Evidence of systemic and pulmonary endothelial dysfunction in the Dimethylarginine Dimethylaminohydrolase I (DDAH I+/-) heterozygous knockout mouse.

Mohammed Malaki
Manasi Nandi
M. Madhani
Herpreet Gill
Caroline L. Smith*
James M. Leiper
Patrick Vallance

Centre for Clinical Pharmacology and Therapeutics, BHF Laboratories, University College London, UK

* Caroline L. Smith now works within the School of Biosciences, University of Westminster

This is an electronic version of an article published in Vascular Biology and Medicine: 3rd European Meeting, Hamburg, September 2005, abstracts. Journal of Vascular Research (42, supplement 2). Karger, Germany, 81. ISBN 3805580355. The definitive version is available online at:

http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowPDF&ProduktNr=224160&Ausgabe=231361&ArtikelNr=89079&filename=89079.pdf

As published in:
Vascular Biology and Medicine: 3rd European Meeting, Hamburg, September 2005, abstracts. Journal of Vascular Research (42, supplement 2). Karger, Germany, 81. ISBN 3805580355

Evidence of systemic and pulmonary endothelial dysfunction in the dimethylarginine Dimethylaminohydrolase I (DDAH I+/-) heterozygous knockout mouse.

M. Malaki, M. Nandi, M. Madhani, H. Gill, C. Smith, J. Leiper, P. Vallance
Centre for Clinical Pharmacology and Therapeutics, BHF Laboratories, University College London, London, GB.

Background: Asymmetric dimethylarginine (ADMA) is a naturally occurring endogenous inhibitor of all three isoforms of nitric oxide synthase. Increased levels of ADMA have been associated with conditions such as hypercholesterolaemia, diabetes and hypertension, where there is evidence of endothelial dysfunction. ADMA is metabolised by the enzyme, dimethylarginine dimethylaminohydrolase (DDAH). Two DDAH isoforms are present in mammals (DDAH I and II). Inhibition of DDAH leads to increased ADMA levels and endothelial dysfunction. Reduced expression of DDAH and/or elevated ADMA levels have been reported in human and animal models of pulmonary hypertension.

Methods: We created a heterozygous knockout DDAH I+/- on a C57Black/SV129 background. Concentration of ADMA and DDAH expression were determined by high performance liquid chromatography and western blotting, respectively. Vascular function was studied in vitro using standard organ bath pharmacology, and in vivo by measuring systemic and right ventricular pressures. Structural differences in pulmonary vessels were assessed histologically.

Results: The DDAH I +/- had reduced DDAH I protein expression in all tissues examined, and had increased circulating (0.69±0.02uM vs.0.87±0.06uM, $p<0.05$, n=12 per group) and tissue ADMA levels (2.87±0.24uM vs 3.68±0.31uM, $p<0.05$, n=12 per group) compared to their wild type littermates. Vascular studies revealed an impairment of endothelium dependent (ACh) relaxations both in the aorta and pulmonary arteries of DDAH+/- compared to wild types (aorta,$p<0.05$, 2- way ANOVA, n=5; pulmonary, $p<0.05$, 2-way ANOVA, n=7). In vivo there were no significant differences in systemic blood pressures, but the DDAH I +/- mice had higher right ventricular pressures (16.79±0.49 mm Hg vs 14.97±0.62 mm Hg, $p<0.001$, n=7). Examination of the pulmonary vasculature revealed increased medial smooth muscle area of resistance vessels in DDAH I +/- mice consistent with the raised RV pressures.

Conclusions: These studies establish DDAH I as a key determinant of ADMA levels in vivo and demonstrate a causal relationship between ADMA and cardiovascular pathophysiology.