MOLECULAR METABOLISM

Commentary

Divide et impera: How mitochondrial fission in astrocytes rules obesity

The human brain is an energetically expensive organ, which uses approximately 20 percent of the resting body's energy production despite occupying only 2% of the body's mass. The energy is required to constantly encode and exchange information that is passing through neural impulses. The energy for these processes is supported by the powerhouses of the cell, the mitochondria. Mitochondria are highly dynamic bioenergetic organelles that can adjust size, shape, and location via fission and fusion events, collectively referred to as 'mitochondrial dynamics', to adjust cellular energy homeostasis by modulating energy efficiency and distribution, thereby responding to dynamic changes in energy demands. In neurons, when cellular energy requirements are high, mitochondrial fusion appears to support higher ATP production, in contrast to mitochondrial fission, which is usually associated with reduced mitochondrial activity and low energy states [1]. Most importantly, however, is the precise regulation by several mitochondrial fusion proteins, such as mitofusin 1 and 2 (Mfn-1 and -2) and mitochondrial dynamin-like GTPase (Opa1), and mitochondrial fission proteins, such as dynamin-related protein 1 (Drp1) and fission protein 1 (Fis1) [2]. The tight control of mitochondrial dynamics in the brain is not only crucial for maintaining cellular integrity, but enables neurons to control glucose homeostasis and whole-body energy balance [1]. The groups of Claret and Horvath previously discovered how alterations of mitochondrial dynamics in Pro-opiomelanocortin (POMC) and Agouti related protein (AgRP) neurons impact on systemic energy balance [3,4]. Later studies have shown how mitochondrial dynamics can influence glucose-induced neuronal activation in specific hypothalamic nuclei, such as the arcuate nucleus (ARC) and the ventromedial nucleus (VMH), as well as in extra-hypothalamic areas, such as the dorsal vagal complex (DVC) for control of glucose metabolism [5–8].

In this issue of *Molecular Metabolism*, Patel et al. advance our understanding of the brain-metabolism axis by showing that not only do mitochondrial dynamics in neurons control energy balance, but mitochondrial dynamics in astrocytes expressing the glial fibrillary acidic protein (GFAP) within brainstem areas play an equally powerful role [9]. A non-cell-specific viral approach in the DVC of rats reveals that increasing the activity of the mitochondrial fission protein Drp1 impairs insulin signaling, leading to increased food intake, subsequent body weight gain, and adiposity. Conversely, inhibiting Drp1 activity in high-fat diet (HFD)-fed rats via viral induction of a dominant negative (DN) form was able to rescue the aforementioned phenotype, while the constitutively active form of Drp1 and HFD both increased levels of inducible nitric oxide synthase (iNOS) in the DVC. The results *in vitro* and *in vivo* suggest that iNOS levels correlate with Drp1 activity. Inhibiting either Drp1 or iNOS in the DVC restores the ability of insulin to reduce food intake in DIO animals and slows down body weight gain. Inhibiting Drp1 activity specifically in DVC GFAP-expressing astrocytes was sufficient to ameliorate metabolic health during short-term HFD feeding, thus confirming the previously observed phenotype of decreased feeding and ameliorated obesity.

Most of the energy consumption in the brain is required to support synapses, and this is reflected by subcellular location of mitochondria preferentially in the synaptic terminals (pre- and post-synaptic elements) and associated glia. The concerted effort of mitochondria from neurons and adjacent astrocyte processes provide the active synapses with rapid local Ca^{2+} buffering and ATP production to match high energetic demands [10]. Metabolic coupling of mitochondria from neurons and astrocytes is crucial to pay off energetic costs and enable adequate functional sustainability of the synapse. Thus, dynamic changes of mitochondrial fusion and fission in any of these cellular compartments could entail mitochondrially-derived energy defects at the synapse and ultimately translate to dysfunction of neuronal connectivity and disease. Astrocytes are more glycolytic than neurons, although they maintain a high capacity for oxidative mitochondrial metabolism, and occupy separate non-overlapping microdomains via their fine processes that unsheathe the vasculature and synapse contacts. It is estimated that a single mouse astrocyte makes contacts with over 100,000 synapses [11], which allows astrocytes to regulate the exchange and processing of high-volume synaptic information. Previous studies have reported that astrocytes modulate their glycolytic/oxidative metabolism, as well as mitochondrial size and shape, in response to circulating hormones, such as insulin. Such adaptations of mitochondrial morphology in astrocytes could well be the result of the cellular adaptive metabolic response to glucose availability, therefore mediating the metabolic signaling output to neurons for peripheral glucose control [12]. In the DVC, other studies have reported that calcium-dependent activation of astrocytes suppressed the nocturnal feeding and fasting-refeeding response, a phenotype which appears to be mediated by activation of secondary neuronal circuits located in the nucleus of the solitary tract (NTS) and the lateral parabrachial nucleus (lPBN) [13]. The current work by Patel et al. advances this concept by revealing mitochondrial dynamics in DVC astrocytes as a potential cellular mechanism of homeostatic neuroendocrine control of systemic metabolism. These findings impact our knowledge of a) how mitochondria coordinate cellular adaptations in astrocytes of metabolically relevant brain areas to trigger signaling pathways for the adjustments of local finely-tuned neuronal responses, thereby meeting whole-body energy demands, and b) how dynamic changes in astrocyte mitochondria promote peripheral aberrant metabolism associated with obesity. Yet, many questions remain: i.e., whether astrocytes strategically change the size, number, and distribution of mitochondria to support the synapses and other aspects of neuronal function such as connectivity and plasticity. Astrocytes also show a great variety of shapes as well as distinctive inter- and intraregional features [14] which is thought to be defined by the surrounding micro-environment and neighboring cells. As for neurons, such astrocyte heterogeneity could also indicate a functional diversity in the control of metabolism, which could entail distinct regulation of mitochondrial dynamics in these glial cells at the synaptic level. In the future, a better understanding of how mitochondrial dynamics and local ATP supply in astrocytes support synaptic quality control would help to advance both the fundamental understanding of information processing in the brain circuitries involved in the regulation of systemic metabolic control and the development of therapies for obesity and other brain diseases (Figure 1).

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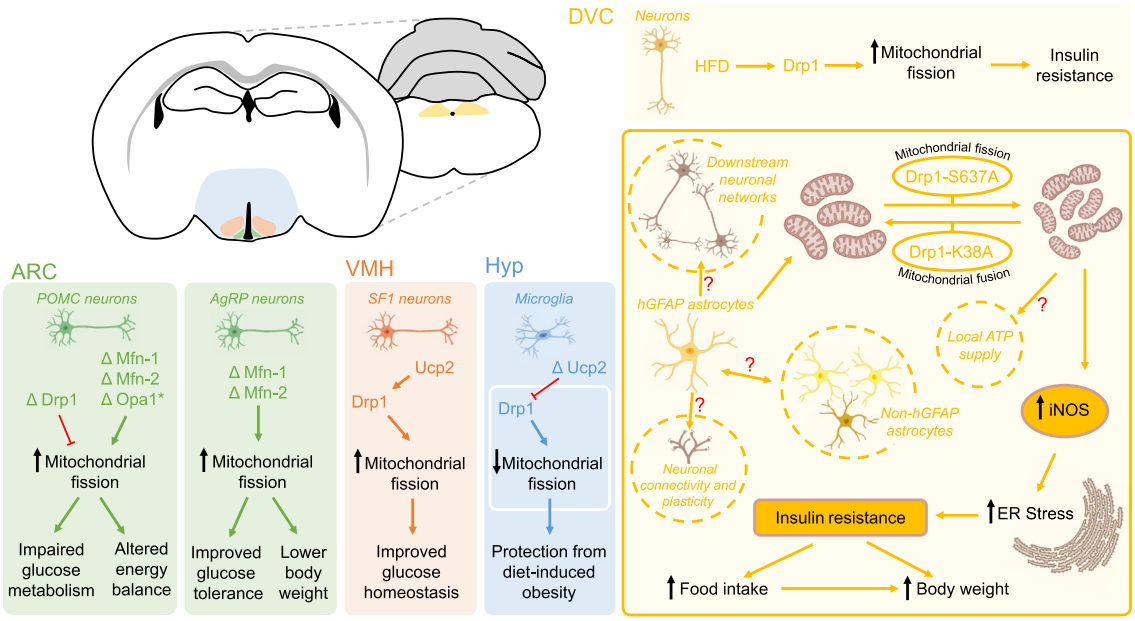

Figure 1: Mitochondrial dynamics in the regulation of metabolism in the central nervous system. Several studies have dissected the role of mitochondrial dynamics in different brain areas and cell types regarding metabolic homeostasis. Within the ARC nucleus of the hypothalamus, alterations of mitochondrial dynamics caused by ablation of key proteins lead to altered glucose metabolism and energy balance or the opposite phenotype depending on the neuronal population studied. In the VMH nucleus, increases in the mitochondrial fission of neurons exert an improved glucose homeostasis. In hypothalamic microglia, decreased mitochondrial fission is associated with diet-induced obesity. In extra-hypothalamic areas, elevated mitochondrial fission in DVC neurons was discovered as a mechanism of diet-induced insulin resistance. In the present study from Patel et al., modulation of astrocytic mitochondrial dynamics, via activation or inactivation of Drp1, induces iNOS and ER stress in the DVC. As consequence, increased mitochondrial fission induces a defective anorectic insulin effect associated with body weight gain. ARC, arcuate nucleus of the hypothalamus; Drp1, dynamin-related protein 1; Drp1-S637A, constitutively active form of Drp1; Drp1-K38A, dominant negative form of Drp1; DVC, dorsal vagal complex; Hyp, hypothalamus; Mfn-1, mitofusin 1; Mfn-2, mitofusin 2; Opa1, mitochondrial dynamin-like GTPase 1; Ucp2, uncoupling protein 2; VMH, ventromedial nucleus of the hypothalamus. Information in this figure was obtained from: [3–9,15]. *It has not been reported that OPA1 deletion in POMC neurons causes impaired glucose metabolism.

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CONFLICT OF INTEREST

Author declares no competing (financial, personal or professional) of interest.

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Ismael González-García[1]
Ophélia Le Thuc[1]
Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany
German Center for Diabetes Research (DZD), 85764, Neuherberg, Germany

Martin Jastroch
Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany
German Center for Diabetes Research (DZD), 85764, Neuherberg, Germany
Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, 106 91, Stockholm, Sweden

Cristina García-Cáceres*
Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany
German Center for Diabetes Research (DZD), 85764, Neuherberg, Germany

*Corresponding author. Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany.
E-mail address: garcia-caceres@helmholtz-muenchen.de

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[1]IG-G and OLT have equally contributed to this work.

