[3]. Transplantation of bone marrow from wild-type or *Gpr21*$^{-/-}$ animals into irradiated wild-type animals fed normal chow (13.5% fat), or high fat diet (HFD; 60% fat) for 27 weeks, revealed no improvement in glucose homeostasis, but an improvement in insulin sensitivity and a decrease in immune cell infiltration into eWAT. Furthermore, a decrease in the migratory ability of isolated CD11b^{+} bone marrow monocytes from *Gpr21*$^{-/-}$ mice compared to wild-type in response to monocyte chemoattractant protein-1 (MCP-1) was observed. These data were confirmed using a PKH26 monocyte tracking study. RNAseq analysis of CD11b^{+} monocytes from *Gpr21*$^{-/-}$mice revealed an overall significant effect on genes involved in inflammation and cell migration, including *Il6*, *Ccl2*, *Cxcl2* and members of the TLR family, supporting the reduced functional response. Significant changes in genes involved in atherosclerosis was also observed, including *Apoe* and *Nr4a1*. These data indicate that GPR21 is involved in the chemotaxis of specific immune cells. Targeting this receptor may prove beneficial for the treatment of T2DM and its complications.

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Stabilization of beta catenin in hypothalamic cell lines

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Beta-catenin is a signalling molecule in the Wnt-signalling pathway, which has typically been associated with embryogenesis and tumorigenesis. More recently, new lines of evidence suggest that it may also be involved in the pathogenesis of type-2 diabetes. In its active form, beta-catenin acts together with the transcription factor T cell-specific transcription factor-7-like 2 (TCF7L2) to activate target genes of the Wnt-signalling pathway. Impairment in this signal transduction pathway in the pancreas may contribute to the development of type-2 diabetes. The role of the hypothalamus in controlling glucose homeostasis is becoming well-recognized, and we have recently found that Wnt signalling is activated in the hypothalamus in response to feeding-related hormones. To investigate possible mechanisms of feeding-induced stabilization of beta-catenin, we have used adult mouse hypothalamic cell lines that express the phenotype for various metabolic neuropeptides and receptors involved in central regulation of metabolism. We surveyed a variety of potential hormone factors that can simulate the effect of feeding: forskolin, exendin-4 and MTII (an α-MSH analogue). After treatment, we firstly measured NPY and AgRP secretion. Treatment with these factors did not affect the secretion of either neuropeptide. After applying KCl to depolarise the cells, however, there was significantly greater release of both AgRP and NPY from treated cells compared with vehicle-controls, indicative of an effect on synthesis or vesicle trafficking. We next treated these cell lines with forskolin and discovered that in one of the cell line, all the Wnt-responsive genes analyzed were markedly up-regulated. In addition we found an increase in total beta-catenin protein expression following treatment with either forskolin, exendin-4 or MTII. These data suggest that the treatment has increased the pool of neuropeptide available for release. These results are consistent with the role of beta-catenin in regulating a feeding response through a central mechanism.

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Glycoprotein acetyls (GlycA) associate with BMI and co-morbidities in childhood obesity

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Introduction: Childhood obesity is a pro-inflammatory state associated with metabolic and cardiovascular complications. In adults, glycoprotein acetyls (GlycA), a newly described inflammatory marker, is associated with cardiovascular disease and all-cause mortality, but there are few paediatric data. In a cohort of children attending a tertiary paediatric obesity clinic, we investigated the relationship between GlycA and obesity-related cardiometabolic co-morbidities.

Methods: Participants were enrolled in COBRA (Childhood Overweight BioRepository of Australia) between 2009–2017. Study site was at the Royal Children's Hospital, Melbourne. Data collected included demographic (age and sex), anthropometric (weight, height, BMI, pubertal stage) and clinical (blood pressure) measures. An 8-hour fasted blood sample was collected for liver function (to assess for non-alcoholic fatty liver disease, NAFLD) and GlycA. An OGTT revealed the status for impaired glucose tolerance (IGT), insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Hypertension (HTN) was determined according to current guidelines. GlycA was analyzed by NMR spectroscopy of serum. Binomial regression modeling, adjusted for age, sex, BMI and pubertal stage, assessed the relationship between GlycA and each of the dichotomized outcome variables (IGT, IR, T2DM, NAFLD and HTN).

Results: 216 participants were included (52% females, mean age 11.9 years (SD ± 3.1), 35% post-pubertal). The mean value for BMI *z*-score was 2.49 (SD ± 0.24), and for GlycA 1.103 mmol/l (SD ± 0.123). GlycA was associated with BMI (pearsons $\rho = 0.29$; $p < 0.001$). Comorbidity prevalences were: IGT:36%, IR:55%, T2DM:2%, sHTN:49%, dHTN:26%, NAFLD:38% and hyperlipidaemia:25%. In fully adjusted models, GlycA was associated with hyperlipidemia ($p < 0.0001$), IR ($p < 0.05$) and NAFLD ($p < 0.05$), but not with IGT, systolic or diastolic HTN.

Conclusion: Increased GlycA, indicative of chronic inflammation, was associated with BMI and its co-morbidities in obese children. Longitudinal studies are warranted to define its role as

a predictive biomarker for adverse obesity-related outcomes in childhood.

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Lower prevalence of performance genes are linked with increased severity of obesity in youth

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Introduction: Obesity mainly arises from an imbalance between activity and energy intake, although some children appear to carry a genetic predisposition for weight gain. The ability to sustain physical activity and effectively induce a favorable metabolic outcome is genetically predetermined. Candidate genes for fitness and muscle strength have been shown to influence muscle function and mass in response to exercise. We aimed to determine whether there is a genetic predisposition limiting effectiveness of training and substrate's utilization.

Methods: Children from the Childhood Overweight BioRepository of Australia (COBRA), presenting at The RCH Weight management Service, were clinically assessed, PBMCs were collected for DNA analysis ($N = 238$) and Actical-accelerometer was worn for 7-days. SNP analysis on a unique performance gene panel included; *ACTN3*-rs1815739, *CNDP1*-rs2887, *HIF1A*-rs11549465, *GALNT13*-rs10196189, *PPARGC1A*-rs8192678, *RPLP1_GEMIN8P1*-rs4776471, *CRHBP*-rs1715747. Correlation analyses were calculated between allele prevalence of fitness genes and BMI *z*-scores, body and truncal fat percentage, waist circumference, blood pressure and accelerometer data.

Results: Genotypes associated with fitness were less prevalent in the COBRA cohort than in reference population studies. A more pro-fitness genotype was associated with lower body weight ($p < 0.05$ for ACTN3,ZFYVE26 and CNDP1), decreased waist circumference ($p < 0.01$ for RPLP1_GEMIN8P1) and decreased body fat ($p < 0.05$ for IL15RA) in females and lower body fat ($p < 0.05$ for SHBG_GENE) for males. Increased daily physical activity was associated with pro-fitness genotypes ($p < 0.05$ for ZFYVE26,CNDP1,HIF1A,CRHBP and SHBG_GENE). Sex dependent variation was observed in blood pressure measurements between genotypes ($p < 0.05$ for UGT2B4 in females; for GALNT13 and PPARGC1A in males).

Conclusion: In an obese cohort, those with higher BMI are less likely to exhibit a favorable 'fitness genotype' and are less physically active which places them at greater risk of cardiometabolic complications. Knowledge about susceptibility for weight gain may identifies individuals at risk for increasing severity of obesity and complications.

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The impacts of cyanidin-3-O-β-glucoside and peptides extracted from yoghurt on glucose uptake and gene expression in human primary skeletal muscle cells from obese and diabetic individuals

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Objective: Incidence of type II diabetes mellitus is rapidly increasing worldwide. This study aimed to investigate whether cyanidin-3-O-β-glucoside (C3G), or peptides with angiotensin converting enzyme (ACE) inhibitory activity, alone or in combination, alter glucose regulation in human primary myotubes derived from obese and obese diabetic individuals.

Research design and methods: In cells treated with 10 μM, 100 μM of C3G, 150 μg/mL, 1500 μg/mL of peptide and their combinations, [3H]-2-deoxyglucose uptake and mRNA expression of multiple genes related to insulin resistance and glucose metabolism were determined by 'real-time' PCR. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, Inc, La Jolla, CA, USA). $P < 0.05$ was considered significant.

Results: In the obese group, both low and high concentration of peptides with ACE inhibitory activity and the combination of these peptides with high C3G concentration significantly enhanced glucose uptake in the presence or absence of insulin. However, only high peptide concentration increased glucose uptake in the absence of insulin in the diabetic group. In the obese group, high concentration of peptide alone and its combination with low C3G down-regulated the mRNA expression of angiotensin II receptor, type 1 (AGTR-1) and FOXO1, and up-regulated the mRNA expression of insulin receptor substrate 1 (IRS-1), GLUT1 and GLUT4. Furthermore, the expression of AGTR-1 and FOXO1 were decreased with high peptide and its combinations of C3G in the diabetic group. Only high peptide concentration increased IRS-1 mRNA expression in the diabetic group.

Conclusions: C3G and peptides with ACE inhibitory activity improve glucose uptake potentially via the regulation of AGTR-1 and insulin-dependent signalling pathway (with insulin-like properties) in human primary myotubes. This provides a potential novel approach for the regulation of glucose metabolism in obese and diabetic individuals.

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Peripheral NPY antagonism reduces HFD-induced adiposity and improves glucose tolerance in ageing mice

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The prevalence of obesity is the leading cause of metabolic syndrome in ageing people. The NPY system plays a critical role in controlling energy balance, centrally and peripherally, but its role in the development of obesity in ageing populations is not clear. To investigate this we treated 20 week-old wild type mice with high fat diet with/without the non-brain-penetrable highly selective Y1 receptor (Y1R) antagonist BIBO3304 (0.5uM) daily for 3 weeks and compared this also to a cohort of younger mice.