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Salt intake promotes browning of white adipose tissue through the NPY-TH pathway

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Activation of brown fat and browning of white fat by cold exposure or beta 3 adrenergic receptor agonists increases energy expenditure and ameliorates metabolic syndrome. However, cold exposure or beta 3 adrenergic receptor agonists induced thermogenesis has achieved limited clinical efficacy, and alternative measures need to be explored to stimulate brown fat and white fat browning. Here we reveal a critical role of sodium chloride in promoting activity of brown fat and browning of white fat. Our study found that 2% salt in drinking water significantly increases energy expenditure (EE) of wild type mice via the activation of BAT activity and WAT browning, as evidenced by the upregulation of UCP1 and PGC-1α at mRNA and protein level in both brown fat and inguinal white fat. Moreover, salt intake significantly increases body temperature without a change in food intake and locomotive activity, leading to a marked decrease in fat mass as well as diet-induced obesity. Mechanistically, salt intake decreases hypothalamic Arc NPY expression, leading to the removal of inhibition on tyrosine hydroxylase (TH) activity in the hypothalamic PVN, thereby resulting in increased sympathetic outflow to peripheral BAT and WATi. Taken together, these data suggest that salt ingestion stimulates the activity of brown fat and browning of white fat and enhances energy expenditure through the modulation of central hypothalamic NPY-TH levels. The results from this study for the first time reveal the novel role of salt intake in controlling thermogenesis. The findings will provide insights into using salt as an alternative treatment option for high fat induced metabolic disorders.

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Distinct populations of Arc NPY neurons control specific aspects of energy homeostasis

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Hypothalamic NPY neurons are critically involved in the complex processes that regulate feeding and energy homeostasis. Considering this wide range of functions it is conceivable that different populations of Arc NPY neurons exist that specialise to undertake different responsibilities. However, no knowledge exists how these Arc NPY neurons differ from each other, where they are located, what controls them and what they control. By employing RNAscope we show that a specific subset of Arc NPY neurons exist that do not contain AgRP. This is confirmed by the selective deletion of NPY from AgRP neurons in mice. Baseline levels of AgRP mRNA is not altered in the absence of NPY in these neurons and both AgRP and the remaining NPY neurons are responsive to fasting. Interestingly, bodyweight is significantly higher in AgRPcre/+;NPYlox/lox mice compared to AgRPcre/+;NPYlox/+ control mice and this is accompanied by significantly elevated fat mass. There is a strong trend to increased food intake and this combined with the observed significant decrease in energy expenditure and reduced activity level in the AgRPcre/+;NPYlox/lox mice are the likely causes for the observed increase in bodyweight and fat mass. Surprisingly, bone mass which is also known to be strongly influenced by hypothalamic NPY is unaltered in AgRPcre/+;NPYlox/lox mice suggesting this NPY population is not critical for the central control of bone homeostasis. Interestingly, activating non-NPY AgRP neurons with stimulatory DREADDs is still able to increase food intake, which is reversed when employing an inhibitory version. Taken together this suggests that non-AgRP positive NPY neurons fulfil important different function in the control of whole body energy homeostasis. This is significant, since most past and current research investigating hypothalamic NPY function employ AgRP driven Cre-lines, and as such functional contributions of other NPY neuronal population in the Arc have either been missed or overlooked.

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Differential benefits of two isocaloric exercise programs on diet-induced non-alcoholic fatty liver disease and circulating extracellular vesicles in mice

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Extracellular vesicles (EVs) are submicron, membrane-bound structures released from activated or stressed cells. They are involved in intercellular signaling and have been shown to be changed in the context of non-alcoholic fatty liver disease (NAFLD), acting as a potential biomarker. While exercise is a commonly prescribed therapeutic intervention for NAFLD, most studies have explored endurance training (END) with few reporting on high-intensity interval training (HIIT). Since little is known about the interaction between exercise and EVs in the context of NAFLD, this study aimed to compare the efficacy of both END and HIIT in their ability to normalise EVs. Ten-week old male C57Bl/6 mice were randomly assigned to high-fat diet (HFD; 45%kcal fat) or standard chow for 20 weeks. After 10 weeks of dietary intervention only, mice were exercised on a treadmill 3×/week for the remaining 10 weeks: 40 min at constant 70% maximal running capacity (MRC) for END, or 5 min cycles of 85–90% and 50% MRC for HIIT. Physical profile, plasma biochemistry, liver histology and phenotype were compared against untrained groups on either diet. Plasma EVs were isolated by ultracentrifugation and enumerated by NanoSight™. Both exercise protocols reduced liver weight (END: $p = 0.003$; HIIT

$p < 0.001$) and improved ALT (both $p < 0.001$) compared to untrained HFD. Liver lipid staining was only decreased by HIIT (END: $p = 0.532$; HIIT: $p = 0.011$), while improvements to the gene expression of tissue remodeling markers (Col1a1, Tgfb1,Timp2) depended upon the protocol. Although HFD had a negligible effect on EVs, they were increased by 2-fold after END training, independent of diet (HFD: $p = 0.068$; chow: $p = 0.014$). While exercise is effective in reducing NAFLD burden, changes to steatosis or tissue remodeling are affected by the specific protocol. Interestingly, exercise had a stronger effect on EV number than obesity. While the literature implicates vascular events, the mechanisms in our model are currently under investigation.

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Vertical sleeve gastrectomy and hypertension in diet-induced obese rodents

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Vertical sleeve gastrectomy (VSG) is a bariatric procedure that involves removal of approximately 80% of the stomach along the greater curvature. VSG leads to decreased body weight and adiposity as well as reduced hypertension. We have observed that VSG reduces blood pressure in rats maintained on high-fat diet (HFD), and that this effect is independent of body weight and obesity, by utilizing a pair-feeding paradigm. We examined potential mechanisms contributing to the reduced arterial pressure following VSG by investigating the effect of VSG on proposed mechanisms linking obesity to hypertension, including hyperactivity of the renin-angiotensin system (RAS), hyperinsulinemia, hyperlipidemia and hyperleptinemia. Male rats were fed an AIN93 M HFD containing approximately 45% fat by kilocalories at a density of 4.73 kcal/g for 14 weeks prior to surgery. Rats were then allocated into three weight-matched groups to undergo the dual surgery: a blood pressure telemetry implant and either VSG or Sham surgery. Producing three groups 1) VSG, 2) Sham- ad libitum fed (AL) and 3) Sham-pair fed (PF). Arterial pressure was recorded continuously for 4 months and animals were given a number of pharmacological challenges to determine cardiovascular responsiveness following VSG surgery to acute injection of the beta-agonist isoproterenol, acute injection of the beta-antagonist propranolol and chronic L-NAME treatment. VSG led to significant reductions in arterial pressure relative to both sham-PF and sham-AL groups, all groups were similarly responsive to sympathetic manipulation and nitric oxide synthase inhibition. Plasma levels of triglycerides, non-esterified fatty acids, insulin and leptin were all similarly reduced in VSG and PF animals, relative to the AL group. However, activity of the RAS was lower only in the VSG group, suggesting that suppression of the RAS may be a major contributor to the reduction in hypertension following bariatric surgery.

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A systematic research review of associations between maternal eating disorders and parent-child feeding interactions

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Evidence suggests both parent-child mealtime interactions and relationship quality play an important role in shaping children's eating and weight-related behaviours [1,2]. Mothers with eating disorders (ED) specifically report finding mealtimes challenging, with research showing a link between parental eating psychopathology and feeding practices implicated in the development of childhood obesity [3]. However, studies have largely focused on parent-level factors only. Therefore the aim of this systematic review was to investigate how maternal EDs influence dyadic parent-child interactions, child weight and eating.

We systematically searched English-language articles published in peer-reviewed journals between January 2008 and January 2018. Studies assessing associations between maternal eating disorders (diagnosis, history or symptomatology) and parent-child feeding interactions of children aged 0–18 years were included in our review.

Results: 12 studies met the inclusion criteria; of these 4 were longitudinal. Children included in the studies were aged 0–6 years. Maternal EDs were assessed via self report (11 studies) and interview (1 study). Most studies implemented unidirectional self-report measures of child feeding practices. Of the 4 observational child feeding assessment tools used, 3 captured the quality of dyadic parent-child feeding interactions. Results varied according to ED, but overall findings showed maternal EDs were associated with higher use of restrictive feeding practices and poorer quality of parent-child feeding interactions (i.e., distressing; less sensitive; unattuned; negative emotional climate). Maternal EDs were associated with problematic child eating behaviours (i.e., emotional overeating; binge eating; disordered eating) but not directly with child BMI.

The findings of this review suggest mothers with histories of EDs, or current symptomology, and their children may experience poorer quality mealtime interactions associated with greater obesity risk. Future research should implement consistent and thorough measures of dyadic relationship quality and child obesity risk outcomes.

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