When Size Matters: How Astrocytic Processes Shape Metabolism

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Abstract

The hypothalamic control of metabolism appears to be a puzzle that cannot be explained by neuronal function alone. Zhang and colleagues (2017) add a few new pieces by demonstrating that astrocytes critically modulate neural circuits controling energy homeostasis through nutritional-status-dependent morphological plasticity and IKKβ/NF-κB signaling, which modulate extracellular neurotransmitter bioavailability.

Main body

Key to the regulation of energy homeostasis is the control by hypothalamic neurons of numerous neuroendocrine functions that integrate metabolic feedback and adapt the response of the organism to physiological demands (Jais and Bruning, 2017). However, it is becoming increasingly clear that glial cells are also actively involved in this process. For instance, recent studies have shown that astrocytes are endowed with metabolic signal-sensing properties. Indeed, astrocytes have been reported to sense insulin (a pancreatic hormone that controls blood glucose levels) and leptin (an anorexigenic hormone produced by adipose tissue), as well as to co-regulate behavioral responses and metabolic processes via the control of brain glucose uptake and the glial ensheathment of anorexigenic proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARH), respectively (Garcia-Caceres et al., 2016; Kim et al., 2014). Other glial cells also play critical roles in the regulation of energy homeostasis. Tanycytes, a specialized group of hypothalamic ependymal cells lining the floor of the third ventricle, act as gatekeepers controlling the access of circulating metabolic signals in two distinct ways: (1) by undergoing nutritional-status-dependent molecular changes that alter their barrier properties, allowing the access of circulating energy metabolites to ARH neurons through passive diffusion (Langlet et al., 2013), and (2) by actively shuttling circulating metabolic hormones such as leptin into the hypothalamus (Balland et al., 2014). In addition, NG2 glia are crucial for the maintenance of the processes of leptin-sensitive neurons outside the blood-brain barrier in the hypothalamic median eminence (Djogo et al., 2016).

A report in this issue of *Cell Metabolism* from the Cai group (Zhang et al., 2017) not only demonstrates that hypothalamic astrocytes control energy metabolism through the remodeling of their processes, but also uncovers the mechanism by which this plasticity is regulated by nutritional status. Using a combination of state-of-the-art genetic tools and an updated Golgi staining method to reveal the complex structure of astrocytic processes, the authors show that fine distal processes of astrocytes are shortened both under conditions of acute fasting and a chronic high-fat diet (HFD). Interestingly, this nutritional-status-dependent morphological plasticity occurs in astrocytes of the ARH and the ventromedial nucleus of the hypothalamus but not in the cerebral cortex, highlighting the still underestimated functional heterogeneity of astrocytes in the central nervous system, and suggesting that astrocytes exhibit distinct properties linked to the specificity of the neural networks in which they are integrated (Khakh and Sofroniew, 2015).

Accumulating evidence suggests that hypothalamic inflammation is associated with the development and progression of obesity and its repercussions on glucose homeostasis (Jais and Bruning, 2017). The molecular pathways underlying this inflammation have been shown to involve the activity of the IκB kinase (IKKβ) and the nuclear translocation of NF-κB, a

process that occurs rapidly following the ingestion of a high fat diet, even prior to significant weight gain (Jais and Bruning, 2017). By using glial fibrillary acidic protein (GFAP) promoter-driven activation and inhibition strategies, Zhang et al. (2017) have intriguingly identified the IKKβ/NF-κB pathway as a key regulator of astrocytic distal process plasticity, with functional consequences to both acutely and chronically-regulated metabolic parameters: while a moderate overactivation of astrocytic IKKβ/NF-κB triggers obesity-associated metabolic features (i.e. glucose intolerance and increased fasting plasma insulin levels and daytime blood pressure), its inhibition in HFD-fed mice reverses metabolic disturbances (see Figure 1). The authors also show that mice in which IKKβ is selectively knocked out in astrocytes are protected against diet-induced obesity and that the conditional invalidation of IKKβ in hypothalamic astrocytes in adult mice counteracts the overfeeding induced by a chronic HFD, a phenomenon that has also recently been reported by others using alternative genetic approaches (Douglass et al., 2017).

How does the remodeling of astrocyte processes influence the activity of the neuronal network controlling food intake and body weight? The Cai group (Zhang et al., 2017) identifies two intermediates in this process: the neurotransmitter γ-aminobutyric acid (GABA) and brain-derived neurotrophic factor (BDNF). Their experimental data suggest that the shortening of astrocytic processes reduces the capacity of astrocytes to take up GABA released at neuronal synapses, leading to increased levels of GABA in the extracellular space, the activation of extrasynaptic GABAB receptors on nearby neurons and the resulting GABAB-dependent decrease in the production of neuronal BDNF, a neurotrophic factor thought to be involved in the control of energy balance (Figure 1). However, as underlined by the authors, even though these changes in extracellular GABA levels and tissue BDNF content appear to be partly accountable for the metabolic effects of diet-induced changes in astrocyte morphology, one cannot rule out the involvement of additional neuromodulators (e.g. glutamate) known to play key roles in the activity-dependent structural and functional plasticity of astrocyte-neuron interactions within the hypothalamus (Theodosis et al., 2008).

Like most new and exciting observations, the current study by Zhang et al. (2017) raises even more questions than it answers regarding the hypothalamic control of metabolism. For instance, what nutritional-status-related signals trigger the morphological remodeling of distal astrocytic processes and how? How does the remodeling of astrocytic processes revealed using Golgi staining translate into modifications of the glial coverage of neurons or synapses at the ultrastructural level? What are the neuronal populations or networks involved and how are their functional or electrical properties altered by this plasticity? In addition, GFAP, shown here to drive the modulation of the IKKβ/NF-κB pathway, is expressed not only by astrocytes but also by subpopulations of tanycytes lining

the ARH and the ventromedial nucleus of the hypothalamus (Robins et al., 2013). Considering the known involvement of tanycytes in mediating the communication between the periphery and the metabolic brain (Balland et al., 2014; Langlet et al., 2013), could this other glial cell type also participate in the IKKβ/NF-κB-dependent regulation of energy metabolism and the associated metabolic phenotype?

While the answers to these and other questions are figured out, the new mechanism uncovered by Zhang et al. (2017), whereby hypothalamic astrocytes control the activity of the neuronal networks regulating energy homeostasis, point to inflammation-related astrocytic signaling pathways as relevant targets in the search for novel therapies to cure obesity and metabolic syndrome.

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Figure 1. Diet-induced changes in hypothalamic astrocyte morphology are associated with an alteration of the IKKβ/NF-κB signaling pathway and energy homeostasis. A chronic high-fat diet (HFD) induces the reversible shortening of high-order hypothalamic astrocytic processes through a moderate overactivation of the IKKβ/NF-κB pathway. These plastic changes are associated with higher extracellular GABA levels, presumably due to impaired astrocytic uptake via GABA transporters enriched in the processes, as well as the increased sensitivity of hypothalamic neurons to GABA stimulation. The activation of GABAB receptors in hypothalamic neurons inhibits BDNF expression, leading to food-intake and body-weight deregulation. Altogether, the authors propose a model in which the moderate overactivation of the IKKβ/NF-κB pathway in hypothalamic astrocytes actively participates in the metabolic disturbances induced by HFD. Notably, the authors identify a decrease in the complexity of astrocytic process arborization after acute fasting that phenocopies the plastic changes induced by HFD; however, the underlying mechanisms remain to be identified.