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# A mouse (and chips) model for NO-activated guanylyl cyclase

John Garthwaite* and Brijesh Roy

Address: Wolfson Institute for Biomedical Research, University College London, UK

Email: John Garthwaite* - john.garthwaite@ucl.ac.uk

* Corresponding author

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A major aim in studying any signal transduction process is to generate a quantitative depiction of that process that is both biologically and physically realistic. The ensuing model then serves as an explicit hypothesis whose predications can be subjected to direct experimental test and (ideally) also a framework for interpreting new data. Although this approach has been fundamental to gaining an understanding of related signalling mechanisms (e.g. neurotransmission at brain synapses), no such model presently exists for NO signal transduction through its guanylyl cyclase-coupled receptors, despite an abundance of experimental data published during the past three decades. The objective was to assemble the existing information, together with results from necessary new experiments, into a comprehensive and overt description of how this system works. An essential first step was to combine an NO-binding module with a catalytic site where, following a conformational change, GTP is converted into cGMP. The NO binding module is a cubic ternary complex mechanism analogous to the one adopted for G protein-coupled receptors [1]. Catalysis is assumed to follow a mechanism similar to that found for adenylyl cyclase [2]. After allocating rates (or equilibrium constants) to the various steps, constrained to fit experimental results, the resulting hybrid mechanism faithfully describes the basic features of NO activation of guanylyl cyclase and provides explanations for some puzzling published results. The core mechanism has been elaborated to include inhibition by ATP [3] and allosteric enhancement by compounds such as YC-1 and BAY 41–2272 [4].

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