Isosorbide-5-mononitrate and endothelial function: a wolf in sheep’s clothing

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This editorial refers to ‘Chronic therapy with isosorbide-5-mononitrate causes endothelial dysfunction, oxidative stress, and a marked increase in vascular endothelin-1 expression’, by M. Oelze et al., on page 3206

In 1846, Ascanio Sobrero first synthesized nitroglycerin and observed that a small quantity of the oily substance placed on the tongue caused a severe headache. In its pure form—without an inert carrier such as lactose—nitroglycerin is explosive. It was therefore used by Alfred Nobel to manufacture dynamite. It took until the end of the 1860s before the antianginal effect of nitroglycerin was discovered. What had happened? Two findings were crucial: first, workers suffering from angina pectoris at the weekend were free of pain during the week; secondly, some workers described severe headaches on Mondays, but felt relief of pain at the end of the week and were absolutely free of pain at the weekends.

Those observations were attributed to the vasodilatory properties of nitroglycerin. More than 100 years later, the mechanisms of action were discovered. The molecule nitric oxide (NO) is produced by nitroglycerin in smooth muscle cells. NO activates guanylyl cyclase, increasing intracellular levels of cyclic guanosine 3’,5’-monophosphate (cyclic GMP), leading to vasodilation. This was the basis for further studies revealing that mammalian cells produce NO, culminating in awarding the Nobel Prize in Medicine and Physiology to Furchgott, Ignarro, and Murad for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system in 1998.

As well-established drugs, organic nitrates still belong to the most important drug classes used in the treatment of acute coronary syndromes, stable coronary artery disease, and acute and chronic congestive heart failure. One major problem with organic nitrates is the development of so-called ‘nitrate tolerance’, which is the result of a complex interplay of distinct mechanisms. In brief, the following mechanisms are involved: (i) a decrease in the endogenous biotransformation of organic nitrates by aldehyde dehydrogenase-2; (ii) desensitization of soluble guanylyl cyclase (sGC) and an increase in phosphodiesterase activity; (iii) release of vasopressor and catecholamines; and (iv) increased production of superoxide anions together with other reactive oxygen species (ROS) by mitochondrial complex-3 and other NADPH oxidases.

In contrast to the high potency nitrates [i.e. glycerol trinitrate (GTN) and pentaerythritol tetranitrate (PETN)], the low potency nitrates such as isosorbide dinitrate (ISDN) and isosorbide-5-mononitrate (ISMN) are bioactivated by cytochrome P450. In the USA, ISMN is the most commonly used long-acting NO donor and one of the most frequently used drugs in the treatment of coronary artery disease. It is well tolerated, and the most frequently reported adverse event, headache, is usually mild to moderate, improves with long-term therapy, and rarely leads to treatment withdrawal. However, there are stains on ISMN’s clean slate. There is emerging evidence from experimental and one clinical study in healthy subjects that the administration of a clinically employed dosing regimen of ISMN is associated with the development of endothelial dysfunction. This finding is surprising and worrying, given the traditional concept that NO donors might have beneficial effects in the setting of decreased NO bioavailability. Results from patients with coronary artery disease and vascular dysfunction and/or from patients with congestive heart failure are lacking. However, results of a meta-analysis demonstrating that treatment of post-infarction patients with monod and dinitrates worsened patients’ outcome are indeed alarming. What is the mechanism behind this? How can the application of exogenous NO harm the source of the endogenous NO, namely the endothelium?

Now Oelze et al. have put things right. The authors reveal the mechanisms of the deleterious effects of chronic ISMN administration on endothelial function and shed light on the dark side of ISMN. In an experimental study in rats they demonstrate that treatment with ISMN over 7 days causes endothelial dysfunction and oxidative stress. This was mediated by an endothelin-dependent activation of the vascular and phagocytic NADPH oxidase activity. Bosentan, a non-selective endothelin receptor blocker, in turn normalized endothelial dysfunction. ISMN up-regulated the

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expression of NADPH subunits and led to uncoupling of the endothelial NO synthase (eNOS) due to down-regulation of the tetrahydrobiopterin-synthesizing enzyme GTP-cyclohydrolase-1 and S-glutathionylation of eNOS. The negative effects of ISMN were blocked by the NADPH oxidase inhibitor apocynin, demasking the vascular NADPH oxidase as an important source for superoxide anion production. Further experiments in gp91phox (Nox2)-deficient mice identified Nox2 as a possible mechanistic link, as a normalization of the activation of leucocytes, decreased serum antioxidant capacity, decreased endothelial dysfunction, and decreased membranous NADPH oxidase activity were observed.

The problem that organic nitrates cause endothelial dysfunction—the so-called ‘phenomenon of cross-tolerance’—has been described in detail for GTN and ISDN. No cross-tolerance has been found for PENTN in the PENTA study. Thomas et al. showed that cross-tolerance also affected ISMN in healthy subjects. However, it remains unclear whether this finding is of relevance for clinical practice, as mechanistic studies on the role of chronic ISMN administration in patients with cardiovascular diseases are lacking. It is speculative as to whether ISMN exerts identical effects in patients compared with healthy volunteers or rats. The mechanistic aspects whereby organic nitrates increase endothelin and subsequently NADPH oxidase-derived ROS production, which leads to uncoupling of eNOS, have also been described for GTN.

So what can we learn from the study by Oelze et al.? The authors show that treatment with the endothelin receptor blocker bosentan reverses organic nitrate-induced endothelial dysfunction. Similar results have been shown for antioxidants such as vitamin C. One may wonder whether novel therapeutic aspects for bosentan and/or antioxidants may arise for treating organic nitrate-induced endothelial dysfunction. The combination therapy of ISDN with hydralazine—a powerful antioxidant—has already been shown to improve prognosis in African Americans with severe congestive heart failure.

Similar approaches may be taken in the future with protein kinase C (PKC) inhibitors. PKC activates the NADPH oxidases in the vasculature, leading to increased ROS formation. Future clinical studies testing PKC inhibitors in humans will provide more insights into the effects of these drugs.

Are there alternatives to increase the endogenous NO pool other than with organic nitrates? There is emerging evidence that inorganic nitrate may fulfill many of the actions of organic nitrate, however, without exerting the side effects of organic nitrates. The supposedly inert anion nitrite, abundant in vegetables, can be stepwise reduced in vivo to form nitrite, and consecutively NO, representing a more physiological alternative to endogenous NO formation by NOSs.

Dietary amounts of nitrate clearly have robust NO-like effects in humans, including blood pressure reduction, inhibition of platelet aggregation, and vasoprotective activity. In animal models, inorganic nitrate protects against ischaemia–reperfusion injuries and several other types of cardiovascular disorders. Further studies in humans are ongoing and we should be excited to see what the future brings and whether—at least in part—a switch from organic to inorganic nitrate is possible.

Taken together, the seminal findings reported by Oelze et al. and emerging data from preclinical studies using PKC, NADPH oxidase inhibitors, and inorganic nitrates may lead to a rethink and re-evaluation of our current therapeutic strategies in using various types of NO donors and oxidative stress-modulating substances in patients with vascular dysfunction and diseases.

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References

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