BMC Pharmacology

Poster presentation

Open Access

Bioactivation of pentaerythrityl tetranitrate by mitochondrial aldehyde dehydrogenase

Martina Griesberger*[1], Gerald Wölkart[1], Antonius Gorren[1], Matteo Beretta[1], Verena Wenzl[1], Juliane Brettschneider[2], Andreas Seeling[2], Jochen Lehmann[2], Michael Russwurm[3], Doris Koesling[3], Kurt Schmidt[1] and Bernd Mayer[1]

Address: [1]Department of Pharmacology and Toxicology, Karl-Franzens University, Graz, Austria, [2]Institute of Pharmacy, Friedrich-Schiller-University, Jena, Germany and [3]Department of Pharmacology and Toxicology, Ruhr-University, Bochum, Germany

Email: Martina Griesberger* - martina.griesberger@uni-graz.at

* Corresponding author

from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P17 doi:10.1186/1471-2210-9-S1-P17

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P17

Background

Organic nitrates represent a class of very effective anti-ischemic drugs used for the treatment of angina pectoris, myocardial infarction and congestive heart failure [1]. A limitation of their clinical use is the development of nitrate tolerance. A remarkable exception is the long-acting drug pentaerythrityl tetranitrate (PETN), which was shown to cause no tolerance [2]. The mitochondrial isoform of aldehyde dehydrogenase (ALDH2) was shown to be involved in bioactivation of nitroglycerin (GTN) [3] and PETN [4]. The present work was carried out to study the molecular mechanisms underlying the pharmacological differences between GTN and PETN at the level of purified ALDH2.

Results

As quantified by liquid chromatography-mass spectroscopy (LC-MS) ALDH2 metabolized 50 μM PETN to 14.84 ± 4.05 nmol/min/mg pentaerythrityl trinitrate (PETriN) in the absence and 62.38 ± 7.21 nmol/min/mg PETriN in the presence of the reducing agent dithiothreitol. Co-incubation of 2 μM [^{14}C]GTN with ALDH2 and increasing concentrations of PETN resulted in only small decreases in 1,2-glyceroldinitrate formation as measured by radio thin layer chromatography (control: 7.98 ± 0.20, 1 μM PETN: 7.95 ± 0.20, 10 μM PETN: 7.41 ± 0.18, 100 μM PETN: 6.66 ± 0.50 nmol/min/mg) indicating that PETN does not compete with GTN metabolism. In the presence of 25 μg of ALDH2 PETN activated soluble guanylate cyclase (sGC) with an EC_{50} of 3.61 ± 0.35 μM and a maximum at 30 μM PETN (2.67 ± 0.12 μmol/min/mg). This effect was enhanced by superoxide dismutase (SOD) resulting in an EC_{50} of 0.64 ± 0.08 μM and maximal sGC activation (18.44 ± 0.27 μmol/min/mg in the presence of 30 μM PETN). ALDH2 activity, measured as formation of NADH from NAD^+ in the presence of acetaldehyde, was rapidly inactivated by GTN but not by PETN (1 mM each).

Conclusion

Low and high affinity pathways of PETN may explain the apparent differences between PETN metabolism and bioactivation, respectively. The reaction of PETN with ALDH2 leads to activation of sGC with markedly higher values in the presence of SOD suggesting formation of superoxide as a co-product of PETN metabolism. The lack of vascular tolerance to PETN may be due to significantly lower rates of ALDH2 inactivation as compared to GTN.

Acknowledgements

This work was supported by the Fonds zur Förderung der Wissenschaftlichen Forschung in Austria.

References

1. Daiber A, Oelze M, Wenzel P, Wickramanayake JM, Schuhmacher S, Jansen T, Lackner KJ, Torzewski M, Münzel T: **Nitrate tolerance as a model of vascular dysfunction: Roles for mitochondrial aldehyde dehydrogenase and mitochondrial oxidative stress.** *Pharmacol Rep* 2009, **61:**33-48.
2. Jurt U, Gori T, Ravandi A, Babaei S, Zeman P, Parker JD: **Differential effects of pentaerythritol tetranitrate and nitroglycerin on the development of tolerance and evidence of lipid peroxidation: a human in vivo study.** *J Am Coll Cardiol* 2001, **38:**854-859.
3. Chen Z, Zhang J, Stamler JS: **Identification of the enzymatic mechanism of nitroglycerin bioactivation.** *Proc Natl Acad Sci USA* 2002, **99:**8306-8311.
4. Daiber A, Oelze M, Coldewey M, Bachschmid M, Wenzel P, Sydow K, Wendt M, Kleschyov AL, Stalleicken D, Ullrich V, Mülsch A, Münzel T: **Oxidative stress and mitochondrial aldehyde dehydrogenase activity: a comparison of pentaerythritol tetranitrate with other organic nitrates.** *Mol Pharmacol* 2004, **66:**1372-1382.