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The impacts of blueberry, yoghurt, cyanidin-3-O-β-glucoside and peptides extracted from yoghurt on high-fat-high-carbohydrate induced obese mice

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Objective: Incidence of type II diabetes mellitus is rapidly increasing worldwide. This study aimed to investigate whether blueberry, yoghurt, cyanidin-3-O-β-glucoside (C3G), or peptides with angiotensin converting enzyme (ACE) inhibitory activity, alone or in combination, alter body fat pad mass or weight and improve glucose tolerance in the C57BL/6 mouse induced obesity with a high-fat-high-carbohydrate (HFHC) diet.

Research design and methods: 6-weeks-old male C57BL/6 mice consumed a HFHC diet for eight week to induced obesity. Obese mice were fed different dietary supplements, including blueberry, C3G, yoghurt, peptides extracted from yoghurt, alone and in combination of blueberry and yogurt, or C3G and peptides for additional eight weeks. Mice were killed via cardiac puncture following deep anaesthesia using isoflurane. Sequentially, heart, epididymal fat, mesenteric fat, liver and kidney were collected and weighed. Body weight was measured twice a week. Echo MRI system was utilised to determine the body composition every four weeks. Intraperitoneal glucose tolerance test was completed before the dietary supplementation (baseline) and at the end of experiment.

Results: Body weight and body fat were significantly decreased and glucose tolerance was improved in yoghurt, peptides and the combination of C3G and peptides at the end of the dietary supplementation, compared to the HFHC group. However, body fat was significantly increased in blueberry group, compared to HFHC group. The ratio of epididymal fat to body weight was significantly decreased in yoghurt group, compared to HFHC group. The ratio of mesenteric fat, liver and kidney to body weight in all treatment groups did not differ from the HFHC group.

Conclusions: Yoghurt and its peptides with ACE inhibitory activity decrease body weight and body fat and improve glucose uptake in obese mice. This provides a potential novel approach for the regulation of glucose metabolism in obese and diabetic individuals.

https://doi.org/10.1016/j.orcp.2018.11.152

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Characterization of AgRP neurons knock out mouse for the Carnitine palmitoyl transferase 1a (CPT1a)

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In the acruate nucleus of the hypothalamus, a key region in the energy homeostasis regulation, the Agouti related peptide (AgRP) neurons were largely described to be involved in this function. These neurons receive various metabolic signals including nutrients and hormones. Growing evidence displayed a role of the fatty acid metabolism in these neurons in their integration. The Carnitine Palmitoyl Transferase1a is a key enzyme involved in the pool of acetyl-CoA in the mitochondria by permitting the long-chain fatty acyl-CoA to enter into the matrix and undergo the beta-oxidation. Previous works have shown that this enzyme is involved in the food intake and glucose homeostasis.

To determine the role of CPT1a in the energy homeostasis, we breeded AgRP^{CRE}-IRES mice with CPT1a$^{floxed/floxed}$ mice to specifically deleted CPT1a in the AgRP neurons compared to the wild type (AgRP^{WT}) mice. A complete phenotypic characterization was undertaken (body weight, food intake, body composition, plasma assays, metabolic parameters). Data were analyzed by Student's *t*-test, two-way anova or two-way anova repetead measure.

Although the AgRP CPT1a$^{-/-}$ mice presented sligh higher food intake no difference in the body weight and body composition were observed compared to the AgRP^{WT} mice. In parallel, in fed and fasted conditions no difference was observed for the energy metabolism and plasmatic parameters. However, the AgRP CPT1a$^{-/-}$ mice presented a higher plasma insulin secretion induce by the glucose. The next step will be to focus on the hypothalamic impact of the knockout as well as the AgRP neurons sensitivity to the insulin.

https://doi.org/10.1016/j.orcp.2018.11.153

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Metabolic characterisation of knock-in mice harbouring the 'obesity variant' of CREBRF

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An Arg457Gln variant in the CREBRF gene (encoding for Cyclic AMP Response Element Binding Protein 3 Regulatory Factor) has recently been identified as an important driver of excess body weight in numerous Pacific/Oceanic populations. Intriguingly, despite the substantial increase in body mass, carriers of the Arg457Gln variant had a paradoxical reduction in their risk for type 2 diabetes, indicating that this gene has a critical role in whole-body metabolism. To study the function of this variant in more detail, we have generated mice on an FVB background where this CREBRF Arg457Gln variant has been knocked in to replace the endogenous CREBRF. The whole-body metabolic phenotype was characterised for male and female mice on a regular chow diet or a high-fat challenge for 8 weeks. Regular assessment of body composition found no genotype effect in either sex: total body weight was not significantly altered at any time-point; measurement of fat mass by EchoMRI similarly showed no influence of the CREBRF variant on total adiposity. No differences were observed in the weights of individual adipose depots. Glucose and insulin tolerance tests demonstrated diet-induced defects in glucose homeostasis and insulin action, with no obvious effect of the CREBRF variant. Fasting blood glucose levels were likewise impacted by diet, but unaffected by genotype. Overall, this novel mouse model appears to show no significant effect of the CREBRF variant on any metabolic characteristics studied, with any visible differentiation due only to sex and/or diet effects. This inability to recapitulate the results of human association studies may invite reconsideration of the precise mechanistic link between CREBRF function and the risk of obesity and diabetes in variant allele carriers.

https://doi.org/10.1016/j.orcp.2018.11.154