SELECTIVE mGluR2 NEGATIVE ALLOSTERIC MODULATORS REVERSE THE SCOPOLAMINE-INDUCED MEMORY DEFICIT IN THE NOVEL OBJECT RECOGNITION TEST

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INTRODUCTION

Group II metabotropic glutamate receptor (mGluR) orthosteric agonists have been reported to inhibit working and spatial memory in rodents and monkeys (Higgins et al., 2004; Spinelli et al., 2005). As shown in mGluR2 KO mice, this effect is specific to mGluR2 receptor activation. In contrast, orthostERIC mGluR2/3 antagonists improved acquisition of short-term working memory, spatial learning and social memory (Higgins et al., 2004; Shimazaki et al., 2007). In addition, it was demonstrated that group II antagonist reversed memory deficits observed in scopolamine-treated rats, in aged rats and in PSAPP mice, a model of Alzheimer’s disease (Knollfach et al., 2005). These results highlight the interest of mGluR2 modulators as a therapeutic approach for treating memory deficits associated with Alzheimer’s disease and other disorders. Interestingly, all the above studies were performed using non-selective mGluR2 molecules which retain affinity for either mGluR3 or group I and/or III mGluRs; this lack of selectivity could lead to toxic effects including neurotoxicity resulting from activation of mGluR5 receptors (Corti et al., 2007). Therefore, our aim was to identify novel, selective and brain penetrant mGluR2 negative allosteric modulators (NAM), and to evaluate their ability to reverse scopolamine-induced memory deficit in the novel object recognition (NOR) test in rats.

METHODS

In vivo experiments: All experiments involving animals were performed in accordance with institutional guidelines. Male Sprague-Dawley rats (275-350 g; Janvier, France) were handled 1 min for 5 days and individually habituated to the opaque observation boxes (30x30x15 cm) for 2 min (no objects present) 24 h before the NOR experiments. To test scopolamine-induced deficit, animals received scopolamine 0.3 mg/kg (i.p.) 10 min before being exposed to 2 objects. A total of 20 rats were tested. Animals were returned to their cage for 2 h post-injection. In Test 2 (12 animals were exposed to one familiar and one novel object for 1 min) and then split-exploring both objects as well as the total distance traveled during the test were recorded. Cps of interest were administered p.o. before T1. Blood was collected at the end of the experiment for exposure measurement.

In vitro pharmacological profile of Cps A and B

<table>
<thead>
<tr>
<th>Compound</th>
<th>Human mGluR2 clone Ca2+ assay IC50 (nM)</th>
<th>Rat mGluR2 clone IC50 (nM)</th>
<th>Human mGluR2 clone Ca2+ assay IC50 (nM)</th>
<th>mGluR2(+/-7)/7a Ca2+ assay IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd A</td>
<td>143</td>
<td>145</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cpd B</td>
<td>69</td>
<td>75</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

In vitro pharmacological profile of Cps A and B

RESULTS

CONCLUSIONS

- Cps A and B were identified from an internal screening campaign.
- These compounds are selective and reversible mGluR2 negative allosteric modulators.
- PK profile of both Cps A and B allowed in vivo studies.
- After oral administration, Cps A and B fully reverse the scopolamine-induced deficit in memory in the NOR model in rats, without having any effect on locomotor activity.
- These effects are related to the concentration of the compound in the plasma and the CSF (data not shown).
- These results reinforce the interest in mGluR2 NAMs for the symptomatic treatment of memory deficits.

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