Role Of Glyceraldehyde-3-Phosphate Dehydrogenase In Nitrate Tolerance And Bioactivation Of Glyceryl Trinitrate

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For over a century, the most common treatment for angina pectoris and cardiac failure has been glyceryl trinitrate (GTN). However, the rapid onset of GTN tolerance limits its clinical utility. It has been suggested that tolerance is caused by the inhibition of an enzyme that metabolizes GTN into physiologically active NO. Recently, mitochondrial aldehyde dehydrogenase (mtALDH) has been identified as one such enzyme.[1]

A related enzyme, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has also been observed to deactivate upon exposure to GTN.[2] The goal of this project was to investigate a possible role for GAPDH in the bioactivation of GTN and nitrate tolerance. The effects of GTN on GAPDH dehydrogenase activity were studied with time and dose dependent enzymatic assays. Results show that with increasing GTN concentration and time exposure, the enzymatic activity of GAPDH is severely decreased. Mass spectrometry was then used to study the protein modifications on GAPDH due to GTN exposure. It was found that following GTN incubation, the GAPDH active site cysteines had been altered. Also, the ability of GAPDH to catalyze the formation of NO_2^- (regarded as the biological precursor to NO) from GTN was investigated using an HPLC-fluorescence assay. This revealed that GAPDH catalyzes the production of low concentrations of NO_2^- from GTN.

[1] Z. Chen, J. Zhang, J. S. Stamler, *PNAS*, **2002**, 99, 8306-8311
[2] B. Jakschik, P. Needleman, *Biochem. Biophys. Res. Com*., **1973**, 53, 539-544