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S-nitrosylation of soluble guanylyl cyclase: a novel mechanism of nitrate tolerance?

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Organic nitrates, such as nitroglycerin (GTN) have been used since the 19th century for the treatment of angina pectoris, ischemia and hypertension. Like S-nitrosothiols, organic nitrates are NO-generating compounds that are vasoactive via NO stimulation of the soluble guanylyl cyclase (sGC). The therapeutic effectiveness of GTN is severely limited by the development of nitrate tolerance, which is the loss of NO-dependent vasodilation after exposure to GTN. More than a century after its first description, the mechanism of nitrate tolerance remains a mystery. Recently, much interest has focused on another NO-dependent signal, S-nitrosylation, which could modulate vascular physiology and pathophysiology.

We recently discovered that sGC is S-nitrosylated in cells following treatment with CSNO (S-nitrosocysteine) and that S-nitrosylation correlates with a decrease in NO-simulated sGC activity. We demonstrated *in vitro* with semi-purified sGC that S-nitrosylation causes directly desensitization (Sayed et al, submitted). We now show that S-nitrosylation induces vascular tolerance *in vivo*: NO-dependent vasorelaxation in the vascular system of hamster's pouches was blunted following topical application of CSNO. The cytosols of CSNO treated tissues contained S-nitrosylated sGC and lost most of NO-stimulated sGC activity. These results suggest that S-nitrosylation of sGC leads to its desensitization, which in turn contributes to NO tolerance.

We hypothesized that GTN could induce tolerance by desensitization of sGC via S-nitrosylation. We demonstrated that treatment of primary aortic smooth muscle cells with GTN induces S-nitrosylation of endogenous sGC together with its desensitization. We established that desensitization and S-nitrosylation both reverse with pre-treatment with N-acetyl-cysteine, which is a precursor of glutathione synthesis and is used clinically to reverse tolerance. Finally, using our *in vivo* model, we established that sGC of treated tissues that exhibited GTN-tolerance was S-nitrosylated. Taken together these results suggest, for the first time, that desensitization of sGC via S-nitrosylation contributes to GTN-induced nitrate tolerance.

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