Mitofusin 2 in POMC Neurons Connects ER Stress with Leptin Resistance and Energy Imbalance

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Mitofusin 2 (MFN2) plays critical roles in both mitochondrial fusion and the establishment of mitochondria-endoplasmic reticulum (ER) interactions. Hypothalamic ER stress has emerged as a causative factor for the development of leptin resistance, but the underlying mechanisms are largely unknown. Recently, we have shown that mitochondria-ER contacts in anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus are decreased in diet-induced obesity. POMC-specific ablation of Mfn2 resulted in loss of mitochondria-ER contacts, defective POMC processing, ER stress-induced leptin resistance, hyperphagia, reduced energy expenditure and obesity. Pharmacological relieve of hypothalamic ER stress reversed these metabolic alterations. Our data establishes MFN2 in POMC neurons as an essential regulator of systemic energy balance by fine-tuning the mitochondrial-ER axis homeostasis and function. This previously unrecognized role for MFN2 argues for a crucial involvement in mediating ER stress-induced leptin resistance.