Summary

Recently, brown adipose tissue (BAT) is considered as a potential tool in fighting obesity and type 2 diabetes. To date, mechanisms of BAT activation and associations between this tissue and clinical parameters are not well described. Metabolomics provides information on thousands of small molecules present in biological material, and subsequently, it reflects metabolic changes. Thus, it seems to be a proper tool for elucidating molecular bases of BAT activation. Literature data also shows the relationship between insulin resistance and other markers of metabolic disorders and BAT.

Therefore, the aim of the study was to determine changes in plasma metabolome induced by cold-activated BAT in young, healthy male adults as well as to indicate metabolites altered during cold exposure and those correlated with BAT activity and volume, measured with PET/MRI. Additionally, the influence of cold exposure and BAT on the level of glucose, insulin and selected serum protein (leptin, FGF21, TNF-α, FABP4) was examined.

To activate BAT, participants underwent two-hours cold exposure (CE), followed by PET/MRI performed to assess BAT activity and volume. Based on PET/MRI results, they were divided into two groups: BAT(+) (n = 17, median age = 24) and BAT(-) (n = 8, median age = 27). Metabolomics analysis of plasma samples collected before, after 60 and 120 minutes of cold exposure was performed using liquid chromatography coupled with mass spectrometry. Additionally, levels of glucose, insulin, leptin, TNF-α, FGF21, and FABP4 were assessed in serum samples to evaluate their alterations in response to cold exposure.

In the BAT(+) group, the level of the following compounds: LPC(17:0), LPE(20:4), LPE(22:4), LPE(22:6), DHA, linoleic acid, and oleic acid significantly increase during CE, whereas the level of sphinganine-phosphate, and sphingosine-1-phosphate significantly decreased during CE. As for the differences between BAT(+) and BAT(-) groups in metabolites levels during and after CE, we observed elevated levels of LPE(O-18:0), 9-HpODE, and oleic acid and reduced level of LPE(20:5) in BAT(+) subjects. The AUCs of the following metabolites: LPC(18:2), LPC(O-18:2)/LPC(P-18:1), and SM(d32:2) were negatively correlated with the activity and volume of BAT. Regardless of the BAT presence, glucose concentration was stable during CE, whereas insulin and leptin levels were decreased in comparison to the initial levels. In the BAT(+) group, the concentration of FABP4 during and after CE decreased, compared to the basal level (at the beginning of CE). No alterations were observed in the

BAT(-) group. No differences in the concentration of TNF-α and FGF21 were noted, neither in BAT(+) nor BAT(-) subjects.

In conclusion, using untargeted metabolomics, we proved that the plasma metabolome is affected by cold-induced BAT activation. Cold exposure does not influence glucose level, but it results in the decrease of insulin activity and leptin concentration, regardless of BAT presence. In the BAT(+) group, cold exposure leads to a drop in FABP4 level. During cold exposure, FGF21 and TNF-α levels remain unaltered regardless of BAT presence.