CHARACTERIZATION OF THE HIGHLY SELECTIVE 5-HT2C AGONISTS LORCASERIN AND CP-809101 ON FOOD AND NICOTINE MOTIVATED BEHAVIORS IN THE RAT

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A. Effect of lorcaserin, Ro 60-0175 and CP-809101 against responding maintained by intravenous lever choice procedure (FR10 schedule). After stable discrimination, substitution tests were conducted. Next, the effect of each drug to modify Nicotine discrimination studies:

under an identical schedule to that used for intravenous nicotine, i.e FR5 schedule requirement with reinforcement delivery accompanied by a ~85% of free feeding body weight. Following a brief period of food magazine training rats were implanted with jugular catheters. Initially rats injecting rats with either mecamylamine (1mg/kg SC) or saline (control) before each test procedure. were trained to self-administer nicotine (0.03 mg/kg/infusion) on an FR1 schedule. Each infusion (2s duration) was accompanied by a 2s tone best used for within drug comparisons across h5-HT2 receptors. Data from: (1) Thomsen et al (2008) JPET 325: 577-587; (2) Porter et al (1999) BJP 128: 13-20; (3) Siuciak et al (2007) Neuropharm. 52: 279-290.

1. The 5-HT2C receptor agonists lorcaserin, Ro 60-0175 and CP-809101 reduced responding for both intravenous nicotine and food made available under an identical FR10/20 schedule of reinforcement. Despite markedly different responses to the same FR schedule, there was no trend to identify any differential selectivity towards each reinforcer type by these drugs.

2. The 5-HT2C receptor agonists had acute effects on food intake. Lorcaserin and CP-809101 did not generalize to a nicotine cue at pharmacologically relevant doses. However each did reliably attenuate a nicotine cue, a feature similar to the nicotine partial agonist varenicline (see also Guerin et al., 2007; Zawadzki et al., 2007).

3. In rats chronically exposed to nicotine, acute administration of mecamylamine produced somatic behavioral signs such as piloerection, wet dog shakes, chewing and a decrease in spontaneous motor activity. Pretreatment with lorcaserin or Ro 60-0175 (both 1 mg/kg SC) failed to attenuate the somatic withdrawal signs occurring when mecamylamine precipitated WD. Interestingly, Zawadzki et al. (2010) recently reported that Ro 60-0175 may attenuate certain effective nicotine WD signs although this has not been investigated yet using the present methods.

4. Plasma levels of lorcaserin (1 mg/kg SC) at a timepoint producing robust efficacy against both nicotine and food maintained behavior was approximately 120-150 ng/ml. Assuming linearity, extrapolation to lower doses will result in plasma levels measured at 0.5 and 1 h post dose in Sprague-Dawley (SD) and Long-Evans (LE) rats. Note the SD rat plasma levels are similar between the LE and SD rats following an equivalent 1 mg/kg dose. These time points were selected as they correspond to when the majority of behavioural investigations were made following drug treatment, using a 24-hr clinic trial each cycle.

5. At a higher dose of lorcaserin (3 mg/kg SC) equivalent to a plasma level in the range of 300-400 ng/ml, side effects such as salivation, flat body posture, ptosis, vacuous chewing become predominant behaviors. Many of these are shared by emaciatges such as nolpad implying they may reflect malaise. Nausea and vomiting are described as the most frequent AE in lorcaserin trials and these preclinical findings may reflect this side effect.

6. Overall the effects of 5-HT2C agonists against a variety of nicotine behaviors which contribute to its abuse liability overlap with doses effective in feeding tests. PK studies using lorcaserin conducted in SD and Long-Evans rats show plasma levels are similar between the LE and SD rats following an equivalent 1 mg/kg dose. These time points were selected as they correspond to when the majority of behavioral investigations were made following drug treatment, using a 24-hr clinic trial each cycle.

B. Characterisation of lorcaserin, Ro 60-0175 and CP-809101 against a nicotine cue. Tests of generalisation to a nicotine cue

C. Effect of lorcaserin and Ro 60-0175 against somatic signs of nicotine withdrawal

D. Characterisation of lorcaserin, Ro 60-0175 and CP-809101 in three feeding tests

E. Characterisation of lorcaserin and CP-809101 on spontaneous behaviour

F. Pharmacokinetic study of lorcaserin

Summary and conclusions

1. The 5-HT2C receptor agonists lorcaserin, Ro 60-0175 and CP-809101 reduced responding for both intravenous nicotine and food made available under an identical FR10/20 schedule of reinforcement. Despite markedly different responses to the same FR schedule, there was no trend to identify any differential selectivity towards each reinforcer type by these drugs.

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7. Despite potential differences between clinical trials, CP809101 with the prototypic agonist Ro 60-0175, there was no obvious difference in efficacy profile suggesting a broad class effect. Side effects profiles may differ...