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The transgenerational effects of obesogenic diets

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Obesity appears to be a perpetuating cycle across generations. In humans, parental obesity is associated with obesity in children for a plethora of reasons. Beyond environmental factors such as child's diet, there are also maternally mediated effects such as metabolic imprinting. Studies conducted across a variety of taxa suggest parental diet of both mothers and fathers prior to conception can have an effect on the phenotype of the resultant offspring. However, very few studies have tested the transgenerational nature of these dietary effects in both parents using a fully factorial design. Our study manipulates the sucrose content of *Drosophila melanogaster* diets across three generations (to the F2 generation), and measures the effects of a high sugar diet across a range of phenotypic traits. Virgin flies are placed onto two diet treatments, either high or low sucrose (with all other ingredients kept constant), for four days before being allowed to mate. Initial results of our study indicate that parental diet has a significant effect on both the parental and offspring phenotypes. In particular, a diet high in sugar reduces fecundity, increases eclosion time, and alters offspring body composition. With the obesity epidemic increasing worldwide, studies such as ours that elucidate the transgenerational effects of obesogenic diets provide valuable insight into the complexities of curbing obesity.

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Effect of intermittent fasting on autophagy in human and C57BL/6 mouse muscle

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Background: Fasting activates autophagy in peripheral tissues, and blocking autophagy increases hepatosteatosis and alters glucose metabolism in mouse liver [1]. This study examined whether intermittent fasting activates autophagy pathways in mouse quadriceps and human vastus lateralis muscle.

Methods: Women ($n = 31{,}51 \pm 2$y, BMI$31.8 \pm 4.3\,kg/m^2$) were randomized to 1 of 2 groups for 8-weeks, and provided with foods at 70% (IF70) or 100% (IF100) of energy requirements. Participants fasted for 24 h from 0800 h, 3 days/week. Samples were collected at baseline (12 h overnight fast) and twice at Week 8 (12 h and 24 h fast). Ten week old C57BL/6J male mice were fed high-fat diet (HFD) (42% energy from fat) or chow for 8 weeks, before randomisation to AL or IF (24 h fasts initiated at ZT11 on 3 non-consecutive days/week) for a further 8 weeks (8–16/group). Mice were sacrificed in fed state (AL, IF-FED) and after 24 h of fasting (IF-FAST). Autophagy related genes *MAPLC3B*, *BECN1*, *TFEB*, *SQSTM* and *LAMP* were assessed by qPCR and SQSTM1 protein by western blot.

Results: In humans, greater weight and fat loss, and reductions in glucose and insulin were observed in IF70 vs IF100 groups (all $P < 0.01$). Increased *SQSTM* mRNA level in muscle was observed in the IF70 group following an overnight fast ($P = 0.05$). In mice, IF reduced body weight in high fat diet only, whereas gonadal and inguinal fat pad weight were reduced by IF in both diet groups (all $P < 0.05$). *SQSTM* mRNA levels in quadriceps were lower in HFD-AL vs chow AL mice ($P < 0.001$) and were increased by IF in IF-FAST vs AL and IF-FED mice that were fed high fat diet ($P < 0.001$). *MAPLC3B*, *BECN1* and *TFEB* mRNA levels in and SQSTM protein level in muscle were unchanged.

Conclusion: IF increased SQSTM mRNA levels in mice and humans who were in overall energy deficit but not when in overall energy balance.

Reference

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Modulation of gastric vagal afferent satiety signalling by endocannabinoids

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Introduction: Gastric vagal afferents (GVAs) relay signals to the hindbrain resulting in satiety and termination of a meal. Endocannabinoids regulate food intake via action at cannabinoid 1 (CB1) receptors and transient receptor potential 1 (TRPV1) channels. TRPV1 and CB1 are expressed on GVAs and the endocannabinoid anandamide (AEA) is expressed in the stomach. This study aimed to determine the relationship between TRPV1 and CB1 in mediating AEA effects on GVA satiety signalling.

Methods: Eight week male C57BL/6 murine ($N = 60$) GVA responses to 3 g tension were obtained using an *in vitro* GVA electrophysiology preparation. The effect of the stable analogue of AEA, methanandamide (mAEA; 1–100 nM), on GVA responses to 3 g stretch was determined in the absence and presence of a CB1 (rimonabant; 300 nM)), TRPV1 (AMG9810; 30 nM), protein kinase A (PKA inhibitor fragment (6–22) amide; 5 nM), protein kinase C (bisindolylmaleimide II; 10 nM), Gαi/o (NF023; 300 nM), or Gαq (YM-254890; 100 nM) antagonist.

Results: Low doses (1–10 nM) of mAEA reduced whereas high doses of mAEA (30–100 nM) increased tension sensitive GVA responses to 3 g stretch. The inhibitory effect of mAEA (1 nM) was lost and the excitatory effect of mAEA (100 nM) was reduced in the presence of rimonabant. The inhibitory and excitatory effects of mAEA were lost in the presence of AMG9810. The PKA inhibitor fragment (6–22) amide or NF023 prevented the inhibitory effect of mAEA on GVA mechanosensitivity but had no effect of the excitatory component. Conversely, in the presence of bisindolylmaleimide II or YM-254890 the excitatory effect of mAEA was reduced or lost respectively whereas the inhibitory effect remained.

Conclusions: Activation of CB1, by mAEA, can activate or inhibit TRPV1 to increase or decrease GVA responses to stretch depending on the second messenger pathway activated. These interactions could play an important role in the fine control of food intake.

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