AN AGRP NEURAL CIRCUIT AVERTS EXTREME BODY WEIGHT THROUGH BIDIRECTIONAL CONTROL OF ENERGY EXPENDITURE

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Background: The extreme body weight phenotype in obese and anorexic subjects reflects severe imbalance of calorie intake and energy expenditure. Although some neural circuits contributing to feeding were recently characterized, neural mechanisms that underlie the thermogenesis control of body weight and the etiological significance to obesity and anorexia remain unclear.

Materials/Methods: All animal care and experimental procedures were approved by the Institutional Animal Care and Use Committees at Baylor College of Medicine. Mice used for data collection were kept in temperature- and humidity-controlled rooms, in a 12/12 hr light/dark cycle. All the mice with brain surgery were performed with the same pre-operative and post-operative care. Stereotaxic Viral Injections, Liquid Chromatography with Tandem Mass Spectrometry, optogenetics and chemogenetics, Pharmacology, CLAMS, Electrophysiology, Fiber Photometry and Cellular Respiration Rates were performed.

Results: 1. A novel thermoregulatory neural circuit where a subgroup of AgRP neurons that send projections to neurons within the MC4RdlDRN neurons , which in turn innervate serotonergic 5-HTdmDRN neurons. 2. This AgRP ARC-MC4R dlDRN-5-HT dmDRN circuit exerts a bi-directional control of energy expenditure via sympathetic outflow that re-programs mitochondrial bioenergetics within brown and beige fat tissues. 3. Food intake, however, does not affected by the manipulation of this circuit. 4. Deletion of the MC4RdlDRN signaling promotes weight gain by a persistent reduction of metabolic rates, whereas re-expression of MC4R dlDRN significantly ameliorates obesity in the Mc4r-null mice through restoration of mitochondrial uncoupling in brown/beige fat tissues. 5. Our findings demonstrate that genetic suppression of this circuit recapitulates Activity-based anorexia (ABA) , whereas activation of this circuit fully abolishes anorexia phenotype by restoration of thermogenesis and mitigation of exercise which mimics the beneficial effect of high ambient temperature.

Conclusions: We reveal a unique causal factor of anorexia that dieting-induced hunger disrupts this thermoregulatory circuit, such that mice respond to hypothermia by reinforcing running, a self-defeat strategy that ultimately leads to anorexia. Together, a unique neural circuit plays a critical role in regulation of body weight via enduring and profound control of energy expenditure, constituting a novel mechanism for developing more efficient treatment of obesity and anorexia.