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### Bioactivation of nitroglycerin by the East Asian variant of aldehyde dehydrogenase-2

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#### Background

The East Asian variant of mitochondrial aldehyde dehydrogenase (ALDH2) exhibits significantly reduced dehydrogenase, esterase and nitroglycerin (GTN) reductase activities [1]. The small molecule Alda-1 was reported to partly restore low acetaldehyde dehydrogenase activity of this variant [2]. In the present study we compared the wild-type enzyme (ALDH2\*1) with the East Asian variant (ALDH2\*2) regarding GTN bioactivation and effects of Alda-1.

#### Results

Alda-1 increased acetaldehyde oxidation by ALDH2\*1 and ALDH2\*2 about 2- and 15-fold, respectively. The effects of this compound on the esterase activities of both enzymes were identical to that of NAD (6- and 10-fold stimulation with ALDH2\*1 and ALDH2\*2, respectively), but in the presence of the nicotinamide Alda-1 stimulated the esterase activity of ALDH2\*1 only 1.7-fold, whereas the ALDH2\*2-catalyzed reaction was increased 73-fold. ALDH2\*1 exhibited a greater affinity for GTN than ALDH2\*2 as well as a 7-fold higher maximal GTN denitration activity. However, bioactivation of the nitrate, measured as soluble guanylate cyclase (sGC) activation, was much more pronounced ( $8.8 \pm 0.2$  and  $18.2 \pm 0.9$   $\mu\text{mol cGMP min}^{-1} \text{mg}^{-1}$  in the presence of 100  $\mu\text{g}/100 \mu\text{L}$  ALDH2 and 100  $\mu\text{M}$  GTN). Alda-1 caused 30–70% inhibition of GTN denitration by ALDH2\*1 but had no effect on the ALDH2\*2-catalyzed reaction and did not affect GTN-induced sGC activation in the presence of either variant.

#### Conclusions

The present results indicate that Alda-1 stimulates established ALDH2 activities by improving NAD binding but does not restore impaired GTN bioactivation by the East Asian variant. In addition, our data revealed an unexpected discrepancy between GTN reductase activity and sGC activation, suggesting that GTN denitration and bioactivation reflect independent reactions catalyzed by ALDH2.

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