



Review

Nitrate tolerance as a model of vascular dysfunction: Roles for mitochondrial aldehyde dehydrogenase and mitochondrial oxidative stress

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Abstract:

Organic nitrates are a group of very effective anti-ischemic drugs. They are used for the treatment of patients with stable angina, acute myocardial infarction and chronic congestive heart failure. A major therapeutic limitation inherent to organic nitrates is the development of tolerance, which occurs during chronic treatment with these agents. The mechanisms underlying nitrate tolerance remain incompletely defined and are likely multifactorial. One mechanism seems to be a diminished bioconversion of nitroglycerin, another seems to be the induction of vascular oxidative stress, and a third may include neurohumoral adaptations. Recent studies have revealed that mitochondrial reactive oxygen species (ROS) formation and a subsequent oxidative inactivation of nitrate reductase, the mitochondrial aldehyde dehydrogenase (ALDH-2), play an important role in the development of nitrate and cross-tolerance. The present review focus first on the role of oxidative stress and second on the role of ALDH-2 in organic nitrate bioactivation leading to the development of tolerance and cross-tolerance (endothelial dysfunction) in response to nitroglycerin treatment. Recently, the role of mitochondrial oxidative stress in the development of nitrate tolerance was demonstrated in a mouse model with a heterozygous deletion of manganese superoxide dismutase (MnSOD^{+/-}), which is the mitochondrial isoform of this enzyme. Studies from our own laboratory have provided evidence for cross-talk between mitochondrial and cytosolic (Nox-dependent) sources of ROS. We close this review by focusing on the protective properties of the organic nitrate pentaerythrityl tetranitrate, which up-regulates enzymes that have strong antioxidative activity, such as heme oxygenase-1 and ferritin, thereby preventing the development of tolerance and endothelial dysfunction.

Key words:

organic nitrate, superoxide, peroxynitrite, mitochondrial aldehyde dehydrogenase, mitochondrial oxidative stress, vascular dysfunction
