–16.

Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, *et al*, the BLOSSOM trial group (2011). A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* **96**: 3067–3077.

Fields S, Collins C, Leraas K, Reynolds B (2009). Dimensions of impulsive behaviour in adolescent smokers and non-smokers. *Exp Clin Psychol* **17**: 302–311.

Filip M, Cunningham KA (2003). Hyperlocomotive and discriminative stimulus effects of cocaine are under the control of serotonin(2C) (5-HT(2C)) receptors in rat prefrontal cortex. *J Pharmacol Exp Ther* **306**: 734–743.

Fitzgerald LW, Burn TC, Brown BS, Patterson JP, Corjay MH, Valentine PA *et al* (2000). Possible role of valvular serotonin 5-HT(2B) receptors in the cardiopathy associated with fenfluramine. *Mol Pharmacol* **57**: 75–81.

Fletcher PJ, Currie PJ, Chambers JW, Coscina DV (1993). Radiofrequency lesions of the PVN fail to modify the effects of serotonergic drugs on food intake. *Brain Res* **630**: 1–9.

Fletcher PJ, Le AD, Higgins GA (2009a). Serotonin receptors as potential targets for modulation of nicotine use and dependence. *Prog Brain Res* **172**: 361–383.

Fletcher PJ, Rizos Z, Sinyard J, Tampakeras M, Higgins GA (2008). The 5-HT(2C) receptor agonist Ro60-0175 reduces cocaine self-administration and reinstatement induced by the stressor yohimbine, and contextual cues. *Neuropsychopharmacology* **33**: 1402–1412.

Fletcher PJ, Tampakeras M, Sinyard J, Higgins GA (2007). Opposing effects of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology* **195**: 223–234.

Fletcher PJ, Tampakeras M, Sinyard J, Slassi A, Isaac M, Higgins GA (2009b). Characterising the effects of 5-HT$_{2C}$ receptor ligands on motor activity and feeding behaviour in 5-HT$_{2C}$ receptor knockout mice. *Neuropharmacology* **57**: 259–267.

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, *et al*, Varenicline Phase 3 Study Group (2006). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, *vs* sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* **296**: 47–55.

Grottick AJ, Corrigall WA, Higgins GA (2001). Activation of 5-HT(2C) receptors reduces the locomotor and rewarding effects of nicotine. *Psychopharmacology* **157**: 292–298.

Grottick AJ, Fletcher PJ, Higgins GA (2000). Studies to investigate the role of 5-HT(2C) receptors on cocaine- and food-maintained behavior. *J Pharmacol Exp Ther* **295**: 1183–1191.

Grottick AJ, Higgins GA (2000). Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. *Behav Brain Res* **117**: 197–208.

Guy-Grand B, Crepaldi G, Lefebvre P, Apfelbaum M, Gries A, Turner P (1989). International trial of long-term dexfenfluramine in obesity. *Lancet* **2**: 1142–1145.

Halberstadt AL, van der Heijden I, Ruderman MA, Risbrough VB, Gingrich JA, Geyer MA *et al* (2009). 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors exert opposing effects on locomotor activity in mice. *Neuropsychopharmacology* **34**: 1958–1967.

Halford JCG, Harrold JA, Boyland EJ, Lawton CL, Blundell JE (2007). Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. *Drugs* **67**: 27–55.

Hayes DJ, Mosher TM, Greenshaw AJ (2009). Differential effects of 5-HT$_{2C}$ receptor activation by WAY 161503 on nicotine-induced place conditioning and locomotor activity in rats. *Behav Brain Res* **197**: 323–330.

Heisler LK, Cowley MA, Tecott LH, Fan W, Low MJ, Smart JL *et al* (2002). Activation of central melanocortin pathways by fenfluramine. *Science* **297**: 609–611.

Henningfield JE, Shiffman S, Ferguson SG, Gritz ER (2009). Tobacco dependence and withdrawal: science base, challenges and opportunities for pharmacotherapy. *Pharmacol Ther* **123**: 1–16.

Hewitt KN, Lee MD, Dourish CT, Clifton PG (2002). Serotonin 2C receptor agonists and the behavioural satiety sequence in mice. *Pharmacol Biochem Behav* **71**: 691–700.

Higgins GA, Fletcher PJ (2003). Serotonin and reward: focus on 5-HT$_{2C}$ receptors. *Eur J Pharmacol* **480**: 151–162.

Hoyer D, Hannon JP, Martin GR (2002). Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* **71**: 533–554.

Hughes JR, Neely J, Naud S (2004). Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* **99**: 29–38.

Keath JR, Lacoviello MP, Barrett LE, Mansvelder HD, McGehee DS (2007). Differential modulation by nicotine of substantia nigra versus ventral tegmental area dopamine neurones. *J Neurophysiol* **98**: 3388–3396.

Kennett GA, Wood MD, Bright F, Trail B, Riley G, Holland V *et al* (1997). SB242,084, a selective and brain penetrant 5-HT$_{2C}$ receptor antagonist. *Neuropharmacology* **36**: 609–620.

Kenny PJ (2011). Reward mechanisms in obesity: new insights and future directions. *Neuron* **69**: 664–679.

Kolokotroni KZ, Rodgers RJ, Harrison AA (2011). Acute nicotine increases both impulsive choice and behavioural disinhibition in rats. *Psychopharmacology* **217**: 455–473.

Mansvelder HD, Keath JR, McGehee DS (2002). Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* **33**: 905–919.

Miyata H, Ando K, Yanagita T (2002). Brain regions mediating the discriminative stimulus effects of nicotine in rats. *Ann NY Acad Sci* **965**: 354–363.

Navarra R, Comery TA, Graf R, Rosenzweig-Lipson S, Day M (2008). The 5-HT$_{2C}$ receptor agonist WAY-163909 decreases impulsivity in the 5-choice serial reaction time task. *Behav Brain Res* **188**: 412–415.

Niesewander JL, Acosta JI (2007). Stimulation of 5-HT$_{2C}$ receptors attenuates cue and cocaine-primed reinstatement of cocaine-seeking behavior in rats. *Behav Pharmacol* **18**: 791–800.

Nilsson BM (2006). 5-Hydroxytryptamine 2C (5-HT$_{2C}$) receptor agonists as potential anti-obesity agents. *J Med Chem* **49**: 4023–4034.

O'Connor EC, Parker D, Rollema H, Mead AN (2010). The $\alpha 4\beta 2$ nicotinic acetylcholine-receptor partial agonist varenicline inhibits both nicotine self-administration following repeated dosing and reinstatement of nicotine seeking in rats. *Psychopharmacology* **208**: 365–376.

Pattij T, Vanderschuren LJMJ (2008). The neuropharmacology of impulsive behaviour. *Trends Pharmacol Sci* **29**: 192–199.

Pentkowski NS, Duke FD, Weber SM, Pockros LA, Teer AP, Hamilton EC *et al* (2011). Stimulation of medial prefrontal cortex serotonin 2C (5-HT$_{2C}$) receptors attenuates cocaine-seeking behavior. *Neuropsychopharmacology* **35**: 2037–2048.

Pierucci M, Di Matteo V, Esposito E (2004). Stimulation of serotonin2C receptors blocks the hyperactivation of midbrain dopamine neurons induced by nicotine administration. *J Pharmacol Exp Ther* **309**: 109–118.

Popke EJ, Mayorga AJ, Fogle CM, Paule MG (2000). Effects of acute nicotine on several operant behaviours in rats. *Pharmacol Biochem Behav* **65**: 247–254.

Quarta D, Naylor CG, Stolerman IP (2007). The serotonin2C receptor agonist Ro-60-0175 attenuates effects of nicotine in the five-choice serial reaction time task and in drug discrimination. *Psychopharmacology* **193**: 391–402.

Reavill C, Stolerman IP (1990). Locomotor activity in rats after administration of nicotinic agonists intracerebrally. *Br J Pharmacol* **99**: 273–278.

Recker MD, Higgins GA (2002). The opioid receptor like-1 receptor agonist Ro 64-6198 (1S,3aS-8-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl-1-phenyl-1,3,8-triaza-spiro[4.5] decan-4-one) produces a discriminative stimulus in rats distinct from that of a mu, kappa, and delta opioid receptor agonist cue. *J Pharmacol Exp Ther* **311**: 652–658.

Robbins TW (2002). The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. *Psychopharmacology* **163**: 362–380.

Rodgers RJ, Holch P, Tallet AJ (2010). Behavioural satiety sequence (BSS): separating wheat from chaff in the behavioural pharmacology of appetite. *Pharmacol Biochem Behav* **97**: 3–14.

Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE (2007). Rationale, pharmacology and clinical efficacy of partial agonists of alpha4beta2nACh receptors for smoking cessation. *Trends Pharmacol Sci* **28**: 316–325.

Rose JE, Levin ED (1991). Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *Br J Addict* **86**: 605–609.

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology* **168**: 3–20.

Shram MJ, Schoedel KA, Barlett C, Shazer RL, Anderson CM, Sellers EM (2011). Evaluation of the abuse potential evaluation of lorcaserin, a serotonin 2C (5-HT2C) receptor agonist, in recreational polydrug users. *Clin Pharmacol Ther* **89**: 683–692.

Siuciak JA, Chapin DS, McCarthy SA, Guanowsky V, Brown J, Chiang P *et al* (2007). CP-809,101, a selective 5-HT$_{2C}$ agonist, shows activity in animal models of antipsychotic activity. *Neuropharmacology* **52**: 279–290.

Somerville EM, Horwood JM, Lee MD, Kennett GA, Clifton PG (2007). 5-HT$_{2C}$ receptor activation inhibits appetitive and consummatory components of feeding and increases brain c-fos immunoreactivity in mice. *Eur J Neurosci* **25**: 3115–3124.

Smith BM, Smith JM, Tsai JH, Schultz JA, Gilson CA, Estrada SA *et al* (2008). Discovery and structure–activity relationship of (1R)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine (lorcaserin), a selective serotonin 5-HT$_{2C}$ receptor agonist for the treatment of obesity. *J Med Chem* **51**: 305–313.

Smith JW, Stolerman IP (2009). Recognising nicotine: the neurobiological basis of nicotine discrimination. *Handb Exp Pharmacol* **192**: 295–333.

Smith SR, Prosser WA, Donahue DJ, Morgan ME, Anderson CM, Shanahan WR, APD356-004 Study Group. (2009). Lorcaserin (APD356), a selective 5-HT$_{2C}$ agonist, reduces body weight in obese men and women. *Obesity (Silver Spring)* **17**: 494–503.

Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, *et al*, Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group (2010). Multicentre, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* **263**: 245–256.

Stolerman IP, Mirza NR, Hahn B, Shoaib M (2000). Nicotine in an animal model of attention. *Eur J Pharmacol* **393**: 147–154.

Thomsen WJ, Grottick AJ, Menzaghi F, Reyes-Saldana H, Espita S, Yuskin D *et al* (2008). Lorcaserin, a novel selective human 5-hydroxytryptamine$_{2C}$ agonist: *in vitro* and *in vivo* pharmacological characterization. *J Pharmacol Exp Ther* **325**: 577–587.

Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR, Varenicline Phase 3 Study Group. (2006). Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* **296**: 64–71.

Vickers SP, Clifton PG, Dourish CT, Tecott LH (1999). Reduced satiating effect of d-fenfluramine in serotonin 5-HT$_{2C}$ receptor mutant mice. *Psychopharmacology* **143**: 309–314.

Vickers SP, Dourish CT, Kennett GA (2001). Evidence that hypophagia induced by d-fenfluramine and d-norfenfluramine in the rat is mediated by 5-HT$_{2C}$ receptors. *Neuropharmacology* **41**: 200–209.

Volkow ND, O'Brien CP (2007). Issues for DSM-V: should obesity be included as a brain disorder? *Am J Psychiatry* **164**: 708–710.

Volkow ND, Wise RA (2005). How can drug addiction help us understand obesity? *Nat Neurosci* **8**: 555–560.

Wacker DA, Miller KJ (2008). Agonists of the serotonin 5-HT$_{2C}$ receptor: preclinical and clinical progression in multiple diseases. *Curr Opin Drug Discov Dev* **11**: 438–445.

Winstanley CA, Olausson P, Taylor JR, Jentsch JD (2010). Insight into the relationship between impulsivity and substance abuse from studies using animal models. *Alcoholism Clin Exp Res* **34**: 1306–1318.

Zaniewska M, McCreary AC, Przegalinski E, Filip M (2007). Effects of the serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor ligands on the discriminative stimulus effects of nicotine in rats. *Eur J Pharmacol* **571**: 156–165.

Zhao-Shea R, Liu L, Soll LG, Improgo MR, Meyers EE, McIntosh JM *et al* (2011). Nicotine-mediated activation of dopaminergic neurons in distinct regions of the ventral tegmental area. *Neuropsychopharmacology* **36**: 1021–1032.