Introduction

Selective agonists targeted to the 5-HT2c receptor have attracted interest as novel therapies for obesity and for the treatment of substance abuse disorders, particularly smoking cessation. We have previously reported that the 5-HT2c agonists Ro 60-0175 (Grottick et al., 2001) and lorcaserin (Higgins et al., 2011 in press) reliably reduce nicotine self-administration and reinstatement. The present studies were designed to expand on this potential by evaluating these nicotine discriminative stimuli and antagonist withdrawal signs evident following abrupt cessation of chronic nicotine exposure (Malin and Goyarzu, 2009) (see also Quarta et al., 2007; Zaniewski et al., 2007, 2010). In addition the highly selective 5-HT2c agonist CP-809101 (Succi et al., 2007) was included in some of these studies. Comparison to effects on food intake are also presented. A preliminary study to evaluate whether rats can be trained to discriminate a CP-809101 cue from saline is also presented.

Results (cont.)

B. Characterisation of a nicotine precipitated withdrawal: effect of lorcaserin and Ro 60-0175 against somatic withdrawal signs.

1. Body weight change during nicotine exposure and somatic signs following a precipitated nicotine withdrawal.

Nicotine substitution

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Veh</th>
<th>0.03</th>
<th>0.1</th>
<th>0.3</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/kg SC</td>
<td>100</td>
<td>120</td>
<td>140</td>
<td>160</td>
<td>180</td>
</tr>
</tbody>
</table>

C. Characterisation of lorcaserin, Ro 60-0175 and CP-809101 in two feeding tests

D. Preliminary studies in rats trained to discriminate CP-809101, a 5-HT2c selective cue?

Summary and conclusions

1. The 5-HT2c receptor agonists lorcaserin, Ro 60-0175 and CP-809101 did not generalise 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 Quarta et al., 2007; Zaniewski et al., 2007).

2. In rats chronically exposed to nicotine, acute administration of mecamylamine produced somatic behavioural signs such as ptosis, wet dog shakes, chewing and a decrease in spontaneous motor activity. At this same regimen, we were unable to observe a robust place conditioning to nicotine W/D.

3. Pre-treatment with either lorcaserin or Ro 60-0175 (both 1 mg/kg sc) failed to attenuate the somatic withdrawal signs to a mecamylamine precipitated W/D.

4. Many of the W/D signs observed following nicotine W/D are similar to unconditioned behaviours observed following emetogenic stimuli (e.g. rolaplim). This suggests the somatic signs are reflective of a malaise, and 5-HT2c agonists may not modify this aspect of nicotine dependence – indeed high doses of lorcaserin did reduce signs.

5. Inhibitory effects of 5-HT2c agonists against a nicotine cue overlap with doses effective in feeding tests highlighting bioequivalence against food and nicotine motivation behaviour. In addition to previously reported effects of lorcaserin and Ro 60-0175 against the stimulant and reinforcing properties of nicotine and in a model of relapse – these experiments support the consideration of 5-HT2c agonists, such as lorcaserin, as treatments to support smoking cessation.

References


