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Poster presentation

Residues stabilizing the heme moiety of the NO sensor soluble guanylate cyclase

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Soluble guanylate cyclase (sGC), the intracellular receptor for the ubiquitous biological messenger NO, exists as heterodimer consisting of an α- and β-subunit. sGC contains a non-covalently linked heme moiety that is crucial for the NO-induced enzyme activation. This heme is bound to the β-subunit via the axial ligand His-105 and the recently identified counterparts of the heme propionic acids, Tyr-135 and Arg-139.

The latter two residues form, together with the invariant Ser-137, the unique heme binding motif Tyr-X-Ser-X-Arg which was very recently confirmed by crystallization studies of a prokaryotic homologue of the sGC heme binding domain. The aim of the present study was to investigate the influence of the invariant Ser-137 on the sGC heme binding capability and the enzyme activation in the presence of NO and the non-NO sGC-activators BAY 41-2272 and BAY 58-2667 respectively. Therefore, we replaced this residue with Ala and investigated the activation profile of the mutant sGC by transient transfection into the novel cGMP reporter cell line using BAY 41-2272, BAY 58-2667, NO and ODQ as experimental tools.

The mutant sGC was activated by BAY 41-2272. A synergistic increase in sGC activity was observed in the presence of additional NO. However, this well known synergism of both heme-dependent sGC-activators was less than observed for the wild-type enzyme. Activation of the Ser-137-Ala-mutant by DEA/NO alone was markedly diminished. BAY 58-2667-induced sGC activation was much stronger with the Ser-137-mutant compared to the wild-type enzyme but the potentiating effect of ODQ on this activation was negligible compared to the wild-type enzyme.

In summary our results show for the first time that Ser-137 is involved in binding and stabilizing the sGC heme moiety and might be also involved in the intramolecular signal transduction upon NO binding leading to sGC activation.