'Energy crisis' in fat cells behind inflammation associated with obesity

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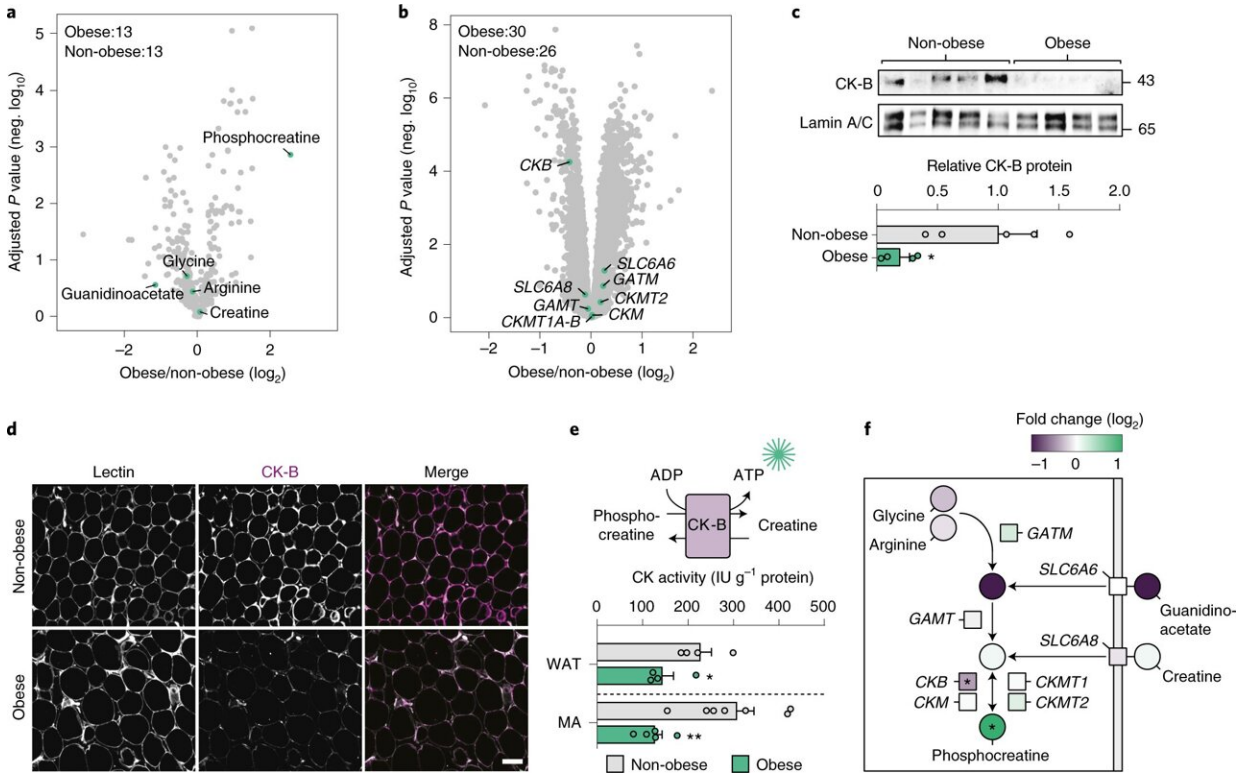

Fig. 1: Obesity is associated with altered phosphocreatine/creatine metabolism in human WAT. a, Polar metabolites in subcutaneous WAT of obese (n = 13) and non-obese (NO, n = 13) subjects (cohort 1) highlighting metabolites in the phosphocreatine/creatine pathway (green dots). Data are represented in a volcano plot with fold changes (log_2) and adjusted P values (negative (neg.) log_{10}). Statistics were calculated by Welch's two-sample t-test followed by false discovery rate (FDR) correction for multiple comparisons (q value), according to standard procedures from Metabolon. b, Expression of genes encoding proteins in the phosphocreatine/creatine pathway in subcutaneous WAT of obese (n = 30)

and non-obese (n = 26) women (cohort 2). Data are represented in a volcano plot with fold changes (log_2) and adjusted P values (neg. log_{10}) calculated using Limma (linear models for microarray and RNA-seq analysis). c, Western blot analysis of CK-B in subcutaneous WAT of obese (n = 4) and non-obese (n = 5) subjects. Lamin A/C was used as a loading control. *P = 0.036 by Student's two-sided t-test. d, Representative immunofluorescence microphotographs of subcutaneous WAT from obese (n = 3) and non-obese (n = 3) subjects. Sections were stained with Lens culiniaris agglutinin (Lectin) and antibodies targeting CK-B. Scale bar, 50 μm. e, Creatine kinase activity was measured in total subcutaneous WAT (n = 4 from obese and n = 4 non-obese subjects) as well as isolated mature adipocytes (n = 5 from obese and n = 7 non-obese subjects). As illustrated in the upper panel, the creatine kinase activity measured in this assay represents the reverse reaction after addition of ADP where ATP is generated from phosphocreatine. Lower CK-B activity is expected to result in attenuated ATP levels. *P = 0.05; **P = 0.003 by Student's two-sided t-test. f, Overview of the phosphocreatine/creatine pathway highlighting the alterations in human subcutaneous WAT linked to obesity. Data are represented as fold changes obese versus non-obese (log_2). *Significant. In c and e, data are shown as mean ± s.e.m. CK-B, cytokine B; MA, mature adipocytes. Credit: DOI: 10.1038/s42255-022-00525-9

In a new study published in *Nature Metabolism*, KI researchers show how disturbances in the energy metabolism in human fat cells, can lead to the development of inflammation and insulin resistance.

Mikael Rydén's and Niklas Mejhert's group at the Department of Medicine, Huddinge, examines what drives the development of inflammation in adipose tissue in people with obesity. The study shows that weight gain leads to altered phosphocreatine / creatine metabolism, which evokes inflammation in the fat cells.

"We believe that the impaired metabolism of creatine in the fat cells leads to an "energy crisis" that causes the body to compensate by

increasing glucose utilization. This stimulates the genes that lead to chronic inflammation in the body with an increased risk of insulin resistance," says Dr. Salwan Maqdasy, one of the study's first authors.

Fat cells may be the key to future treatments

The adipose tissue consists of many different cell types, and it hasn't been completely clear which cell types are behind disturbed adipose tissue function in obesity and insulin resistance. Previous studies have mainly focused on the role of immune cells in adipose tissue, but anti-inflammatory treatments do not appear to have had any effect on the adipose tissue function. The findings from Mikael Rydén's and Niklas Mejhert's group, indicate that the fat cells themselves are the driving factor and that future treatments therefore should be directed at the fat cells instead.

"To determine the causes behind the development of adipose tissue inflammation, the next step is to investigate how the regulation of the enzymes that control the creatine metabolism in the body leads to altered glucose utilization," says Simon Lecoutre, the second lead author of the study.

More information: Salwan Maqdasy et al, Impaired phosphocreatine metabolism in white adipocytes promotes inflammation, *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00525-9

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