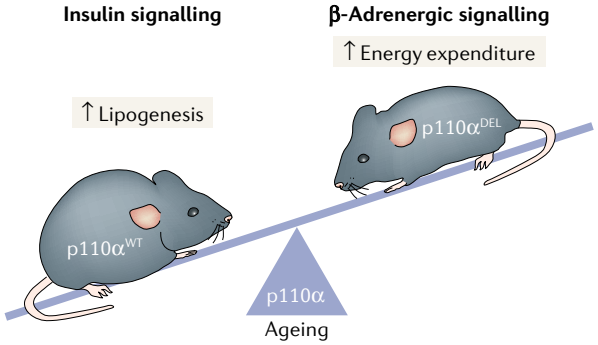


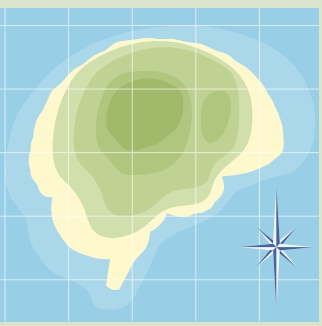
PI3K p110α is involved both in insulin and in β-adrenergic signalling. p110α inactivation (p110α^{DEL}) promotes β-adrenergic signalling, thus increasing thermogenic energy expenditure and leanness over ageing despite insulin resistance.

inhibitors could be co-administered with β3-adrenergic receptor agonists to enhance the efficacy and safety profile of the latter," says Foukas. p110α inhibitors at low doses have already been tested for other indications, and have limited adverse effects. "Therefore, there is scope for testing such compounds for prevention and/or amelioration of age-related obesity and associated comorbidities in human patients," concludes Foukas.

Claire Greenhill

> Enhanced adrenergic signalling resulted in elevated glucose uptake by brown adipose tissue

ORIGINAL ARTICLE Araiz, C. et al. Enhanced β-adrenergic signalling underlies an age-dependent beneficial metabolic effect of PI3K p110α inactivation in adipose tissue. *Nat. Commun.* **10**, 1546 (2019)



Credit: Jennie Vallis/Springer Nature Limited

To overcome this obstacle, the authors developed a genetic approach that enabled them to isolate nuclei from neurons that respond to leptin. "These nuclei were sorted from mice treated under different leptin conditions and were used to identify the genes (via RNA-seq) and regulatory elements (via ChIP-seq and ATAC-seq) that respond to leptin," says Ahituv.

The authors now hope to expand their gene map. "Not all the obesity-associated GWAS variants map to the regulatory elements identified in these neurons," concludes Vaisse. "By extending our approach to other neuronal populations implicated in the regulation of energy homeostasis, we hope to understand the mechanisms by which additional genetic variants predispose to obesity."

Alan Morris

> Nadav Ahituv and colleagues have established a comprehensive map of genes and regulatory elements in leptin-responsive neurons

ORIGINAL ARTICLE Inoue, F. et al. Genomic and epigenomic mapping of leptin-responsive neuronal populations involved in body weight regulation. *Nat. Metab.* **1**, 475–484 (2019)

OBESITY

Repurposed — a BAT activator

Credit: Springer Nature Limited

In translational obesity research, pharmacological activation of brown adipose tissue (BAT) thermogenesis is being investigated as a potential weight loss strategy. Current efforts, however, require further optimization.

Now, in a new study, Grandoch and co-workers test the effects of a prescription-free drug, 4-methylumbelliferone (4-MU), on BAT activity in mice. 4-MU, which inhibits the synthesis of the extracellular matrix component hyaluronan, is marketed as a choleretic drug in Europe and Asia.

"The hyaluronan-rich extracellular matrix of adipose tissue is highly responsive to inflammatory and metabolic changes," says lead author Maria Grandoch. The authors hypothesized that inhibiting hyaluronan synthesis in BAT could alter intracellular substrate flux and thus promote BAT function.

In mice that were fed a fat- and carbohydrate-rich diet, supplementation with 4-MU reduced weight gain, improved glucose homeostasis and limited white adipose tissue hypertrophy and inflammation. The authors also observed beneficial metabolic effects when feeding already obese, insulin-resistant mice with 4-MU.

In order to assess the effects of 4-MU on BAT activity in the mice, the authors first developed a new, non-invasive MRI approach. "For this technique, we harnessed the susceptibility of MRI relaxation time, T2, to regional magnetic-field inhomogeneities," explains Grandoch. "Because of its heterogeneous tissue composition, high iron content and rich vasculature, BAT has substantially lower baseline T2 values than other tissues. We expected that this effect would be even more pronounced under BAT activation."

Using this approach, the authors determined that 4-MU treatment activated BAT in a manner that was not affected by inhibition of the β3-adrenergic receptor, suggesting that 4-MU activates BAT via mechanisms independent of adrenergic receptor signalling.

To better understand how 4-MU enhances BAT activation, the authors examined changes in metabolites in BAT from animals treated with the drug. They observed that glucose and lactate concentrations were increased. In fact, inhibiting glycolysis blocked the expression of thermogenic gene *Ucp1*.

Genetic deletion of the two most abundant hyaluronan-synthase enzymes, HAS2 and HAS3, mimicked some of the beneficial metabolic effects of 4-MU treatment.

Both 4-MU treatment as well as MRI-based BAT imaging could prove to be clinically meaningful. "4-MU's beneficial effects occurred independent of adrenergic stimulation thereby minimizing unwanted side effects," highlights Grandoch. "The described T2 mapping approach has the potential to assess BAT activity in humans without the use of a harmful contrast agent or radiation and works furthermore independent from any substrate uptake."

Further studies are needed to test 4-MU treatment and the MRI imaging approach in humans.

Anna Kriebs, Associate Editor,
Nature Communications

ORIGINAL ARTICLE Grandoch, M. et al. 4-Methylumbelliferone improves the thermogenic capacity of brown adipose tissue. *Nat. Metab.* **1**, 546–559 (2019).