

ALDH2 Activator (Alda-1) for Heart Benefit: A Look Ahead

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We thank Ferreira and Mochly-Rosen [1] for their innovative ideas and thorough discussion on the molecular mechanisms associated with the benefits and risks of glyceryl trinitrate (GTN) in myocardial infarction (MI). Mitochondrial aldehyde dehydrogenase2 (ALDH2) plays a major role in acetaldehyde detoxification, that has proven to protect various alcohol-related diseases, including cancer [2], asthma [3] and heart disease [4]. ALDH2 is involved in antioxidant defense and its deficiency enhances oxidative stress [5]. In addition, ALDH2 contributes to a variation in the efficacy of nitroglycerin treatment for angina and heart failure [6,7]. Recently, mitochondrial ALDH2 is identified as a protein kinase C epsilon (PKCε) substrate, whose activity strongly correlates with cardioprotection [7].

GTN has been proven effective in treating angina, ischemia and heart failure [8,9]. GTN is converted in smooth muscle cells to nitric oxide (NO), which activates soluble guanylate cyclase to generate the cyclic GMP that in turn results in vascular smooth muscle relaxation, ensuing in increase blood flow to the myocardium [1]. Unfortunately, after chronic application, its therapeutic efficacy is blunted because of the development of nitrate tolerance [10]. Besides, the dehydrogenase activity of ALDH2 is downregulated by GTN tolerance, leading to accumulation of toxic aldehydes (ie, 4-hydroxy- 2-nonenal) inside the mitochondria [1]. Given the importance of ALDH2 in cytoprotective signaling in different tissues (including the heart), GTN tolerance should be considered.

The recent discovery of a novel small molecule, Alda-1 (a selective ALDH2 activator) given concomitantly with GTN prevented the GTN-induced increase in cardiac dysfunction after MI in animal [11]. Alda-1 can ameliorate ischemia through metabolism of reactive aldehydes (such as 4-hydroxy- 2-nonenal) and through its role in the bioconversion of nitrates to NO [12]. Many people of East Asian descent are deficient in ALDH2, which processes alcohol [13]. Further studies are required, however, to clarify the molecular mechanisms of GTN tolerance, as well as clinical research to evaluate the use of sustained GTN treatment in patients with cardiovascular diseases, especially in East Asian patients.

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