BMC Pharmacology

BioMed Central

Oral presentation

Yin and Yang of cGMP signalling in hydrostatic lung edema

Jun Yin[2,3], Stephanie M Kaestle[1], Michael Mertens[1] and Wolfgang M Kuebler*[1,2,3,4]

Address: [1]Institute of Physiology, Charité – Universitätsmedizin Berlin, 14195 Berlin, Germany, [2]German Heart Institute, 13353 Berlin, Germany, [3]The Keenan Research Centre of the Li Ka Shing Knowledge Institute at St. Michael's Hospital, Toronto, ON M5B 1W8, Canada and [4]Department of Surgery, University of Toronto, ON M5S 1A1, Canada

Email: Wolfgang M Kuebler* - wolfgang.kuebler@charite.de

* Corresponding author

from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):S22 doi:10.1186/1471-2210-9-S1-S22

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/S22

Background

Hydrostatic lung edema is a characteristic complication of acute left-sided ventricular or valvular heart failure that if untreated has a high mortality due to the resulting respiratory failure. Traditionally, formation of hydrostatic lung edema has been attributed to an imbalance of Starling forces, i.e. transcapillary hydrostatic and oncotic pressure in the pulmonary circulation resulting in interstitial and finally, alveolar edema. Yet, mechanosensitive cell responses may play a critical regulatory role in this scenario.

Results

In isolated perfused rat and mouse lungs, we have identified lung capillary endothelial and alveolar epithelial responses relevant to the pathogenesis of cardiogenic lung edema. Hydrostatic stress causes influx of Ca^{2+} into endothelial cells via mechanosensitive cation channels of the vanilloid-type transient receptor potential (TRPV) family. The endothelial Ca^{2+} influx increases lung microvascular filtration coefficient (K_f) via a myosin light chain kinase-dependent mechanism, thus increasing lung microvascular permeability and promoting edema formation. Yet simultanesouly, Ca^{2+} influx stimulates endothelial formation of NO which attenuates endothelial Ca^{2+} influx and permeability increase by a cGMP-dependent inhibition of mechanosensitive TRPV channels. Hence, endothelial NO formation limits the hydrostatic stress-induced increase in lung microvascular permeability via a negative feedback loop. A similar protective mechanism of NO seems to apply for the induction of permeability-type lung edema by platelet-activating factor (PAF), which induces lung edema formation by stimulating endothelial Ca^{2+} influx via cation channels of the canonical-type transient receptor potential (TRPC) family and simultaneously blocking endothelial NO formation via a acid sphingomyelinase-dependent mechanism.

Nitric oxide generated by lung microvascular endothelial cells in response to lung hydrostatic stress also serves as intercompartmental signal to epithelial cells outlining the adjacent alveolar space. Endothelial-derived NO impairs alveolar fluid clearance, a protective mechanism driven primarily by epithelial ion transport via amiloride-sensitive Na^+ channels and the Na^+, K^+-ATPase. Over and above that, endothelial-derived NO reverses the direction of transalveolar chloride transport, thus stimulating active alveolar fluid secretion which can be blocked by inhibitors of Na^+, K^+-ATPase, cystic fibrosis transmembrane conductance regulator (CFTR) or the Na^+, K^+, $2Cl^-$-Cotransporter NKCC1.

Conclusion

The presented data demonstrate that hydrostatic lung edema is not simply the result of passive fluid fluxes as a result of imbalanced Starling forces, but is largely regulated by active cellular responses opening the potential for new targeted strategies in the prevention and therapy of

cardiogenic edema. NO and cGMP are identified as key regulators in this scenario with both pro- and anti-edematous effects.

Acknowledgements

Supported by DFG GRK 865, DFG KU 1218/4-1,4-2 and 5-1, Pfizer GmbH, and the Kaiserin-Friedrich Foundation Berlin.