

Meeting abstract

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The effect of carbamylation on the functionality of high-density lipoprotein

Michael Holzer*¹, Martin Gauster², Ruth Birner-Grünberger³ and Gunther Marsche¹

Address: ¹Institute of Experimental and Clinical Pharmacology, Medical University of Graz, 8010 Graz, Austria, ²Institute for Cell Biology, Histology and Embryology, Medical University of Graz, 8010 Graz, Austria and ³Core Facility Mass Spectrometry, Medical University of Graz, 8010 Graz, Austria

Email: Michael Holzer* - michael.holzer@medunigraz.at

* Corresponding author

from 15th Scientific Symposium of the Austrian Pharmacological Society (APHAR) Joint meeting with the Hungarian Society of Experimental and Clinical Pharmacology (MFT) and the Slovenian Pharmacological Society (SDF) Graz, Austria. 19-21 November 2009

Published: 12 November 2009

BMC Pharmacology 2009, 9(Suppl 2):A6 doi:10.1186/1471-2210-9-S2-A6

This abstract is available from: <http://www.biomedcentral.com/1471-2210/9/S2/A6>

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Background

Increasing interest has focused on the relative functionality of high-density lipoprotein (HDL), highlighted by observations that cardiovascular events can occur even in the presence of high levels of HDL cholesterol. Myeloperoxidase (MPO), a heme protein abundant in leucocytes, colocalizes with HDL in the human artery wall and has emerged as a potential participant in multiple phases of the atherosclerotic process. Recently, the MPO/H₂O₂/SCN⁻ system has been demonstrated as a dominant pathway to promote protein carbamylation within atherosclerotic plaques. Therefore, we determined whether HDL is carbamylated in the human artery wall.

Methods and results

Immunohistochemical studies confirmed colocalization of carbamylated epitopes with apoA-I and macrophages in human atherosclerotic lesions. We performed shotgun proteomic analysis of in vitro carbamylated HDL to identify specific carbamylation sites of apoA-I. We could identify apoA-I-associated lysine residues in the α -helical lipid binding domains that are specifically carbamylated, indicating that carbamylation of apoA-I affects the functional integrity of HDL. In line with this observation, we observed that carbamylation of HDL (i) leads to "non-productive" binding to the HDL receptor (SR-BI), (ii)

decreased SR-BI-mediated cholesterol efflux, and (iii) reduced HDL mediated anti-inflammatory activity.

Conclusion

Taken together, our data provide strong evidence that carbamylation renders HDL dysfunctional and proinflammatory.