BMC Pharmacology

Oral presentation

Open Access

Structural insights into sGC

Xiaolei Ma[1], Nazish Sayed[2], Annie Beuve[2] and Focco van den Akker*[1]

Address: [1]Case Western Reserve University, Cleveland, USA and [2]UMDNJ New Jersey Medical School, Newark, USA

Email: Focco van den Akker* - focco.vandenakker@case.edu

* Corresponding author

from 3rd International Conference on cGMP Generators, Effectors and Therapeutic Implications
Dresden, Germany. 15–17 June 2007

Published: 25 July 2007

BMC Pharmacology 2007, **7**(Suppl 1):S37 doi:10.1186/1471-2210-7-S1-S37

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S1/S37

The soluble guanylyl cyclase (sGC) is the main receptor for nitric oxide (NO). Upon NO binding, sGC undergoes a conformational change leading to the 200-fold stimulation of the production of the second messenger cGMP. sGC is a heterodimeric α/β protein with the NO sensory domain located on the N-terminus of the β-subunit, the H-NOX domain. Carbon monoxide (CO) can also activate sGC although only about 4-fold and CO has also a much lower affinity compared to NO. The coordination state of NO and CO activated sGC is also different. These intriguing differences in sGC are not well understood and we have therefore set out to crystallize a homologous bacterial H-NOX domain from *Nostoc sp* for X-ray crystallographic studies. Its ~35% sequence identity with sGC suggests that *Ns* H-NOX is a good model for sGC. The crystal structure of this *Ns* H-NOX domain [1] in the presence and absence of these diatomic ligands reveals that, prior to ligand binding, *Ns* H-NOX is in the 5-coordinated state with H105 as its proximal ligand (Fig. 1). Upon soaking NO or CO into the *Ns* H-NOX crystals, both ligands were found to bind to the distal face of the heme leading to the formation of the 6-coordinated state; CO binds in a more perpendicular fashion compared to NO. The heme moiety was found to pivot upon ligand binding with the CO ligand displaying a larger pivot compared to NO. These steric hindrance-relieving pivot motions are attributed to residue W74 (F74 in sGC) which is postulated to serve as a molecular ruler to dampen the affinity for CO. Structure-guided mutagenesis experiments aided in proposing that full activation of sGC in the 5-coordinated NO-bound state involves concomitant heme bending and N-terminal subdomain shift within the H-NOX domain.

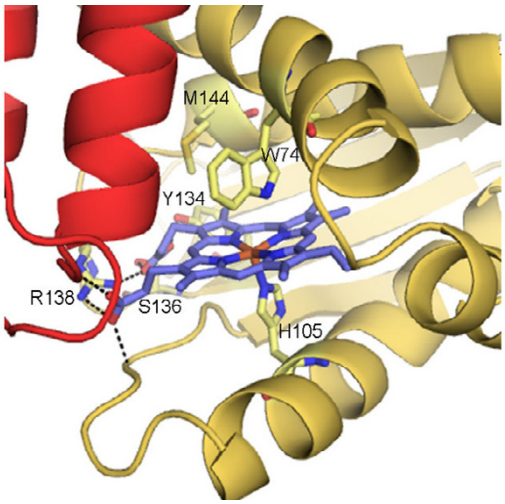

Figure 1
Close-up view of heme pocking in the free *Ns* H-NOX structure. The heme (blue), N-terminal subdomain (red), and key residues proximal to the heme are depicted.

References

1. Ma X, Sayed N, Beuve A, van den Akker F: **NO and CO differentially activate soluble guanylyl cyclase via a heme pivot-bend mechanism.** *EMBO J* 2007, **26:**578-588.