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Desensitization of soluble guanylyl cyclase, the NO-receptor, by S-nitrosylation

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Signaling cascades initiated by nitric oxide (NO) are crucial in the physiology and pathophysiology of the cardiovascular system. NO signal is mediated by the soluble guanylyl cyclase (sGC), which is a heme-containing heterodimer that produces cGMP. In spite of its importance, little is known about the mechanisms of regulation of sGC, even though dysfunctions in the NO-cGMP signaling pathway are thought to be responsible for diseases as prevalent as hypertension and atherosclerosis. In particular, the mechanism of desensitization of sGC remained unresolved. Desensitization of sGC is the loss of sGC activation by NO following an initial exposure to NO.

Post-translational modification has been postulated to affect sGC sensitivity to NO but evidence is still lacking. We show here, that sGC is S-nitrosylated and that this S-nitrosylation results in decreased responsiveness to NO characterized by the loss of NO-stimulated sGC activity. Using primary aortic smooth muscle cells and S-nitrosocysteine (CSNO), we provide evidence that desensitization of sGC is concentration and time dependent, and that sensitivity of sGC to NO is restored, and S-nitrosylation reverses with cellular increase of thiols. We confirmed *in vitro* using semi-purified sGC and peroxynitrite that S-nitrosylation directly causes desensitization, suggesting that other cellular factors might not be involved. By using Mass Spectrometry, we have identified two cysteines, one in each subunit that are potentially S-nitrosylated. Replacement of these cysteines with Alanine created mutants that were mostly resistant to desensitization. This study suggests that S-nitrosylation of sGC could be a mean by which memory of NO exposure is kept in smooth muscle cells.

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