A Computational Model of the Nitric Oxide/cGMP Signaling Dynamics

Hong Zhang[1], Jin Yang[1]

***Short Abstract* — The nitric oxide (NO)/cGMP pathway plays an important role in the regulation of a variety of physiological responses. Here, we construct a comprehensive model to study the temporal profile of cGMP level under diverse conditions. We would give a specific explanation about competing processes of cGMP synthesis and degradation. We focus on influence of sGC desensitization on cGMP synthesis and PDE phosphorylation on cGMP degradation. At last we will give the dynamics of NO/cGMP under different conditions by simulating NO/cGMP pathway using our model.**

***Keywords* — computational model, reaction kinetics.**

I. INTRODUCTION

Nitric Oxide (NO) regulates cell functions by producing the second messenger cGMP. [1] The synthesis and degradation processes of cGMP serve as important drug targets to modulate NO-induced cellular effects including smooth muscle relaxation, platelet aggregation and synaptic transmission. The different cGMP responses to NO affect downstream pathways.

The temporal profile of cGMP is modulated by the balancing effects of cGMP synthesis and cGMP degradation processes. NO activates soluble guanylyl cyclase (sGC) which catalyzes the conversion of GTP into cGMP. cGMP is hydrolyzed to GMP by PDE which is activated by cGMP binding to its GAF-A domain [2]. PDE can be further phosphorylated by protein kinase G (PKG) which enhances the activity of PDE by increasing cGMP's affinity to its regulatory GAF-A domain [3]. The working model is illustrated in Fig.1. This model includes all possibly important loops in this pathway.

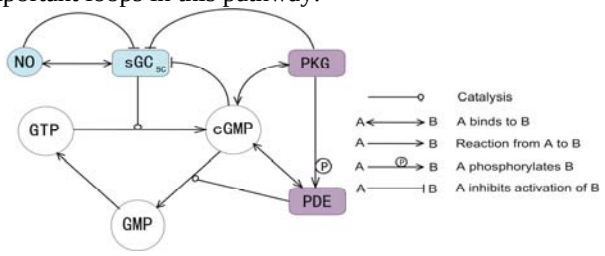

Figure 1: Schematic diagram of NO/cGMP signaling pathway.

II. RESULTS

First, we identified parameters in order to be consistent with experimental data [2,4] under different experimental conditions (Fig.2).

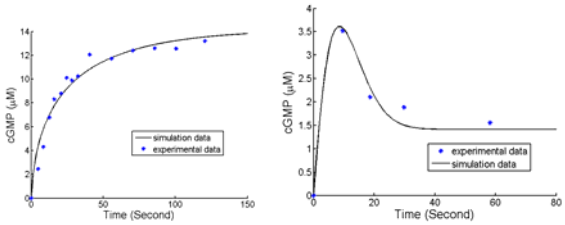

Figure 2: Simulation data are consistent with experimental data from early literatures [2,4].

A. Mutual influence of sGC desensitization and PDE on temporal profile of cGMP

In this pathway, cGMP concentration increases to reach a steady state. Also, NO can induce a spike-like cGMP response. What mechanism contributes the temporal profile of cGMP? In our model, results suggest that both sGC and PDE influence temporal profile of cGMP. Then we would like to test their influences on cGMP level individually.

B. sGC desensitization and PDE phosphorylation

Based on above results, we test following mechanisms: NO-dependent sGC desensitization (feed-forward), PDE and PKG-dependent sGC desensitization (feedback), PDE phosphorylation by PKG, lack of GTP to investigate cGMP response to NO.

III. CONCLUSION

We intend to use a computational model to explain behaviors of NO/cGMP signaling pathway including sGC desensitization by feed-forward and feedback loops, cGMP decrease by GTP consumption, PDE phosphorylation by PKG. This comprehensive model would be a general framework to investigate NO/cGMP signaling pathway.

REFERENCES

[1] Murad F, (1994) Adv. Pharmacol. 19-33
[2] Mullershausen F, et al. (2003) Direct activation of PDE5 by cGMP long-term effects within NO/cGMP signaling. J. Cell Biol. 719-727
[3] Corbin JD, et al. (2003) Phosphorylation of phosphodiesterase-5 by cyclic nucleotide-dependent protein kinase alters its catalytic and allosteric cGMP-binding activities. FEBS J. 2760-2767
[4] Bellamy TC, et al. (2000) Rapid desensitization of the nitric oxide receptor, soluble guanylyl cyclase, underlies diversity of cellular cGMP responses. PNAS 2928-2933
[5] Yang J, et al. (2005) Mathematical modeling of the nitric oxide/cGMP pathway in the vascular smooth muscle cell. Am J Physiol Heart Circ Physiol. H886-H897.

[1] CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, CAS, Shanghai, China
E-mail: zhanghong@picb.ac.cn