Short-term pharmacological inhibition of peripheral Y1R did not affect body weight in HFD-fed older mice compared to age-matched controls, but reduced body weight gain in HFD-fed younger mice. However, despite no change in body weight, fat weights of inguinal and mesenteric depots were markedly reduced in BIBO3304-treated older mice, whereas all fat depots in younger mice were markedly reduced by the antagonism of Y1R. This is associated with a significant increase in UCP1 mRNA expression in inguinal WAT of BIBO3304-treated DIO mice, suggesting the induction of browning of white fat by the inhibition of Y1R. There was no difference in lean mass in either age group. More importantly, despite its different extents in decreasing fat weights, Y1R antagonism by BIBO3304 was able to improve glucose tolerance in both younger and older mice. Elevated basal insulin level was observed in both age groups.

These data demonstrates that short-term peripheral Y1R blockade is effective to induce metabolic benefits in both younger and ageing DIO mice. This is achieved, at least in part by increasing WAT browning. Increased dosage of BIBO3304 or treatment duration in ageing mice may be required to achieve further improved metabolic outcomes. These findings demonstrate that NPY-Y1R signalling in peripheral tissues plays an important role in HFD-induced age-related obesity, and the blockade of Y1R will promote healthier ageing.

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The effect of atypical cannabinoid compounds on skeletal muscle homeostasis in a diet induced obese rat model

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Introduction: Atypical cannabinoid ligands O-1602 and O-1918 have an affinity to putative cannabinoid receptors including GPR18. The endocannbinoid system is involved in regulating energy homeostasis in obesity and skeletal muscle metabolism. Currently the expression of GPR18 in skeletal muscle and the effect that atypical cannabinoids have on skeletal muscle homeostasis is unclear.

Aim: To determine whether GPR18 is expressed in skeletal muscle in diet induced obesity (DIO) and if the receptor's expression is altered by treatment with atypical cannabinoids. To determine the effect of atypical cannabinoids on mRNA expression of markers involved in skeletal muscle homeostasis in red (RG) or white gastrocnemius (WG) in DIO.

Methodology: Male Sprague Dawley rats were fed a high fat diet (41% energy from fat) for 9 weeks to induce obesity. DIO rats were treated with 1 mg/kg-O-1918, 5 mg/kg-O-1602 or vehicle for 6 weeks. Rats were deeply anaesthetised, RG and WG were collected and snap frozen, then rats were administered sodium pentabarbitone. mRNA expression of markers of adiponectin signalling, oxidative capacity and fatty acid oxidation were determined.

Results/discussion/conclusion: In DIO rats, GPR18 mRNA was expressed in gastrocnemius muscle and expression was higher in RG compared to WG. Treatment with atypical cannabinoids did not alter GPR18 expression. The development of more selective ligands for GPR18 to pharmacologically target this receptor in skeletal muscle may be beneficial for obesity.

In DIO, O-1602 did not alter markers of energy homeostasis in RG or WG and may not be a beneficial obesity pharmacological target in skeletal muscle. O-1918 altered some markers of skeletal muscle metabolism in a fibre type-specific fashion. Further investigation into O-1918-treated skeletal muscle tissue is required.

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The likely role of brown adipose tissue as a mediator of improved glucose regulation after vertical sleeve gastrectomy

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Bariatric surgery remains the only effective treatment for morbid obesity. Vertical sleeve gastrectomy (VSG) is the most widely performed of the bariatric surgeries, largely because it confers not only significant weight loss but improved glucose regulation. We have recently demonstrated that brown adipose tissue (BAT) temperature and UCP1 protein expression in BAT are elevated following VSG and contribute substantially to weight loss. However, the importance of BAT in the mediation of improved glucose regulation following VSG is unclear.

Diet-induced obese male Sprague-Dawley rats underwent VSG (or sham) surgery and were also implanted with a telemeter to measure local changes in brown fat temperature, indicative of brown fat activity. Eight weeks following VSG surgery, oral and intraperitoneal glucose tolerance tests (GTTs) were performed to assess glycemic function. To localize glucose uptake in specific tissues, an oral GTT (1.5 g/kg) was combined with an intraperitoneal injection of 40 μCi of deoxy-D-glucose,2-[1-14C] (2DG-14C), administered intraperitoneally. Blood was collected immediately before the injection of 2DG-14C and glucose gavage (time 0) as well as 2, 5, 10, 20, 30 min later. Immediately after the final blood collection (30 min), rats were killed and tissues were rapidly dissected for assessment of 2DG-14C uptake.

Following VSG, there is a rapid reduction in body weight that is maintained for 8 weeks post- surgery. VSG is associated with increased BAT temperature 3 days post-surgery that is also maintained throughout the 8-week treatment period. There is improved glucose regulation coincident with the elevation in BAT activity following VSG as demonstrated by improved glucose clearance during the GTT and elevated glucose stimulated insulin secretion. Importantly, the pivotal role of brown fat is demonstrated by significantly *elevated* (4-fold) glucose uptake into BAT followed VSG compared to sham operated animals.

Collectively, these data support a role for BAT in mediating the improvement in glucose regulation following VSG surgery.

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