BMC Pharmacology

Poster presentation

Open Access

GAF domain-induced activation of phosphodiesterases 2 and 5

Ronald Jäger*, Corina Russwurm, Doris Koesling and Michael Russwurm

Address: Institut für Pharmakologie und Toxikologie, Medizinische Fakultät, Ruhr-Universität Bochum, 44780 Bochum, Germany

Email: Ronald Jäger* - ronald.jaeger@ruhr-uni-bochum.de

* Corresponding author

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):P28 doi:10.1186/1471-2210-9-S1-P28

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P28

The second messenger cGMP is involved in several physiological functions such as smooth muscle relaxation and inhibition of platelet aggregation. Besides cGMP synthesis, hydrolysis of cGMP by cyclic nucleotide phosphodiesterases (PDEs) determines the shape of cGMP signals. Eleven PDE families are known differing in regulation and cAMP/cGMP specificity. PDEs are homodimers; each monomer being composed of different N-terminal regulatory domains and a C-terminal catalytic domain highly conserved between the PDE families. Five PDEs contain a tandem of so called GAF domains in their N termini that have been shown to bind cGMP or cAMP. At least in PDEs 2, 5 and 6, binding of cGMP to the GAF domains leads to stimulation of the enzymes. Here, we focussed on the GAF-mediated stimulation of PDEs 2 and 5.

PDE2 hydrolyzes both cyclic nucleotides, cGMP and cAMP; binding of cGMP to the regulatory GAF domains stimulates cAMP hydrolysis. Because PDE5 lost its regulation by cGMP upon purification, the enzyme has initially been described as "cGMP-binding cGMP-specific PDE". Difficulties to analyse a stimulatory effect of cGMP, the enzyme's substrate, further delayed the recognition of the cGMP-induced stimulation of PDE5.

Here, we screened cyclic nucleotide analogs to identify ligands specifically binding to the regulatory GAF domains without binding to the catalytic domains. We used GAF domain-containing FRET (fluorescence resonance energy transfer) constructs to study binding of the analogs to the GAF domains. Several analogs, specific for the GAF domains of either PDE2 or 5 were identified by this approach and consecutively analyzed regarding their ability to stimulate the holoenzymes. PDE 2-mediated cAMP and cGMP hydrolysis was stimulated 30- and 40-fold by the analogs, respectively. In PDE5, a 20-fold stimulation was observed and surprisingly, the stimulation of PDE5 by GAF domain ligands turned out to be rather slow requiring up to 10 min at low concentrations of the nucleotides.