XVI JCET LECTURE, 15.03.2013, 9.00

On the Role of Nitric Oxide in Hypoxia Tolerance: From Thin Air to Critical Care

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In the UK, about 20% of the population will end up on Intensive Care at some stage of their life, and more than one third of those admitted will not leave the hospital alive. Cellular hypoxia, with systemic inflammation, is a near-ubiquitous pathophysiological challenge in this setting, with many important and costly treatment decisions guided by limited 'hard' data. Reasons for inter-individual differences in outcome are unclear, and patient stratification is almost exclusively based on simple physiological read-outs. Current biomarker approaches focus on the early detection of tissue damage, with supplementary oxygen given frequently to treat conditions of low peripheral O2 saturation and reduced arterial pO2.. Hypoxic signalling, innate immunity and inflammation are linked at the level of the transcription factor NF-κB, which is under tight redox control. The production and availability of nitric oxide (NO) and reactive oxygen species (ROS) are fundamental to "redox signalling" and thus O2 utilisation, cellular energy production and inflammation. While these processes are relatively well characterised in cellular systems, their relevance for regulation of human physiology is less well understood. This is in part due to the difficulties associated with carrying out controlled clinical studies in the critical care setting. This presentation will present first results from an alternative experimental approach that employs a combination of whole-body physiology and multi-biomarker research focussing on the NO/oxidative stress/redox signalling pathway during exposure to increasing levels of environmental hypoxia. The data obtained so far suggest that an adequate production or availability of nitric oxide is crucial for the ability of humans to tolerate a reduction in oxygen availability. Thus, NO enhancing strategies rather than O2 supplementation may improve survival from conditions associated with reduced O2 availability.

BRIEF CURRICULUM VITAE OF MARTIN FEELISCH

PERSONAL DETAILS

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DEGREES

1997	*Venia legendi* ("Habilitation") for Pharmacology & Toxicology, University of Cologne
1988	PhD (*Summa cum laude*; Pharmacology), Heinrich Heine University, Düsseldorf

CURRENT & PREVIOUS POSTS

04/12- to date	Prof. of Experimental Medicine & Integrative Biology, University of Southampton
07/07- 03/12	Prof. of Experimental Medicine & Biology, University of Warwick
08/03-06/07	Prof. of Medicine & Biochemistry, Boston University School of Medicine, Boston, USA
10/99-07/03	Prof. of Mol. & Cell. Physiology (*tenure*), LSU Health Sciences Center, Shreveport, USA
10/97-09/99	Senior Lecturer & Scientific Coordinator, Wolfson Institute, University College London
1990-97	Director of Pharmacology, Head of Drug Discovery; Schwarz Pharma AG, Monheim
1988-89	Postdoctoral Fellow, Pharmacology/Physiology, Heinrich Heine University, Düsseldorf

AWARDS & HONOURS

1987-88	Smith Kline and Dauelsberg Fellow
1990	Fritz-Kulz-Prize, German Society for Experimental & Clinical Pharmacology & Toxicology
1992	Co-Founder and Director, Nitric Oxide Society
1992-2011	Local Organiser/Co-Organiser of 9 international scientific meetings and workshops
1993-to date	Editorial Board, Nitric Oxide Chemistry and Biology
2003-06	Member, Scientific Advisory Board (NitroMed, Inc., Lexington)
2005-09	Associate Editor, British Journal of Pharmacology
2011	Chair, Gordon Research Conference on Nitric Oxide, Ventura, CA

SELECTED MONOGRAPHS AND REFEREED JOURNAL ARTICLES

(from >100 original papers, 20 reviews/editorials, 38 book chapters, 3 monographs, 9 patents; h' Factor (WoS): 58)

Umbrello M, Dyson A, ***Feelisch M***, Singer M. The Key Role of Nitric Oxide in Hypoxia: Hypoxic Vasodilation and Energy Supply-Demand Matching. *Antioxid Redox Signal*. 2013; in press

Cortese-Krott MM, Rodriguez-Mateos A, Sansone R, Kuhnle GC, Sivarajah S, Krenz T, Horn P, Krisp C, Wolters D, Heiß C, Kröncke KD, Hogg N, ***Feelisch M***, Kelm M. Human Red Blood Cells at Work: Identification and visualization of erythrocytic eNOS activity in health and disease. *Blood* 2012, 120(20):4229-37.

Garcia-Saura MF, Saijo F, Bryan NS, Bauer S, Rodriguez J, ***Feelisch M***. Nitroso-redox status and vascular function in marginal and severe ascorbate deficiency. *Antiox Redox Signal.* 2012;17(7):937-50.

Milsom AB, Fernandez BO, Garcia-Saura MF, Rodriguez J, ***Feelisch M.*** Contributions of nitric oxide synthases, dietary nitrite/ nitrate, and other sources to the formation of NO signaling products. *Antiox Redox Signal.* 2012; 17(3):422-32.

Dyson A, Bryan NS, Fernandez BO, Garcia-Saura MF, Saijo F, Mongardon N, Rodriguez J, Singer M, ***Feelisch M***. An integrated approach to assessing nitroso-redox balance in systemic inflammation. *Free Radic Biol Med.* 2011;51(6):1137-45.

Levett DZ, Fernandez BO, Riley HL, Martin DS, Mitchell K, Leckstrom CA, Ince C, Whipp BJ, Mythen MG, Montgomery HE, Grocott MP, ***Feelisch M***; for the Caudwell Extreme Everest Research Group. The role of nitrogen oxides in human adaptation to hypoxia. *Sci Rep.* 2011;1:109.

Perlman DH, Bauer SM, Ashrafian H, Bryan NS, Garcia-Saura MF, Lim CC, Fernandez BO, Infusini G, McComb ME, Costello CE, ***Feelisch M***. Mechanistic Insights Into Nitrite-Induced Cardioprotection Using an Integrated Metabonomic/Proteomic Approach. *Circ Res* 2009; 104(6):796-804.

Nagasaka Y, Fernandez BO, Garcia-Saura MF, Petersen B, Ichinose F, Bloch KD, **Feelisch M**, Zapol WM. Brief Periods of Nitric Oxide Inhalation Protect against Myocardial Ischemia–Reperfusion Injury. *Anaesthesiology* 2008; 109:675-82.

Butler A & ***Feelisch M***. Therapeutic Uses of Inorganic Nitrite and Nitrate: From the Past to the Future. *Circulation* 2008;117:2151-9.

Erzurum SC, Ghosh S, Janocha A, Xu W, Bauer S, Bryan NS, Tejero JB, Hemann C, Hille R, Stuehr DS, ***Feelisch M***, Beall C. Higher blood flow and circulating NO products offset high-altitude hypoxia among Tibetans. *PNAS* 2007;104(45):17593-8.

Heiss C, Lauer T, Dejam A, Kleinbongard P, Hamada S, Rassaf T, Matern S, ***Feelisch M***, Kelm M. Plasma nitroso compounds are decreased in patients with endothelial dysfunction. *J Am Coll Cardiol*. 2006;47(3):573-9.

Feelisch M, Stamler JS. Methods in Nitric Oxide Research. John Wiley & Sons, Chichester, 1996. 712p.