Role of mitochondria in neurons and astrocytes for the regulation of systemic metabolism

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Tight regulation of whole-body metabolism is essential in maintaining energy homeostasis and for preventing several diseases such as obesity. In the brain, the hypothalamus is considered the core of this metabolic regulation. More specifically, AgRP neurons in the arcuate nucleus of the hypothalamus (ARC) promote food intake and control systemic insulin sensitivity.

Mitochondria are highly energetic dynamic organelles, which can undergo fission and fusion events also in adaptation to the energy state. One of the critical proteins of these processes is the mitochondrial fission factor (MFF), which is implicated in the initiation of mitochondrial fragmentation. Additionally, mitochondrial dynamics was identified as a critical regulator of synaptic transmission. Indeed, AgRP activity and function were influenced by alterations in mitochondrial fusion. Thus, we aimed to define the role of MFF in AgRP neurons and its possible role in the regulation of whole-body metabolism.

To this end, we generated mice with AgRP-neuron specific *Mff* inactivation together with several reporter proteins to study mitochondrial morphology, electrophysiological properties, as well as, mitochondrial Ca^{2+} signaling. $MFF^{\Delta AgRP}$ mice showed increased mitochondrial network with swollen mitochondria. Interestingly, electrophysiological recordings indicated an increased neuronal excitability due to differences in the spike frequency adaptation in AgRP cells of $MFF^{\Delta AgRP}$ mice due to alterations in Ca^{2+} handling. However, despite altered AgRP neuron excitability, $MFF^{\Delta AgRP}$ animals showed no overall changes either in body weight or glucose homeostasis. Nevertheless, increased AgRP neuron excitability translates into an enhanced refeeding response. Collectively, partially impairing mitochondrial fragmentation in AgRP neurons increases their neuronal excitability due to changes in mitochondrial Ca2+ handling.

Moreover, astrocytes are also key players for the regulation of metabolism due to the capacity of sensing and responding to peripheral hormones. Glucagon-like peptide 1 (GLP-1) is secreted peripherally by intestine L-cells, and centrally by the GLP-1 producing neurons (PPG) located in the NTS being implicated on lowering glucose levels as well as suppressing food intake. Since hypothalamic astrocytes control energy homeostasis responding to insulin and leptin we asked whether GLP-1R signaling in hypothalamic astrocytes also play a role in this control. For this purpose, C57Bl/6 and GLP-1R KO primary astrocytes were used. First, GLP-1 enhances a change in substrate utilization by increasing fatty acid oxidation *in vitro*. Second, GLP-1R KO astrocytes revealed impaired mitochondrial integrity and function which, in turn, triggers an integrates stress response enhancing the expression of *Fgf21* and increased glucose uptake and glycolysis.