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Impact of the short-chain fatty acid propionate on mesenteric adipose tissue and insulin sensitivity

B. Lu[1,2], M. Christian[2], A. Hanyaloglu[1], A. Frampton[3] and G. Frost[1]

[1]*Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, UK,*
[2]*School of Science & Technology, Nottingham Trent University, Nottingham, UK and*
[3]*Targeted Cancer Therapy Research Group, Section of Clinical Medicine, School of Biosciences and Medicine, University of Surrey, Surrey, UK*

Metabolic syndrome increases the risk of non-communicable diseases such as type 2 diabetes (T2D)[(1)]. Abdominal adiposity, the accumulation of both visceral adipose tissue (mesenteric and omental) and subcutaneous adipose tissue (SCAT), is one of the metabolic syndrome's most predominant and pathogenic factors[(2)]. Propionate, a metabolite produced by gut microbes from the fermentation of non-digestible carbohydrates, could modulate insulin resistance through adipose tissue signalling. Limited studies have investigated the relationship between proportionate and three kinds of adipose tissues and their further impact on metabolic disease. This study aims to investigate the mechanism of propionate on the physiological and histological changes in human AT and adipocytes *in vitro* and to determine whether such impact is selective on mesenteric depots.

Mesenteric, omental and subcutaneous AT were collected from 8 patients. Tissue explants and membrane-cultured adipocytes were treated with propionate (1mM) or control (1mM NaCl) for 24 hours. The expression of genes related to the short-chain fatty acid receptors (FFAR2 FFAR3), adipogenesis (PPARγ, C/EBPα), and the browning process (UCP1, PGCα) was determined in both tissue and adipocyte. Basal and isoproterenol-stimulated lipolysis abilities were detected in adipocytes only. The pro-inflammatory response was evaluated in both AT and adipocytes. All data were analyzed by SPSS28.0. Normally distributed data were analyzed using paired t-tests between two groups and one-way ANOVA between three kinds of depots.

In AT, propionate significantly increased FFAR2 ($P < 0.01$, $P = 0.026$, $P = 0.037$, respectively), C/EBPα ($P = 0.015$, $P = 0.002$, $P = 0.014$, respectively), and UCP1 ($P = 0.044$, $P < 0.01$, $P = 0.014$, respectively) levels in MAT, OAT and SAT compared to the NaCl group. In adipocytes, only in mesenteric, propionate significantly increased PPARγ ($P < 0.01$), C/EBPα($P < 0.01$), and UCP1($P = 0.029$) expression. When compared to three kinds of adipose depots, mesenteric AT and adipocyte increased the greatest PPARγ and C/EBPα after propionate treatment. There was no difference in the basal FFA release after propionate treatment in all three kinds of adipocytes. After a 4-hour isoproterenol stimulation, propionate significantly decreased glycerol release in mesenteric($P = 0.025$) and omental($P = 0.044$) adipocytes compared to the positive group. In AT, propionate significantly decreased IL-6 release in MAT($P = 0.029$) and OAT ($P = 0.032$) compared to the NaCl group. In Adipocytes, only in mesenteric, propionate significantly decreased IL6 release($P = 0.043$).

First, by upregulating adipogenesis genes, propionate could promote free fatty acid storage which causes a decrease in harmful metabolite release. Second, propionate by upregulation of the beiging process, will upregulate the lipid oxidation and increase tissue energy expenditure [(3)]. Third, propionate could moderate the proinflammatory response in adipose depots by reducing the IL6. It could help reduce hypertrophy, lipid accumulation and lipolysis[(4)]. All three ways highlight that propionate does generate positive changes in adipose tissue, especially in the mesenteric. The positive changes could stimulate insulin sensitivity locally and systematically and further increase metabolic health.

References

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