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Molecular steps in soluble guanylate cyclase activation

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Soluble guanylate cyclase (sGC) is a hemoprotein that is selectively activated by specifically binding NO. Once activated sGC synthesizes cyclic GMP from GTP which then triggers reactions essential to animal physiology. sGC essentially functions as a selective sensor for NO. sGC belongs to a recently identified group of proteins termed the H-NOX family (Heme Nitric oxide/OXygen binding proteins) that includes bacterial counterparts from aerobic and anaerobic organisms [1-4]. Based on our recent structure of a family member [3], a molecular basis for the ligand discrimination against O_2 in NO-regulated sGCs has been established. Further studies have pointed towards O_2-regulated sGCs in *C. elegans* [5]. NO binding to the heme remains as a key molecular activation step; however, it has become clear that activation and deactivation are regulated in a complex manner [6,7]. In the accepted model shown below, NO binds to the sGC heme, activating the enzyme after conversion to the 5-coordinate nitrosyl complex.

Our most recent results show that in the presence of physiological concentrations of ATP and GTP, NO dissociation from the sGC heme is ~500 times slower than the rate of enzyme deactivation *in vitro*. Deactivated sGC still has NO bound to the heme, and full activation requires additional NO. We propose an activation model shown below where, in the presence of both ATP and GTP, tonic NO forms a stable heme complex with low sGC activity; acute production of NO transiently and fully activates this NO-bound sGC.

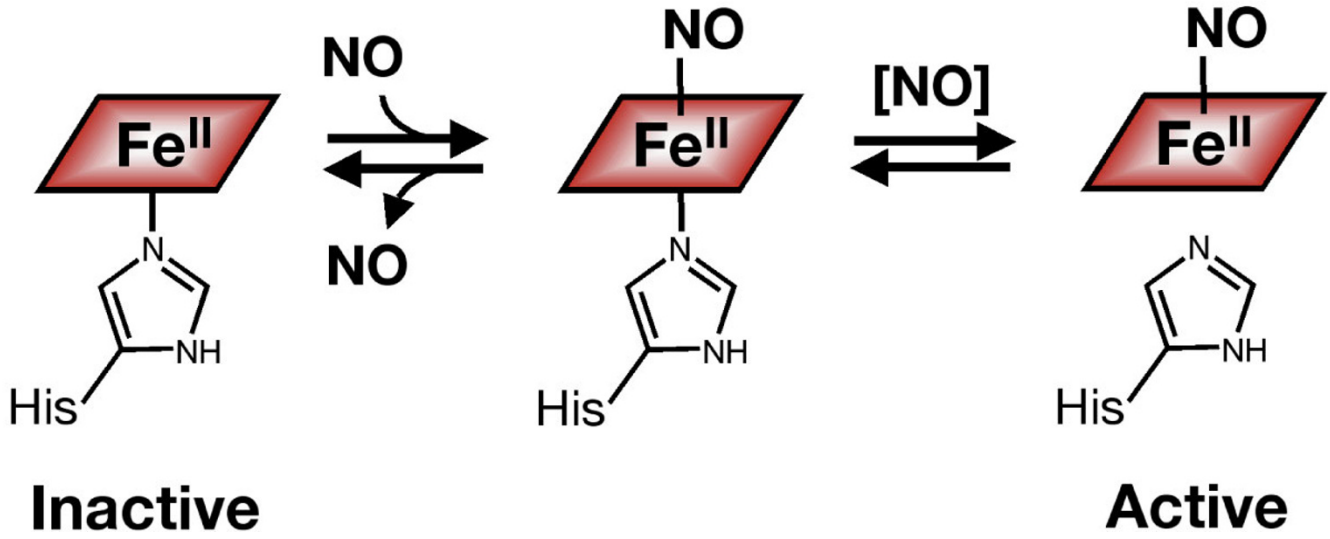

Figure 1

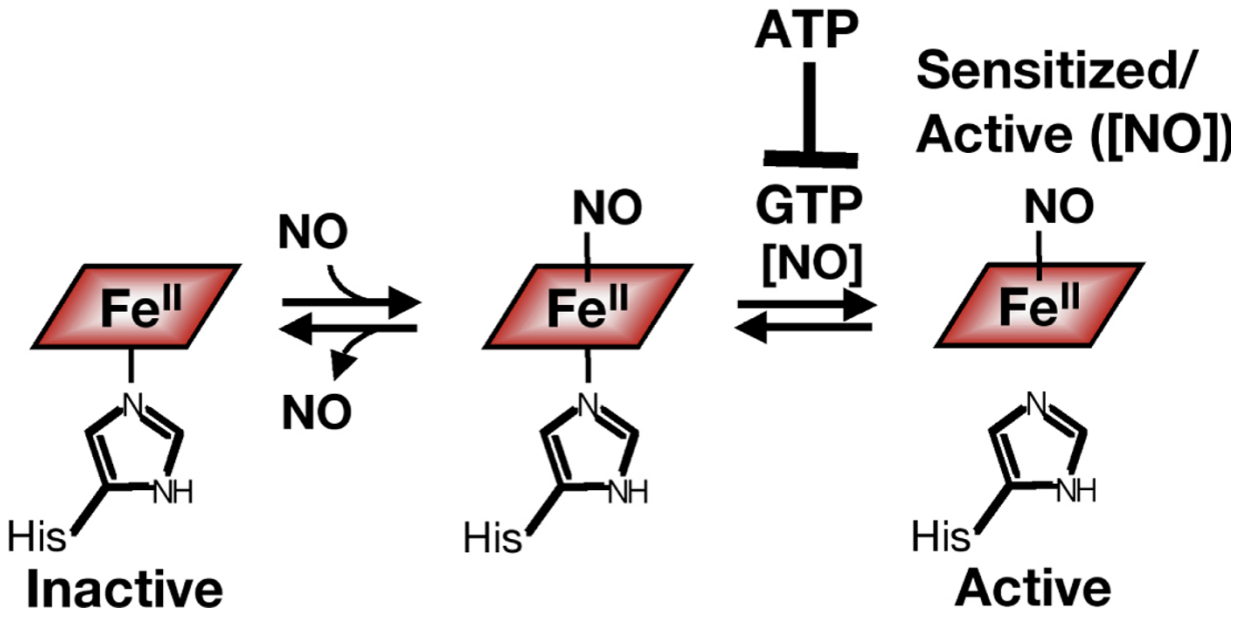

Figure 2

Acknowledgements

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