BMC Pharmacology

Poster presentation

Open Access

Pharmacological characterization of receptor guanylyl cyclase reporter cell lines

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from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P73 doi:10.1186/1471-2210-9-S1-P73

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P73

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Background

Particulate guanylyl cyclases are implicated in a growing number of pathophysiologies and, therefore, represent an important target class for drug development. We report here the generation and pharmacological characterization of three receptor guanylyl cyclase reporter cell lines.

Methods

Plasmid constructs encoding the natriuretic peptide receptors GC-A and GC-B, and the heat-stable enterotoxin receptor GC-C, were stably transfected in a parental reporter cell line expressing the cyclic nucleotide-gated (CNG) cation channel CNGA2, acting as the biosensor for intracellular cGMP.

Results

In our reporter cell lines, receptor guanylyl cyclase activity can be monitored in real-time via aequorin luminescence stimulated by calcium influx through the CNG channel. By using different natural as well as synthetic receptor ligands of the natriuretic and guanylin peptide families, we could show that our reporter assay monitors guanylyl cyclase activity with unrivalled high sensitivity. Receptor antagonists were also tested and, unexpectedly, were characterized as partial agonists.

Conclusion

The results imply that our novel guanylyl cyclase reporter cell lines are well suited for the characterization of receptor pharmacology. This novel reporter system may be used for drug discovery by (u)HTS and for natural ligand characterization of guanylyl cyclase orphan receptors.