Hypothalamus-dependent control of liver organelle dynamics during metabolic transitions

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Proopiomelanocortin (POMC)- and agouti related peptide (AgRP)-expressing neurons in the arcuate nucleus of the hypothalamus (ARH) are critical regulators of food intake and energy homeostasis. They rapidly integrate the energy state of the organism through sensing fuel availability via hormones, nutrient components and even rapidly upon sensory food perception. Importantly, they not only regulate feeding responses, but numerous autonomic responses including glucose and lipid metabolism, inflammation and blood pressure. We could demonstrate that sensory food cue-dependent regulation of POMC neurons primes the hepatic endoplasmic reticulum (ER) stress response to prime liver metabolism for the postprandial state. We also identify a novel pathway, how food perception-dependent regulation of POMC neurons rapidly controls mitochondrial dynamics, through a novel posttranslational modification of the mitochondrial fission factor MFF. Finally, we expand the concept of cell-non autonomous control of liver organellar function by identifying a novel pathway how AgRP neuron activation in fasting promotes autophagy induction in liver via activation of the hypothalamic pituitary adrenal (HPA) axis. HPA activation is mediated via NPY release from AgRP neuron terminals in the PVH to pre-synaptically inhibit NPY-1R-GABAergic terminals, which otherwise inhibit CRH neurons. Collectively, the presentation will discuss the role of melanocortin neurons in control of metabolic adaptation of liver to energy state transitions.