The selective 5-HT$_{2C}$ receptor agonist, lorcaserin, reduces indices of nicotine reward as well as food intake in the rat

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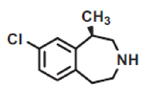
Introduction

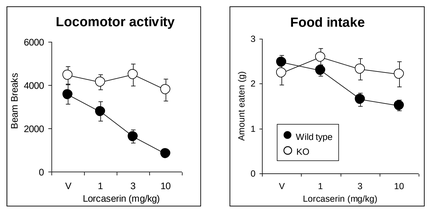
Selective agonists at the 5-HT$_{2C}$ receptor have attracted interest as novel therapies for obesity. The most advanced compound of this class, lorcaserin, has recently completed two Phase III trials, the outcomes of which support the potential of this drug class for the treatment of obesity (Smith et al, 2010). It is becoming increasingly recognised that there is considerable overlap in CNS systems that regulate behaviours related to excessive feeding and the intake of drugs of abuse (e.g. Volkow & Wise, 2005; Fletcher & Higgins, 2010). Indeed we have previously demonstrated that the prototypic 5-HT$_{2C}$ agonist, Ro 60-0175, reduces nicotine self-administration and hyperactivity in rats (Grottick et al, 2001). Accordingly in the present series of studies we have evaluated lorcaserin against both the stimulant and reinforcing properties of nicotine. For comparative purposes we have also tested acute effects of lorcaserin in a rat feeding assay.

Lorcaserin is a selective 5-HT$_{2C}$ agonist: in-vitro and in-vivo evidence



	h5-HT$_{2C}$	h5-HT$_{2A}$	h5-HT$_{2B}$
EC50 (nM)	9 ± 0.5	168 ± 11	943 ± 90
Efficacy	1.00	0.75	1.00
5-HT$_{2C}$ Selectivity	-	18-fold	104-fold

Lorcaserin has ~18-fold functional selectivity for h5-HT$_{2C}$ receptor compared to h5-HT$_{2A}$ receptor and ~109-fold selectivity for h5-HT$_{2C}$ receptor compared to h5-HT$_{2B}$ receptor as determined by in-vitro screening in HEK293 cells transiently expressing relevant h5-HT$_2$ receptor. Agonist property measured by inositol accumulation assay. Efficacy (Emax) response is relative to 5-HT (10uM) which = 1.0. (*Data taken from Thomsen et al, 2008*)



Lorcaserin (1-10 mg/kg) reduces locomotor activity and food intake in wild type mice. In 5-HT$_{2C}$ receptor KO mice, these equivalent doses of lorcaserin have no effect on either measure (*data adapted from Fletcher et al, 2009*).

Methods

Locomotor activity studies: Test subjects were male, Sprague-Dawley rats. Following a defined pretreatment the animals were singly placed within test chambers where locomotor activity (defined as distance travelled) was measured by photocell interruptions. Lorcaserin was evaluated over a 90min test session against a hyperactivity induced by nicotine (0.4 mg/kg s.c.) or on basal activity. Test design was essentially identical across all studies, with the animals first being familiarised to test chambers, before formal tests which were run using a repeated measures design with 2-3 treatment free days between each cycle. In the nicotine hyperactivity studies, test subjects were first sensitized to nicotine by daily injection of 0.4mg/kg s.c. dose over 10 days. Over the course of the locomotor studies the rats continued to be treated with the same dose of nicotine.

Nicotine self-administration: Test subjects were male, Long Evans rats which have been previously shown to reliably self-administer nicotine (REF). Following a brief period of magazine training rats were trained to self-administer nicotine (

Tests of nicotine reinstatement :

Feeding studies: Male, Sprague-Dawley rats were trained to consume their daily food over a 2h period each day. After intakes became stable (~18±2g intake/day), the effect of lorcaserin on intake was assessed according to a repeated measures design, with each animal receiving each treatment in a balanced sequence. Test cycles were run with a 2-3 treatment free period between each cycle. N=12 rats.

Treatments: Lorcaserin was prepared in saline in a dose volume of 1ml/kg with dose expressed as that of base. Drug was administered by the s.c. route, 5-10min pre-test.

Results

A. Effect of Lorcaserin on locomotor activity in rats

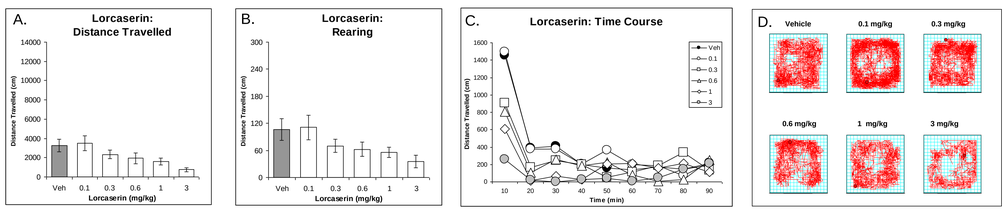


Figure 1. Effect of Lorcaserin (0.1-3 mg/kg s.c.) on **(A)** total distance travelled over a 90min test session, **(B)** total number of rearing episodes recorded over the same period, **(C)** time course of effect of lorcaserin on distance travelled measured over the same period. **(D)** Representative path plots of a single rat at each treatment dose. N=8 rats. * P<0.05 vs. vehicle control.

B. Effect of Lorcaserin against nicotine induced hyperactivity in rats

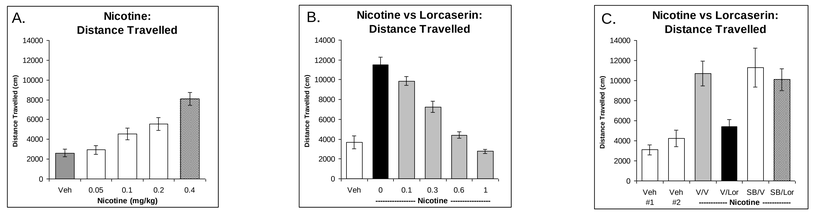


Figure 2. **(A)** Nicotine dose-response in rats previously sensitized to nicotine (0.4 mg/kg s.c. x 10 days). Based on these data the 0.4 mg/kg s.c. dose was selected for subsequent drug interaction studies. **(B)** Effect of lorcaserin (0.1-1 mg/kg s.c.) against nicotine-induced hyperactivity. **(C)** Reversal of the suppressant effect of lorcaserin (0.6 mg/kg) against nicotine hyperactivity by the 5-HT$_{2C}$ receptor antagonist SB-242084 (0.5 mg/kg). * P<0.05 vs. vehicle control. # P<0.05 vs. lorcaserin/vehicle treatment group. Veh #1 and Veh #2 represent saline injections at the start, i.e. cycle #1, and end of the study, i.e cycle #6.

Results (cont.)

C. Effect of Lorcaserin against nicotine induced self-administration

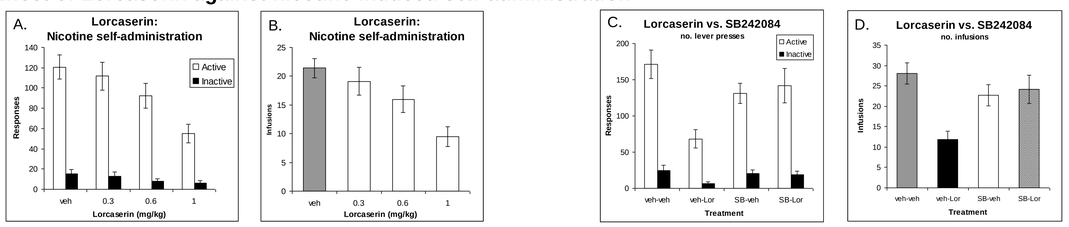


Figure 3.……,

D. Effect of Lorcaserin in a model of cue-induced reinstatement of nicotine self-administration

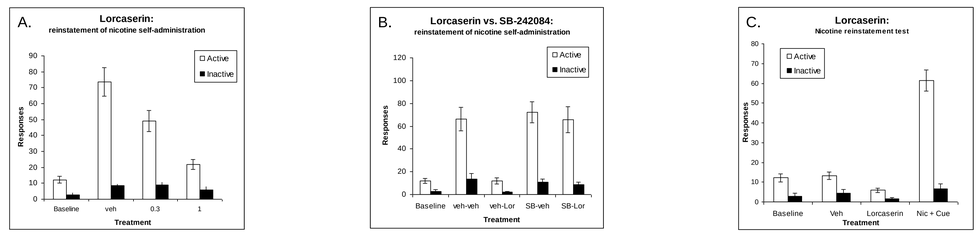


Figure 4. ……,

E. Effect of lorcaserin on food intake in 22h deprived rats

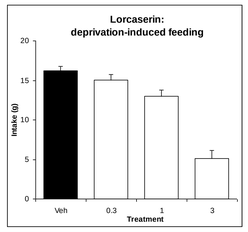


Figure 5. Effect of lorcaserin (0.3-3 mg/kg s.c.) on the intake of standard lab chow in rats trained to consume food over a 2h period each day. At doses of 1-3 mg/kg s.c. lorcaserin significantly reduced food intake relative to vehicle controls. * P<0.05 vs. controls.

Summary and conclusions

1. **Lorcaserin is one of the most selective 5-HT$_{2C}$ receptor agonists identified to date, having ~20-fold functional selectivity for 2C vs. 2A, and ~120-fold functional selectivity for 2C vs. 2B (Thomsen et al, 2008). In vivo this apparent selectivity is demonstrated by the fact that acute effects of this drug in wild type C57BL/B6 mice, evident over a 10-fold dose range is completely eliminated in 5-HT$_{2C}$ receptor KO mice across same dose range (Fletcher et al, 2009).**
2. **In rats habituated to test chamber, lorcaserin produces a modest decrease in distance travelled and rearing at doses of 0.6 mg/kg s.c. and above.**
3. **Lorcaserin (0.3-1mg/kg s.c.) produces a robust dose dependent decrease in a nicotine hyperactivity. This effect of lorcaserin is blocked by pretreatment with the selective 5-HT$_{2C}$ receptor antagonist, SB-242084.**
4. **Lorcaserin (0.6-1 mg/kg s.c.) reduces the intravenous self-administration of nicotine. This effect of lorcaserin is blocked by SB-242084.**
5. **In rats previously extinguished to the self-administration of nicotine, self-administration behaviour (i.e lever pressing on a lever previously associated with nicotine delivery) is reliably reinstated by a compound cue comprising of an experimenter delivered nicotine priming injection and a cue-tone CS previously paired with nicotine delivery.**
6. **Lorcaserin (0.3-1 mg/kg s.c.) reduces the reinstatement of nicotine self-administration produced by the compound cue. This effect of lorcaserin is blocked by SB-242084.**
7. **Consistent with its clinical efficacy as a potential treatment for obesity, lorcaserin reduces food intake produced by 22h food deprivation in rats. Drug doses for this effect overlap with those necessary for antagonism of nicotine behaviours.**
8. **Assuming lorcaserin has a safety profile in the clinic acceptable to regulatory agencies, it may represent a viable approach for the treatment of smoking cessation, either as a stand alone medication, or in conjunction with other treatment approaches. With the recent withdrawal of Chantix® there may be opportunities to test this experimentally.**

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camh Centre for Addiction and Mental Health / Centre de toxicomanie et de santé mentale