

MECHANISM-BASED INVESTIGATION INTO ADAPTATION TO OXIDATIVE ACUTE LUNG INJURY

G. Pellegrini^{*,†}, D. Williams[†] and A. Kipar^{*,†}

**Laboratory for Animal Model Pathology (LAMP), Institute of Veterinary Pathology, VetSuisse Faculty, University of Zürich, Switzerland and †Centre for Drug Safety Science, Department of Pharmacology and Therapeutics, University of Liverpool, UK*

Introduction: Acute lung injury (ALI) remains an important source of morbidity in human and veterinary patients, and experimental animal models are key tools to elucidate its pathophysiological mechanisms. We present here the morphological and functional aspects of oxidative pulmonary injury in rats induced by small thiourea-based molecules. Rats exposed to a normally lethal dose of thioureas, after prior administration of a small dose, develop rapid adaptation (tolerance) and those mechanisms are investigated here.

Materials and Methods: Groups of rats were treated with a phenylthiourea compound to induce ALI and adaptation, and assessed by light microscopy including immunohistology, transmission electron microscopy, glutathione (GSH) measurements, enzyme assays and molecular methods for assessment of flavin-containing monooxygenases (FMOs), a class of enzymes involved in the bioactivation of thioureas.

Results: Thiourea-induced ALI was characterized by ultrastructural alterations in pulmonary vascular endothelial cells that resulted in increased vascular permeability (VP). The lungs of tolerant rats showed mild and transient increased VP and mildly increased cellularity (alveolar macrophages and type II pneumocytes), while FMO and GSH levels were unaltered.

Conclusions: We speculate that the adaptive response of the lungs to thioureas is related to irreversible inhibition of FMOs, rather than increased clearance of the oedema fluid by macrophages and type II pneumocytes, down regulation of FMOs or decreased GSH levels. Thiourea-induced injury in rats represents an interesting animal model to investigate the pathogenesis of ALI. Understanding the defence mechanisms involved in adaptation may open new avenues for the therapy of lung diseases.

MERS CORONAVIRUS INFECTION IN DROMEDARY CAMELS

J.M.A. van den Brand^{*}, P. Wohlsein[†], V. Stalin Raj^{*}, S.L. Smits^{*}, D. Schippers^{*}, J. Segalés[‡], A. Bensaid[‡], D. Solanes[‡], A. Volz[‡], T. Kuiken^{*}, W. Baumgärtner[†], A.D.M.E. Osterhaus^{*,†}, G. Sutter[§] and B.L. Haagmans^{*}

**Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands, †Department of Pathology, University of Veterinary Medicine, Hannover, Germany, ‡Centre de Recerca en Sanitat Animal (CRESA), Barcelona, Spain and §Institute for Infectious Diseases and Zoonoses, LMU University of Munich, Munich, Germany*

Introduction: Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel coronavirus causing an ongoing outbreak in man, sometimes resulting in severe or even fatal pneumonia. Dromedary camels are suggested to be the reservoir host for MERS-CoV. Infected dromedaries shed the virus predominantly from the nose, but show no or only mild disease. To elucidate the pathogenesis of MERS-CoV infection, we inoculated dromedary camels with MERS-CoV.

Materials and Methods: Four 6- to 8-month-old dromedaries, serologically negative for MERS-CoV, were inoculated intranasally with MERS-CoV. Collection of swabs and evaluation of clinical signs were performed daily. The dromedaries were killed 4 or 14 days ($n = 2$ per day) after inoculation. Necropsy examinations were performed and samples of respiratory and extra-respiratory tissues were taken for pathology, immunohistochemistry (IHC), in-situ hybridization (ISH) and virology.

Results: The dromedaries demonstrated moderate rhinitis with nasal discharge, tracheitis and bronchitis associated with the presence of MERS-CoV by virus titration, intralesional virus antigen by IHC and viral RNA by ISH. High virus titres were excreted from the nose up to 6 days after inoculation. Virus antigen was present in a few cells of lymphoid organs such as pulmonary, tracheal and cervical lymph nodes and tonsils, but not in other respiratory or extra-respiratory tissues.

Conclusions: Experimental MERS-CoV infection in dromedaries predominantly causes upper respiratory tract disease with no/mild clinical respiratory signs, which corresponds with the role of dromedaries as a reservoir for MERS-CoV. Studies on the vaccination of dromedaries against MERS-CoV are still ongoing.