SL12 **Reactive Metabolism Runs Amuck: A Novel Unifying Mechanism of Nitroglycerin Action and Tolerance**

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Nitroglycerin (NTG) belongs to an important group of cardiovascular drugs called organic nitrates, which are used for the acute relief of coronary ischemia and for prophylaxis against angina pectoris. A "mystery" of organic nitrate action, lasting now about 130 years since its discovery, concerns how continuous organic nitrate use rapidly produces therapeutic tolerance (loss of effect). Although several hypotheses have been proposed, a consensus opinion has not been reached regarding how this phenomenon is initiated, and how the myriad of events associated with nitrate tolerance (viz., sulfhydryl dependence, reduced metabolic activation, superoxide formation, vascular gene regulation, etc.) can be reconciled with the initiating mechanism(s). Intriguingly, long-term organic nitrate use did not produce significant benefits in patient outcomes, and, according to some reports (including several from Japan), it may even engender increased cardiovascular risk. The potential mechanism for this phenomenon is also not understood.

We had proposed (Annu Rev Pharmacol Toxicol 2004;44:67-85) that these wide-ranging actions of organic nitrates is underpined by the multiple biochemical reactions between protein cysteine residues (PSH) and NTG. These reactions cause structural thiol modifications in cellular proteins, forming reversible products such as sulfenic acid (PSOH), PS-glutathione conjugates (PSSG) and PSSP, and irreversible oxidation products such as PSO_2H and PSO_3H . We now obtained LCMS evidence documenting the formation of these products, as well as the transient and elusive thionitrate ($PSNO_2$) intermediate, between NTG and a wide array of cellular proteins and peptides. We showed that S-oxidation of metabolizing enzymes such as aldehyde dehydrogenases (I and II) resulted in reduced metabolic bioactivation to produce nitric oxide (NO), the pharmacological active end-product. Enhanced superoxide production associated with NTG tolerance was shown to be mediated by S-oxidation and activation of the xanthine oxidoreductase system. Additionally, cellular signaling and gene regulation could be mediated via the redox regulators PSOH and PSSG, including those in cysteine-dependent regulating factors like p21Ras and NFκB. S-oxidation of the “cysteine switch” in the pro-forms of matrix metalloproteinases (MMPs) led to their activation and enhanced activity, and the potential destabilization of atherosclerotic plaques in blood vessels.

We believe that the present mechanism can provide a unifying hypothesis to explain the century-old mystery of nitrate tolerance, as well as for the observed long-term deleterious effects of organic nitrates in patients.

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