Effect of orphan GPR88 on delta opioid signaling in vitro and in vivo

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Orphan GPR88 localization and function

GPR88 is an orphan G protein coupled receptor (GPCR) and the most expressed GPCR in the striatum.

RNA in situ hybridization

Highly expressed in striatum (also in Cortex and Amygdala)

Orphan GPR88 is a risk factor for psychiatric diseases.

- Gpr88 gene expression regulated by methamphetamine, the mood stabilizers valproate and lithium and by antidepressant treatments.
- Behaviour: response to drugs, cognitive impairments
- mimic = several deficits of psychiatric diseases.

How does GPR88 inhibit DOR and other striatal GPCR signaling?

Heterodimerisation with striatal GPCRs

No specific and saturated BRET signal are observed between GPR88 and MOR, M4, D1, D2 and VOR.

GPR88 display specific and saturated BRET signals with GPR88 itself, DOR and muscarinic M3.

Effect of GPR88 on DOR signalling

Effect on G protein signaling:

- Compounds 19
- Gi/Go/Gz basal activity
- Gi/Go/Gz agonist-induced activity

Effect on other signaling pathways:

- \(\beta\)-arrestin2 recruitment
- Internalisation
- Late endosome

Pharmacological profile of orphan GPR88

<table>
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<tr>
<th>Synthetic agonist</th>
<th>Gi/Go/Gz activity</th>
<th>Gi/o activity</th>
<th>Inhibition of EcAMP production</th>
<th>Endosomal transport</th>
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<tr>
<td>DOR</td>
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<tr>
<td>MOR</td>
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<td>GPR88</td>
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Effect of GPR88 on MOR signalling

GPR88 doesn’t reduce MOR basal activity and agonist-induced G protein dependent activity. The increased activity with DAMGO observed in Gpr88 knockout mice might result from DOR receptors stimulated with DAMGO.

Conclusions & Perspectives

GPR88 appears to form heterodimers with DOR, as well as itself and muscarinic M1 receptors, but not MOR. Co-expression of GPR88 with DOR results in an inhibition of DOR activity (G protein-mediated and G protein-independent signalling). In contrast, BRET experiments suggest that GPR88 does not affect protein-mediated signalling of MOR.

In a next step, we will investigate the effects of GPR88 expression on G protein-independent signalling of MOR as well as G protein dependent and independent signalling of M1 receptors. Further, we plan to modelise in silico the pharmacological interactions between GPR88 and DOR.