Initiation of fat-induced changes in energy metabolism and insulin resistance

Elisa Álvarez Hernández[1,2], Sabine Kahl[1,2,3], Anett Seelig[4], Paul Begovatz[1,2], Martin Irmler[5], Yuliya Kupriyanova[1,2], Bettina Nowotny[1,2,3!], Peter Nowotny[1,2], Christian Herder[1,2], Cristina Barosa[6], Filipa Carvalho[6], Jan Rozman[4,5], Susanne Neschen[2,4,5,#], John G. Jones[6,7], Johannes Beckers[2,5,8], Martin Hrabě de Angelis,[2,5,8] Michael Roden[1,2,3*]

[1] Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, 40225 Düsseldorf, Germany; [2] German Center for Diabetes Research, 85764 München-Neuherberg, Germany; [3] Department of Endocrinology and Diabetology, Medical Faculty, Heinrich-Heine University Düsseldorf, 40225 Düsseldorf, Germany; [4] Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), 85764 Neuherberg, Germany; [5] Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Germany, Ingolstädter Landstr.1 8674 Neuherberg, Germany; [6] Center for Neurosciences and Cell Biology, UC Biotech, 3060-197 Cantanhede, Portugal; [7] Portuguese Diabetes Association (APDP), 1250-203 Lisbon, Portugal; [8] Technische Universität München, Chair of Experimental Genetics, 85354, Freising, Germany

[!] Clinical Research Services GmbH, Mönchengladbach, 41061, Germany

[#] Current affiliation: Sanofi-Aventis Deutschland GmbH, R&D Diabetes Research & Translational Medicine, Frankfurt am Main, 65926, Germany

* Corresponding author: Prof. Dr. Michael Roden, Auf'm Hennekamp 65, 40225, Düsseldorf, Germany, Tel. +49-(0)-211-33-82-201, e-mail: michael.roden@ddz.uni-duesseldorf.de

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Abstract

Background: Dietary intake of saturated fat likely contributes to non-alcoholic fatty liver disease (NAFLD) and to insulin resistance, but the initial mechanisms in humans remain unclear. We examined effects of a single oral saturated fat load on insulin sensitivity, and on hepatic glucose and lipid metabolism in humans. Similarly, initiating mechanisms were examined after an equivalent challenge in mice.

Methods: Fourteen lean, healthy individuals randomly received either palm oil (PO) or vehicle (VCL). Hepatic metabolism was analyzed using in vivo $^{13}C/^{31}P/^{1}H$ and ex vivo ^{2}H magnetic resonance spectroscopy, before and during hyperinsulinemic-euglycemic clamps with isotope dilution. Mice underwent identical clamp procedures and hepatic transcriptome analyses.

Results: PO administration decreased whole body, hepatic and adipose tissue insulin sensitivity by 25%, 15% and 34%, respectively. Hepatic triglyceride and adenosine triphosphate content rose by 35% and 16%, respectively. Hepatic gluconeogenesis increased by 70% and net glycogenolysis declined by 20%. Mice transcriptomics revealed that PO differentially regulates predicted upstream regulators and pathways, including lipopolysaccharide (LPS), members of the toll-like (TLR) and peroxisome proliferator-activated (PPAR) receptor families, nuclear factor kappa b (NFκB) and tumor necrosis factor related weak inducer of apoptosis (TWEAK).

Conclusion: Saturated fat ingestion rapidly increases hepatic lipid storage, energy metabolism and insulin resistance. This is accompanied by regulation of hepatic pathways, which predispose or protect from NAFLD.

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