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Aldehyde dehydrogenase 2 protects human umbilical vein endothelial cells against oxidative damage and increases endothelial nitric oxide production to reverse nitroglycerin tolerance

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ABSTRACT. Medical nitroglycerin (glyceryl trinitrate, GTN) use is limited principally by tolerance typified by a decrease in nitric oxide (NO) produced by biotransformation. Such tolerance may lead to

endothelial dysfunction by inducing oxidative stress. *In vivo* studies have demonstrated that aldehyde dehydrogenase 2 (ALDH2) plays important roles in GTN biotransformation and tolerance. Thus, modification of ALDH2 expression represents a potentially effective strategy to prevent and reverse GTN tolerance and endothelial dysfunction. In this study, a eukaryotic expression vector containing the *ALDH2* gene was introduced into human umbilical vein endothelial cells (HUVECs) by liposome-mediated transfection. An indirect immunofluorescence assay showed that ALDH2 expression increased 24 h after transfection. Moreover, real-time polymerase chain reaction and western blotting revealed significantly higher ALDH2 mRNA and protein expression in the gene-transfected group than in the two control groups. GTN tolerance was induced by treating HUVECs with 10 μM GTN for 16 h + 10 min, which significantly decreased NO levels in control cells, but not in those transfected with *ALDH2*. Overexpression of ALDH2 increased cell survival against GTN-induced cytotoxicity and conferred protection from oxidative damage resulting from nitrate tolerance, accompanied by decreased production of intracellular reactive oxygen species and reduced expression of heme oxygenase 1. Furthermore, ALDH2 overexpression promoted Akt phosphorylation under GTN tolerance conditions. *ALDH2* gene transfection can reverse and prevent tolerance to GTN through its bioactivation and protect against oxidative damage, preventing the development of endothelial dysfunction.

Key words: Aldehyde dehydrogenase 2; Oxidative damage; Transfection; Nitric oxide; Nitroglycerin tolerance; Bioconversion

