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Poster presentation

Activation of soluble guanylate cyclase in the presence of purified human aldehyde dehydrogenases

Matteo Beretta*[1], Alexander Kollau[1], Michael Russwurm[2], Doris Koesling[2], Wing Ming Keung[3], Kurt Schmidt[1] and Bernd Mayer[1]

Address: [1]Department of Pharmacology and Toxicology, Karl-Franzens-Universität Graz, 8010 Graz, Austria, [2]Department of Pharmacology and Toxicology, Ruhr-Universität Bochum, 44780 Bochum, Germany and [3]Department of Pathology, Harvard Medical School, Boston, 02115, MA, USA

Email: Matteo Beretta* - Matteo.Beretta@uni-graz.at

* Corresponding author

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Mitochondrial aldehyde dehydrogenase (ALDH2) was reported to catalyze bioactivation of nitroglycerin (GTN), resulting in the formation of a nitric oxide (NO) – like species activating soluble guanylate cyclase (sGC). However, the reaction product is thought to be nitrite, which does not activate sGC, so the link between GTN metabolism and sGC activation is not clear yet.

Since we found no link between ALDH2-catalyzed GTN metabolism and mitochondrial nitrite reduction (Kollau A., Beretta M. & Mayer B.; unpublished), we investigated the possibility that an activator of sGC is produced directly in the course of ALDH2 reaction by co-incubation of purified human ALDH2 with purified sGC in the presence of GTN. In the absence of ALDH2, GTN had no effect on sGC activity (0.28 ± 0.07 μmol/mg/min). In the presence of 25 μg of ALDH2 there was a biphasic stimulation of cGMP formation with an EC50 (half-maximally effective concentration) of ~1 μM GTN and a maximum at 10 μM GTN (1.66 ± 0.22 μmol/mg/min). The effect of ALDH2 was dependent on the protein concentration, with a linear increase from 1 to 100 μg (2.10 ± 0.23 μmol/mg/min) and saturation between 100 and 250 μg of ALDH2. ALDH2-dependent sGC activation was inhibited by 1 mM chloral hydrate (41.5% of control) and by 100 μM daidzin (18.9% of control). The effect of ALDH2 on cGMP formation was almost completely inhibited by the NO scavenger oxy-haemoglobin, the superoxide generator flavin adenine dinucleotide, and the heme site sGC inhibitor ODQ (0.1 mM, each).

The cytosolic ALDH isoform (ALDH1) also metabolized GTN to 1,2- and 1,3-GDN (dinitroglycerin) and triggered sGC activation. In line with the about 1,000-fold lower substrate affinity of ALDH1, significantly higher GTN concentrations were required for sGC activation. There was a linear increase in cGMP formation by sGC co-incubated with 50 μg of ALDH1 and 10 μM to 1 mM GTN. At the highest GTN concentration tested (1 mM), sGC activity was 4.25 ± 0.15 μmol/mg/min. As observed with ALDH2-mediated sGC activation, the response to ALDH1 was dependent on the protein concentration with a linear increase from 5 to 100 μg ALDH1. The effect of ALDH1 on cGMP formation was inhibited by 1 mM chloral hydrate (57% of control) but not by 100 μM daidzin.

These results suggest that both ALDH1 and ALDH2 catalyze GTN bioactivation by direct formation of NO or a NO-like activator of sGC.