Potential therapeutic benefit of novel DDAH inhibitors for the treatment of endotoxemia.

Manasi Nandi
Sharon Rossiter
B. Torondel
Mohammed Malaki
Caroline L. Smith*
R. Stidwell
James M. Leiper
Patrick Vallance

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, pp. 103. 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

In: Vascular Biology and Medicine: 3rd European Meeting, Hamburg, September 2005, abstracts. Journal of Vascular Research (42, supplement 2). Karger, Germany, 103. ISBN 3805580355

Potential therapeutic benefit of novel DDAH inhibitors for the treatment of endotoxemia.

M. Nandi, S. Rossiter, B. Torondel, M. Malaki, C. Smith, R. Stidwill, J. Leiper, P. Vallance University College London, London, GB.

INTRODUCTION During the onset of sepsis, the induction of inducible nitric oxide synthase (iNOS) and the subsequent generation of large amounts of nitric oxide (NO) is thought to be partly responsible for the marked hypotension ultimately leading to inadequate organ perfusion and cardiovascular collapse. A potential therapeutic target in sepsis is inhibition of excess NO generation, although to date, direct NOS inhibition has proved unsuccessful. Asymmetric dimethylarginine (ADMA) is an endogenously occurring competitive inhibitor of NOS. ADMA is subject to hydrolysis catalysed by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). We have developed novel DDAH inhibitors to pharmacologically elevate endogenous ADMA levels as a potential therapeutic intervention in the treatment of sepsis.

METHODS Novel inhibitors of DDAH were synthesised and characterised using: in vitro enzyme assays and in vitro and in vivo rat models of acute endotoxemia.

RESULTS Isolated enzyme studies revealed that the novel DDAH inhibitor L-291 resulted in a concentration dependent inhibition of DDAH activity whilst having no direct effect on NOS activity. In vitro functional studies using isolated rat aorta demonstrated that L-291 reversed the iNOS mediated dilatation produced by
LPS treatment by 16% ± 4.4 at 100uM and 25%± 4.1 at 200uM.
In anaesthetised rats, a bolus dose of LPS induces iNOS mediated vasodilatation resulting in a gradual fall in blood pressure. Administration of L-291 in LPS treated rats elevated circulating ADMA levels when compared with saline control
(2.42 ± 0.12uM vs. 1.17±0.09uM) and attenuated the fall in blood pressure.

CONCLUSION We have generated a novel highly selective DDAH inhibitor, which elevates circulating ADMA levels in vivo. In a rat model of acute endotoxemia DDAH inhibition attenuates iNOS mediated hypotension and stabilises blood pressure.