UKE Paper of the Month September 2018

Lipolysis Triggers a Systemic Insulin Response Essential for Efficient Energy Replenishment of Activated Brown Adipose Tissue in Mice

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ABSTRACT: The coordination of the organ-specific responses regulating systemic energy distribution to replenish lipid stores in acutely activated brown adipose tissue (BAT) remains elusive. Here, we show that short-term cold exposure or acute β3-adrenergic receptor (β3AR) stimulation results in secretion of the anabolic hormone insulin. This process is diminished in adipocyte-specific Atgl-/- mice, indicating that lipolysis in white adipose tissue (WAT) promotes insulin secretion. Inhibition of pancreatic β cells abolished uptake of lipids delivered by triglyceride-rich lipoproteins into activated BAT. Both increased lipid uptake into BAT and whole-body energy expenditure in response to β3AR stimulation were blunted in mice treated with the insulin receptor antagonist S961 or lacking the insulin receptor in brown adipocytes. In conclusion, we introduce the concept that acute cold and β3AR stimulation trigger a systemic response involving WAT, β cells, and BAT, which is essential for insulin-dependent fuel uptake and adaptive thermogenesis.

STATEMENT: *A number of recent studies has demonstrated the relevance of brown adipose tissue (BAT) for systemic energy metabolism in mice and humans. Notably, it became apparent that impaired BAT function caused metabolic alterations associated with the development of obesity-associated diseases such as atherosclerosis and type 2 diabetes. Conversely, we and others could demonstrate that activation of BAT emerges as a new therapeutic concept for the treatment of metabolic diseases. One hallmark of activated BAT is a very high metabolic rate necessitating efficient flux of glucose and lipids delivered by triglyceride-rich lipoproteins. However, the regulatory pathways coordinating systemic energy distribution to replenish lipid stores in activated BAT remain elusive. Here, we show by pharmacological and genetic approaches that cold and β 3-adrenergic receptor stimulation trigger a systemic response coordinating white adipose tissue lipolysis, insulin secretion by pancreatic β cells and insulin-dependent fuel uptake into BAT and consequently adaptive thermogenesis in mice. Furthermore, we offer a mechanistic basis for very relevant yet descriptive results of recent BAT activation studies in humans (e.g. Chrondonikola et al., Cell Metabolism 2016; Cypess et al., Cell Metabolism 2015). From a general perspective, this is the first study providing a systemic concept how anabolic refilling of lipid stores in brown adipocytes is achieved during highly catabolic thermogenesis*.

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. Markus Heine is supported by a grant from the Fondation Leducq - Triglyceride Metabolism in Obesity and Cardiovascular Disease and by EU FP7 project RESOLVE. 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.