In vivo characterization of a novel highly potent GPR88 agonist

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INTRODUCTION

GPR88 is an orphan member of the G-protein coupled receptor (GPCR) superfamily. This receptor is enriched in the striatum and was therefore proposed as a potential therapeutic target for motor dysfunctions such as Parkinson’s disease or Huntington’s disease (Massart et al 2009). Its roles in psychiatric disorders have also been studied and GPR88 KO mice were shown to display psychosis-like behavior (Logue et al 2009) and hyperactivity (Quintana et al 2012). Using multiple screening approaches, new GPR88 agonists were discovered. These molecules are characterized using a native system that involves a GTPγS assay based on striatal membranes from wild type and GPR88 KO mice. Hit-to-lead efforts enable the discovery of potent agonist showing EC50 < 50nM. One of these agonists was used in vivo and the results of its characterization will be presented in the present poster.

1. GPR88 introduction & ATH-505

- Highly enriched in the striatum - promising drug target for basal ganglia-associated disorders
- GPR88 KO mice showed disrupted prepulse inhibition of the startle response, increased locomotion and impaired motor coordination (Logue SF, 2009)
- GPR88 silencing in ventral striatum of adult rats inhibits amphetamine-induced hyperlocomotion and reduces social novelty discrimination deficits (Ingallinesi M, 2014)
- Few tool compounds available as GPR88 agonists (2-PCCA from BMS - Jin C, 2014)
- Drug discovery effort was initiated with multiple screening approaches toward identification of novel GPR88 ligands
- Compound characterization is performed on GTPγS test on native tissues
- Novel series of GPR88 agonist were identified, represented by ATH-505
- ATH-505 is as active as 2-PCCA in GTPγS assay, but shows low oral F% in mice
- To demonstrate animal PoC activity, we choose to test ATH-505 after chronic dosing and to profile it against GPR88 KO mice in a series a 3 behavioral tests

2. ATH-505 GTPγS binding assay on native tissue

3. Emotional response: elevated plus-maze

In the elevated plus-maze, GPR88 KOs spent more time in the open arms of the maze, indicative of reduced anxiety. Conversely, ICV administration of ATH-505 decreased time spent in the open arm, suggestive of hyperanxiety.

4. Motor coordination: rotarod task

In the accelerating rotarod task, GPR88 mutant animals performed poorly, suggesting impaired locomotor coordination. Conversely, ICV administered ATH-505 increased the time spent on the rod in WT C57BL/6 mice, suggesting improved motor coordination.

5. Working memory: Y-Maze exploration

In the Y-maze task, Gpr88 null mice show higher alternation rates than WT controls, by making less perseverative errors (same arm returns). ATH-505 impaired alternation in WT mice by increasing the number of perseverative errors, and had no effects in KOs.

CONCLUSION

- A collaborative drug discovery effort leads to the identification of novel GPR88 agonists represented by ATH-505 showing high potency (46 nM) and efficacy (261%) in a native GTPγS assay performed on striatal membrane preparation.
- Administered in vivo to wild-type animals, ATH-505 produces opposite effects as compared to genetic invalidation of the Gpr88 gene:
  - it decreases the time spent in the open arms of the elevated plus maze
  - it increases motor performance in the rotarod task
  - it decreases spontaneous alternation in the Y-maze.
- Moreover, no effect of ATH-505 was detected on GPR88 knockout mice in the Y-maze task, demonstrating “on-target” in vivo effects of the compound.
- ATH-505 therefore represents a unique tool compound to better understand therapeutic potential of GPR88 modulation.

References:
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