Adipose tissue secreted ceramides and related sphingolipids - potential modulators of vascular redox signalling in cardiovascular disease

Authors:
N Akawi¹, A Checa², C Kotanidis¹, I Akoumianakis¹, E Daskalakis², L Herdann¹, C Wheelock², C Antoniades¹, John Radcliffe Hospital, Division of Cardiovascular Medicine, Radcliffe Department of Medicine - Oxford - United Kingdom of Great Britain & Northern Ireland, Karolinska Institute, Department of Medical Biochemistry and Biophysics - Stockholm - Sweden,

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Background: Adipose tissue (AT) plays a vital role in the modulation of vascular biology via known adipokines and other yet unidentified secreted molecules. Recent technological advances of omics-based approaches have enabled the identification of more metabolites that drive the currently recognised cross talk between the AT and the vasculature.

Purpose: The main aim of this study is to explore the role of AT secreted ceramides on the regulation of vascular superoxide (O2.-) generation in cardiac patients.

Methods: Untargeted metabolic profiling for the secretome of paired thoracic and subcutaneous ATs from 48 patients undergoing cardiac surgery (the Oxford cohort for heart, vessels and fat) along with the subsequent sphingolipids-targeted quantification were performed using liquid-chromatography/mass-spectrometry. Immortalized human aortic endothelial cells (teloHAEC) were treated exogenously with C6-ceramide (CerC6) for 20min and O2.- production was measured using lucigenin-enhanced chemiluminescence.

Results: Metabolomics differential (A) and enrichment analysis (not shown) highlighted the significant differences in sphingolipids secretion levels between the two fat depots. Higher amount of ceramides were produced and secreted from the thoracic depot with C16-ceramide (CerC16) representing the most abundant differentially secreted ceramide (B). Compared to the lowest tertile, the middle and highest tertiles of ceramides in thoracic AT were significantly associated with higher O2.- generation in patients’ vessels namely saphenous veins (SV) and internal mammary arteries (IMA) (C). Exogenous treatment of teloHAEC with ceramide increased O2.- generation and eNOS uncoupling evidenced by more negative O2.- after addition of L-NAME, an inhibitor of eNOS (D).

Conclusions: In this study, we demonstrate for the first time that sphingolipids, in particular ceramides, secreted from AT of cardiac patients may modulate their vascular redox state via dysregulating vascular eNOS signalling leading to endothelial dysfunction — a hallmark of cardiovascular disease.

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