117

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

Xin Zhou [1], Chen-liang Zhang [1], Zhi-yuan Song [1], Yan-Chuan Shi [2], Shu Lin [1,3,*]

[1] *Southwest Hospital Third Military Medical University (Army Medical University), Shapingba, Chongqing, China*
[2] *Neuroscience Division, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[3] *University of Wollongong, Wollongong, NSW, Australia*

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.

https://doi.org/10.1016/j.orcp.2018.11.122

200

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

Qi Yue*, Nicola Lee, Lei Zhang, Ron Enriquez, Herbert Herzog

Neuroscience Division, Garvan Institute of Medical Research, St Vincent's Hospital, Darlinghurst, NSW, Australia

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.

https://doi.org/10.1016/j.orcp.2018.11.123

201

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

Linda A. Ban [1,*], Sergio F. Martinez Huenchullan [1,2], Luisa F. Olaya Agudo [1], Babu Raja Maharjan [1], Christine Yee [1,3], Charmaine S. Tam [4], Stephen M. Twigg [5,1], Susan V. McLennan [1,6]

[1] *Greg Brown Diabetes and Endocrine Laboratory, University of Sydney, Sydney, NSW, Australia*
[2] *School of Physical Therapy, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile*
[3] *Ingham Institute, Sydney, NSW, Australia*
[4] *Northern Clinical School and Centre for Translational Data Science, University of Sydney, Sydney, NSW, Australia*
[5] *Department of Endocrinology, Univeristy of Sydney and Royal Prince Alfred Hospital, Sydney, NSW, Australia*
[6] *NSW Health Pathology, Sydney, NSW, Australia*

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