UKE Paper of the Month March 2016

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FGF21 Lowers Plasma Triglycerides by Accelerating Lipoprotein Catabolism in White and Brown Adipose Tissues

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ABSTRACT:
FGF21 decreases plasma triglycerides (TGs) in rodents and humans; however, the underlying mechanism or mechanisms are unclear. In the present study, we examined the role of FGF21 in production and disposal of TG-rich lipoproteins (TRLs) in mice. Treatment with pharmacological doses of FGF21 acutely reduced plasma non-esterified fatty acids (NEFAs), liver TG content, and VLDL-TG secretion. In addition, metabolic turnover studies revealed that FGF21 facilitated the catabolism of TRL in white adipose tissue (WAT) and brown adipose tissue (BAT). FGF21-dependent TRL processing was strongly attenuated in CD36-deficient mice and transgenic mice lacking lipoprotein lipase in adipose tissues. Insulin resistance in diet-induced obese and ob/ob mice shifted FGF21 responses from WAT toward energy-combusting BAT. In conclusion, FGF21 lowers plasma TGs through a dual mechanism: first, by reducing NEFA plasma levels and consequently hepatic VLDL lipidation and, second, by increasing CD36 and LPL-dependent TRL disposal in WAT and BAT.

STATEMENT:
Obesity is a consequence of excess weight gain and is characterized by disturbed lipid and glucose metabolism. These metabolic abnormalities trigger inflammatory responses in e.g. adipose tissues and liver, thereby strongly contributing to the development of non-alcoholic steatohepatitis, type 2 diabetes and atherosclerosis. In recent years fibroblast growth factor-21 (FGF21) and synthetic derivatives are becoming promising therapeutic approaches for the treatment of metabolic diseases, as they reveal beneficial effects on glucose homeostasis, lipid metabolism and body weight in mice and humans. The current study unravel the exact mechanism how FGF21 lowers harmful plasma lipid values. Notably, we show that particularly under obese conditions brown adipose tissue can be reactivated to combust the excess of stored energy. Today, obesity and elevated blood lipids represent an epidemic threat to public health and as our findings are related to every day dietary intake of lipids and how to handle their mismanagement, our study is of great importance not only for the scientific community.

BACKGROUND:
This work was performed at the Department of Biochemistry and Molecular Cell Biology in the group of Prof. Dr. Heeren who recently obtained a Heisenberg Professorship for Immunometabolism. Christian Schlein is supported by the MD/PhD program of the UKE. This work was supported by a grant from the Fondation Leducq - Triglyceride Metabolism in Obesity and Cardiovascular Disease, by EU FP7 project RESOLVE and in in part by Pfizer Worldwide Research and Development. The authors have strong interest to understand the development of obesity-induced metabolic diseases such as diabetes and NASH by implementing an immune-metabolic centred view of disease development.