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Impact of endurance exercise training on adipocyte miRNA expression in overweight men

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Adipocytes are major regulators of metabolism and dysregulated adipocyte function in obesity is linked to the metabolic syndrome. Endurance-exercise training improves adipocyte function; however, the molecular mechanisms that regulate the chronic adaptive responses are incompletely described. microRNAs (miRNAs) influence adipocyte differentiation and metabolism, yet their role in exercise-induced adipocyte phenotypes is unknown. We used next generation sequencing (NGS) to profile miRNA expression of adipocytes isolated from subcutaneous abdominal (ABD) and gluteofemoral (GF) adipose tissue of overweight men before and after six weeks of endurance-exercise training. Differentially expressed miRNAs were over-expressed or silenced in 3T3-L1 adipocytes and lipid metabolism examined. NGS identified 526 miRNAs in adipocytes and there were no statistical differences in miRNA expression when comparing the pre- and post-training samples for both ABD and GF adipocytes. miR-10b expression was increased in ABD compared with GF, while miR-204, miR-3613 and miR-4532 were more highly expressed in GF compared with ABD adipocytes. Blocking miR-10b in adipocytes suppressed β-adrenergic lipolysis but had a minor effect on lipid metabolism in general. Unlike their critical role in adipogenesis, stable changes in miRNA expression do not play a prominent role in the regulation of adipocyte function in response to endurance-exercise training.

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CNS reward pathways and anorexia nervosa (AN) — Insights from a rat model

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Patients suffering anorexia nervosa (AN) become anhedonic; unable or unwilling to derive normal pleasures and tend to avoid rewarding outcomes, most profoundly in food intake. Conversely, obesity is a condition that may be potentiated by excessive reward seeking and enhanced motivation for the rewarding properties of food. The activity-based anorexia (ABA) model allows investigation of the underlying neurobiology of AN, especially because it displays many characteristics in common with the human condition, including anhedonia. We aim to exploit this model to highlight the importance of CNS reward in the maintenance of body weight. We hypothesise that increasing the neuronal activity of circuits with predicted involvement in the anhedonia/reward pathways of ABA will prevent associated weight loss.

Female rats ($n = 24$; 6 weeks old) underwent separate bilateral stereotaxic injections of canine adenovirus-2-Cre (CAV-2-Cre) and activating DREADDs [AAV-hSyn-DIO-hM3D(Gq)-mCherry] into the NAcc (shell) and the VTA, respectively. DREADDs reorient in the presence of retrogradely-transported Cre and systemic clozapine-n-oxide (CNO) administration causes mCherry-labelled cells to depolarise with temporal and anatomical specificity. The ABA protocol involves free access to running wheels and time-limited (90 min) access to food, with daily i.p. injections of CNO or saline (control) at the onset of the feeding period.

CNO activates DREADD-expressing, VTA neurons as evidenced by colocalisation with elevated levels of Fos protein, a marker of neuronal activation. Importantly, excitation of this pathway with CNO attenuates the rapid weight loss associated with ABA with a profound effect on survival [$\chi^2(1) = 8.14$, $p = 0.004$]. Activation also increases food anticipatory activity (FAA) and decreases basal running

activity at discrete time periods. The contribution of energy expenditure to body weight maintenance during activation is unclear. These results will inform not only the neurobiological underpinnings of AN but also provide an insight into the mechanisms of reward pathways relevant to feeding and weight loss.

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Harnessing the sun to halt obesity: Vitamin D, nitric oxide and brown adipose tissue

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The role of vitamin D in curtailing the development of obesity and comorbidities like the metabolic syndrome (MetS) and type-2 diabetes has received much attention recently. However, clinical trials have failed to conclusively demonstrate the benefits of vitamin D supplementation. In most studies, serum 25-hydroxyvitamin D (25(OH)D) decreases with increasing BMI above normal weight. These low 25(OH)D levels may also be a proxy for reduced exposure to sunlight-derived ultraviolet radiation (UVR). We have found that frequent skin exposure to a low non-burning dose of UVR reduced weight gain in C57Bl/6 male mice fed a high fat diet. Ongoing exposure to UVR also significantly suppressed glucose intolerance, insulin resistance, signs of non-alcoholic fatty-liver disease and serum levels of fasting insulin and glucose. These findings were independent of circulating 25(OH)D, and most could not be mimicked by vitamin D supplementation. We are now starting to characterise the effects of biological mediators induced by exposure to UVR, such as nitric oxide, and their potential to prevent obesity in already 'overweight' mice, as well as the potential involvement of brown adipose tissue using the uncoupled protein-1 luciferase transgenic mouse (''Thermomouse''), in which thermogenesis in brown adipose tissue can be tracked *in vivo*. Our studies suggest that UVR (sunlight exposure) may be an effective means of suppressing the development of obesity and MetS through mechanisms that are partially dependent on nitric oxide, and other novel UVR-induced mediators.

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Investigating the molecular basis and therapeutic potential of the heme oxygenase-1 (HO-751) — Adiponectin axis

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Adiponectin is a beneficial hormone produced primarily by adipocytes. Paradoxically, circulating adiponectin levels are reduced in the context of obesity and associated diseases. This hypoadiponectinemia is implicated in the aetiology of obesity-related cardiometabolic diseases making therapeutic strategies to increase adiponectin attractive. An emerging body of literature suggests that increasing heme oxygenase 1 (HO-1) may increase adiponectin levels, prompting the proposal of an 'HO-1 — adiponectin axis'. We have performed a series of investigations to explore this possibility.

Using two *in vitro* models of human adipocytes, combined with a comprehensive array of pharmaceutical (cobalt protoporphyrin (CoPP) or hemin) and genetic modulators of HO-1, we found that neither acute[1] nor chronic induction of HO-1 results in increased adiponectin production. However, in a mouse model of diet-induced obesity we observed that systemic induction of HO-1 with CoPP increased circulating adiponectin levels and this was concurrent with decreased food intake, body weight gain and adipocyte size as well as enhanced insulin sensitivity and reduced liver steatosis. Importantly only the effect on adiponectin was blunted when mice were co-treated with an inhibitor of HO-1 activity (SnMP) [1].

Taken together, our *in vitro* and *in vivo* observations suggest that CoPP increases circulating adiponectin levels in an indirect manner that is, at least partly, dependent on HO-1 activity. Furthermore, our *in vivo* studies indicate that systemic treatment with CoPP results in reduced food intake and improvements in a range of metabolic