BMC Pharmacology

Oral presentation

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Endothelium-mediated actions of the ANP/cGMP system

Markus N Kruse[1], Karim Sabrane[1], Larissa Fabritz[2], Bernd Zetsche[1], Danuta Mitko[1], Boris V Skryabin[3], Melanie Zwiener[2], Hideo A Baba[4], Masashi Yanagisawa[5] and Michaela Kuhn*[1,6]

Address: [1]Institute of Pharmacology and Toxicology, Universitätsklinikum Münster, Germany, [2]Department of Cardiology and Angiology, Universitätsklinikum Münster, Germany, [3]Institute of Experimental Pathology, Universitätsklinikum Münster, Germany, [4]Institute of Pathology, Universität Ruhr-Essen, Germany, [5]Department of Molecular Genetics and Howard Hughes, Medical Institute, Southwestern Medical Center, Dallas, Texas, USA and [6]Institute of Physiology, University of Würzburg, Germany

Email: Michaela Kuhn* - michaela.kuhn@mail.uni-wuerzburg.de

* Corresponding author

from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):S31 doi:10.1186/1471-2210-5-S1-S31

Atrial natriuretic peptide (ANP) via its vasodilating and diuretic effects has an important physiological role in the maintenance of arterial blood pressure and volume. Its guanylyl cyclase-A (GC-A) receptor is highly expressed in vascular endothelium, but the functional relevance is controversial. To dissect the endothelium – mediated actions of ANP *in vivo*, we inactivated the *GC-A* gene selectively in endothelial cells by homologous loxP/Tie2-Cre-mediated recombination. Notably, despite full preservation of the direct vasodilating effects of ANP, mice with endothelial-restricted GC-A deletion (EC *GC-A* KO mice) exhibited significant arterial hypertension and cardiac hypertrophy. Echocardiographic and Doppler flow evaluations demonstrated that cardiac output and stroke volume as well as the mean pressure gradient and maximal flow velocity across the aortic valve were increased in EC *GC-A* KO as compared to control mice with normal GC-A expression levels. Application of the Evan's Blue dilution technique showed that the total plasma volume of EC *GC-A* KO mice was increased by 11–13%, even under conditions of normal dietary salt intake. Infusion of ANP caused immediate raises in hematocrit in control but not in EC *GC-A* KO mice, indicating that ablation of endothelial GC-A completely prevented the acute contraction of intravascular volume by ANP. Furthermore, intravenous ANP acutely enhanced the rate of clearance of radio-iodinated albumin from the circulatory system in control mice but not in EC *GC-A* KO littermates. We conclude that GC-A – mediated increases in endothelial permeability are critically involved in the hypovolemic, hypotensive actions of ANP.