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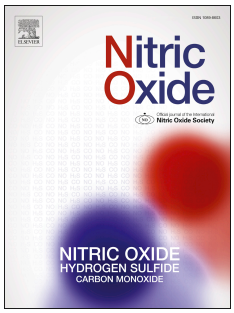

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Physiological Activation and Deactivation of Soluble Guanylate Cyclase

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Keywords: Soluble guanylate cyclase, nitric oxide, heme, activation

Abstract

Soluble guanylate cyclase (sGC) is responsible for transducing the gaseous signaling molecule nitric oxide (NO) into the ubiquitous secondary signaling messenger cyclic guanosine monophosphate in eukaryotic organisms. sGC is exquisitely tuned to respond to low levels of NO, allowing cells to respond to non-toxic levels of NO. In this review, the structure of sGC is discussed in the context of sGC activation and deactivation. The sequence of events in the activation pathway are described into a comprehensive model of *in vivo* sGC activation as elucidated both from studies with purified enzyme and those done in cells. This model is then used to discuss the deactivation of sGC, as well as the molecular mechanisms of pathophysiological deactivation.

Box 1

The heme cofactor in sGC has an inherent sidedness as defined by the presence of the coordinating histidine residue (H105 in humans). The histidine binds to the ferrous iron of the heme cofactor from one side, termed the proximal side, as shown. The opposing side of the heme is referred to as the distal side. Upon binding of NO to the distal side of the heme, the strong σ trans effect induces rupture of the iron–histidyl bond, which is thought to be the first step in signal transduction. However, this cleavage event results in the opening of the proximal coordination site for an additional NO molecule to bind. To clarify the potential heme ligation states in sGC, the following naming convention will be used in this review: 4/5/6c (proximal ligand)–Fe^{2+}–(distal ligand), where 4/5/6c refers to the coordination number of the Fe^{2+} center. For example, unliganded ferrous sGC with the proximal histidine bound would be described as 5c His–Fe^{2+}, whereas a distal ferrous nitrosyl complex would be termed 5c Fe^{2+}–NO.

I. Introduction

In the 1980s, nitric oxide (NO) was first characterized as critical to both innate immunity and endogenous signaling in animals.[1–5] NO was the first gaseous signaling molecule synthesized by animals to have its biochemical signaling pathway fully described.[2] Physiologically, NO signaling causes relaxation of vascular smooth muscle, inhibition of platelet aggregation in the vasculature, and modulation of various forms of neurotransmission.[6,7] Beyond these well-established functions, additional aspects of NO signaling continue to emerge, including in insect development and sensory systems,[8] as well as in human pathologies, such as early-onset achalasia[9] and cancer proliferation.[10]

Soluble guanylate cyclase (sGC), a eukaryotic nitric oxide receptor, is a central component in NO-dependent signaling.[3,11] sGC converts 5′-guanosine triphosphate (GTP) to 3′,5′-cyclic guanosine monophosphate (cGMP). When NO binds to sGC,