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Review article

The role of astrocytes in the hypothalamic response and adaptation to metabolic signals

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ABSTRACT

The hypothalamus is crucial in the regulation of homeostatic functions in mammals, with the disruption of hypothalamic circuits contributing to chronic conditions such as obesity, diabetes mellitus, hypertension, and infertility. Metabolic signals and hormonal inputs drive functional and morphological changes in the hypothalamus in attempt to maintain metabolic homeostasis. However, the dramatic increase in the incidence of obesity and its secondary complications, such as type 2 diabetes, have evidenced the need to better understand how this system functions and how it can go awry. Growing evidence points to a critical role of astrocytes in orchestrating the hypothalamic response to metabolic cues by participating in processes of synaptic transmission, synaptic plasticity and nutrient sensing. These glial cells express receptors for important metabolic signals, such as the anorexigenic hormone leptin, and determine the type and quantity of nutrients reaching their neighboring neurons. Understanding the mechanisms by which astrocytes participate in hypothalamic adaptations to changes in dietary and metabolic signals is fundamental for understanding the neuroendocrine control of metabolism and key in the search for adequate treatments of metabolic diseases.

Contents

Abbreviations: ACBP, acyl-CoA binding protein; ACC, acetyl-CoA carboxylase; AgRP, agouti-related protein; ALKO, astrocytic leptin-receptor knockout; AMPK, AMP-activated kinase; ApoE, apolipoprotein E; AR, androgen receptor; BBB, blood brain barrier; CART, cocaine-and-amphetamine-regulated transcript; CB1, cannabinoid receptor 1; DMH, dorsal-medial hypothalamus; DBI, diazepam-binding inhibitor; DAG, diacylglycerol; DIO, diet-induced obesity; DR, diet-resistant; ER, estrogen receptor; GABA, gamma-amino-butyric acid; FA, fatty acid; GFAP, glial fibrillary acidic protein; GHSR1a, growth hormone secretagogue receptor 1a; GLUT, glucose transporter; GnRH, gonadotropin-releasing hormone; HFD, high fat diet; IGF, insulin-like growth factor; IL, interleukin; IPSC, inhibitory post-synaptic currents; JNK, c-Jun N-terminal kinase; KO, knock-out; LCFA, long-chain fatty acids; LH, lateral hypothalamus; MC4R, melanocortin 4 receptor; mIPSCs, mini inhibitory post synaptic currents; MSH, melanocyte stimulating hormone; NCAM, neural-cell adhesion molecule; NfKB, nuclear factor KB; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NPY, neuropeptide Y; OBR, leptin receptor; ODN, octadecaneuropeptide; PeN, periventricular nucleus; POMC, proopiomelanocortin; PPARγ, peroxisome proliferator-activated receptor gamma; PSA, polysialic acid; PVN, paraventricular nucleus; SCN, subrachiasmatic nucleus; sEPSCs, spontaneous excitatory post-synaptic currents; SNAP25, synaptosomal-associated protein 25; SON, supraoptic nucleus; STAT, signal transducer and activator of transcription; T2D, type 2 diabetes; TAG, triacylglycerol; TNF, tumor necrotizing factor; VMH, ventromedial hypothalamic nucleus; WT, wild-type.

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1. Introduction

Being obese is associated with an increased risk in developing type 2 diabetes (T2D), dyslipidemia, asthma and cardiovascular problems (Martin-Rodriguez et al., 2015), as well as of specific types of cancer (Hursting and Dunlap, 2012) and dementia (Emmerzaal et al., 2015). The propensity to become obese is influenced by various factors including an individual's genetic make-up, epigenetic factors, a poor or overabundant diet, insufficient physical activity, early developmental influences, medication and the interactions between these factors (Levian et al., 2014; Ross and Desai, 2013). The secondary consequences of being obese also vary amongst individuals (Candib, 2007), suggesting that these sequelae may depend on the underlying cause of the obese state and the degree and duration of excess weight gain, in addition to the individual's genetic make-up. Understanding the diverse causes of obesity and its associated comorbidities is fundamental in order to achieve satisfactory treatment, with the need for individualized treatments becoming increasingly apparent.

The hypothalamus is the main integrative center in the central nervous system (CNS) for incoming nutritional and hormonal signals (Cone et al., 2001; Kim et al., 2014a; Schneeberger et al., 2014) and the ability of this brain area to adapt to both rapid and long-term changes in information regarding an individual's nutritional/metabolic status is fundamental for correct homeostatic control. These inputs are integrated in specialized neuronal circuits that in turn rapidly signal to higher brain centers to modify appetite and energy expenditure (Webber et al., 2015). Numerous studies have focused on understanding how these neuronal circuits maintain energy homeostasis, as well as on what goes awry when they are unable to do so. However, approximately a decade ago, interest in how glial cells participate in obesity was sparked by studies indicating that inflammatory processes in the hypothalamus in response to high fat diet (HFD)-induced weight gain are correlated with the onset of some obesity-associated complications (De Souza et al., 2005). The possibility that glial cells could be a therapeutic target in these pathological processes has intensified research in this area. This new interest in understanding how glial cells might cooperate in the development of obesity-associated health problems has also highlighted their role in the physiological control of metabolic homeostasis.

It has been almost 4 decades since astrocytes were first reported to actively participate in neuroendocrine processes (Tweedle and Hatton, 1977). These initial studies focused on glial cell involvement in the neuroendocrine control of osmotic homeostasis, lactation, and reproduction (Olmos et al., 1989; Perlmutter et al., 1985; Theodosis et al., 1986a; Tweedle and Hatton, 1977). These studies set precedence for the hypothesis that astrocytes are involved in additional neuroendocrine processes, such as the control of energy homeostasis, as well as providing valuable information regarding the mechanisms that may be used by these glial cells to do so. Hence, we will briefly describe these early observations regarding astrocytes in the control of neuroendocrine systems before reviewing the more recent advances in our understanding of how they participate in the control of energy homeostasis.

In the hypothalamus, astrocytes perform various functions that can directly affect energy homeostasis. These glial cells are involved in nutrient sensing and transport (Belanger et al., 2011; Leloup et al., 2015) and express receptors for and respond to diverse metabolic hormones (Diano et al., 1998; Hsuchou et al., 2009a,b; Jung-Testas and Baulieu, 1998) and neuropeptides (Caruso et al., 2013), with these processes having direct effects on neurons controlling metabolic homeostasis. Astroglia respond to stimuli in various ways, including modifications in their transport of nutrients and hormones, release of gliotransmitters, growth factors and metabolites, up-take of neurotransmitters and cytokine/chemokine production, as well as morphological changes that can affect their physical association with neuronal perikarya and synapses (Khakh and Sofroniew, 2015). All of these astroglial responses could potentially have profound effects on neighboring neurons. Indeed, hypothalamic inflammation and gliosis have been suggested to underlie processes that can lead to insulin and leptin resistance (Benzler et al., 2015; De Souza et al., 2005; Reis et al., 2015), which are harbingers of obesity related complications such as type 2 diabetes. However, whether this is a cause-and-effect relationship has been recently questioned (Dorfman and Thaler,