Karen R Jonscher, Metabolomics 2014, 4:2
http://dx.doi.org/10.4172/2153-0769.S1.024

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference and Exhibition on
Metabolomics & Systems Biology
March 24-26, 2014 Hilton San Antonio Airport, San Antonio, USA

Spaceflight alters liver metabolic function in mice

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Spaceflight is known to induce deleterious physical effects, particularly muscle atrophy, however little is known about the effect of microgravity on liver metabolic function. We obtained liver tissue from n=6 mice flown aboard STS-135, a 13 day mission, compared with age- diet, and environment-matched ground controls. Samples were analyzed using a multi-'omics and systems biology approach, combining data from histology, microscopy, metabolomics and transcriptomics. Spaceflight resulted in profound depletion of liver glycogen stores (PAS staining), with a concomitant and significant increase in lipid droplet deposition (Oil Red O staining and Coherent anti-Stokes Raman Spectroscopy (CARS)). Raman spectroscopy, as well as Stimulated Raman Scattering (SRS), revealed a spectral band, corresponding to retinol, which was only present in liver lipid droplets from ground mice. Additional bands at lower wavenumbers suggest the presence of retinoic acid, a ligand for lipid-activated lipogenic gene expression, in the flight mice lipid droplets. These data are supported by microarray results showing flight-induced activation of genes involved in metabolism of retinol to 9-cis-retinoate with subsequent upregulation of the transcriptional activator RXR-α, as well as genes in PPARα downstream pathways (Ingenuity Pathway Analysis). In particular, pathways important in fat uptake and glucose homeostasis appeared to be activated. Indeed, metabolomic discovery revealed increased concentrations of the bile acids cholate and taurodeoxycholate in spaceflight mouse liver tissue as well as concentrations of essential fatty acids, particularly n3-DPA and linoleate. Omega-3 fatty acids were more abundant than saturated or polyunsaturated omega-6 fatty acids and thioesterases were also upregulated. 'Omics' data suggest an increase in triglyceride biosynthesis in spaceflight mice, as would be expected by the increase in lipid droplets. Genes involved in ketogenesis were upregulated, and ketone bodies, as well as products of omega oxidation, were increased in flight, suggesting the potential for dysfunctional β oxidation. Finally, fixed sections stained with picrosirius red and visualized with cross-polarized light showed a significant increase in collagen deposition in livers from spaceflight mice as compared with ground controls, potentially representing early signs of fibrosis. Taken together, these data demonstrate that short-term spaceflight is associated with a novel pattern of liver metabolite changes coupled with increased gene activation and liver lipid accumulation with a potential for fibrosis. Similar studies on mice exposed to microgravity for longer duration should provide insights into potential health risks for humans as space exploration extends to longer duration.

Biography

Karen Jonscher earned her Ph.D. in Applied Physics in 1996 from the California Institute of Technology, pioneering mass spectrometry instrumentation and large-scale analytical methods for proteomics applications. She directed proteomics facility at the University of Colorado and has recently transitioned from core facility direction to biomedical research. Her lab seeks to characterize the effect of maternal obesity on offspring liver and kidney mitochondrial function, and with collaborators at the University of Colorado Boulder and Loma Linda University, is also interested in effects of microgravity and low-level radiation on liver lipid metabolism.

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