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The hypothalamic neural–glial network and the metabolic syndrome

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Despite numerous educational interventions and biomedical research efforts, modern society continues to suffer from obesity and its associated metabolic diseases, such as type 2 diabetes mellitus, and these diseases show little sign of abating. One reason for this is an incomplete understanding of the pathology of the metabolic syndrome, which obstructs the development of effective therapeutic strategies. While hypothalamic neuropathy is a potential candidate that may contribute to the pathogenesis of the metabolic syndrome, the specific causes of hypothalamic neuropathy remain largely unknown. During different stages of high-calorie diet-induced metabolic syndrome, the hypothalamus undergoes gliosis and angiogenesis, both of which potentially reflect ongoing inflammatory processes. This overview discusses current data suggesting a role for hypothalamic inflammation-like processes in diet-induced metabolic diseases and provides a perspective on how to unravel molecular mechanisms of "hypothalamic inflammation" in order to develop anti-obesity therapeutic strategies.

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Introduction

Obesity and its associated metabolic diseases, particularly type 2 diabetes mellitus, represent one of the most severe health threats to modern society. In the last two decades since leptin was identified as a key regulator of food intake and energy metabolism via its signaling pathway in the central nervous system (CNS) [1], the CNS has been implicated in having a major role in the control of systemic metabolism and in the pathophysiological processes leading to the metabolic syndrome. Under physiological (metabolically homeostatic) conditions, the CNS receives two types of input regarding its energy state. Cholecystokinin (CCK) and glucagon like peptide (GLP-1) as well as nutrients from food intake act as short-term feedback signals. Leptin and adiponectin, released from white adipose tissue, on the other hand, act as long-term feedback signals. Together with neuronal inputs from peripheral organs and tissues, these signals convey the overall peripheral energy status to the brain. The brain then integrates this feedback at multiple levels and generates appropriate efferent signals to control feeding behavior and related metabolic processes that maintain a balanced metabolic profile and a stable body weight. In a hypercaloric environment, however, the communication between the CNS and peripheral metabolic feedback is impaired. This leads to erroneous nutrient sensing in the CNS, and, as a result, the specific brain circuits that normally promote metabolic homeostasis exacerbate hyperphagia and inappropriately increase endogenous glucose production, thus accelerating the drive toward the pathologies of the metabolic syndrome, including obesity and diabetes [2].

The hypothalamus is well characterized as a key player in controlling energy metabolism [3]. Because specific hypothalamic neuronal circuits regulate the final neuroendocrine message from the CNS to the periphery, most of the studies examining the mechanisms underlying metabolic control of the hypothalamus have focused on impaired neural networks and/or endocrine mechanisms. However, it is unclear how the different metabolic feedback signals are integrated within the hypothalamus with its heterogenous nuclei. Furthermore, hypothalamic metabolic sensing and regulation has been poorly studied in non-neuronal cells, such as glia.

Hypothalamic metabolic sensing

A variety of metabolically relevant hormones and nutrients have receptors and transporters on neurons in different hypothalamic nuclei [4]. These hormones and nutrients include insulin, leptin, ghrelin, glucocorticoids, estrogen, thyroid hormone, GLP-1, CCK, gastric inhibitory polypeptide (GIP), oxyntomodulin (OXM), peptide YY (PYY), glucose, free fatty acids (FFAs) and amino acids (including leucine and other branched chain amino acids). The well-established cellular downstream signals for these blood-borne factors are leptin, insulin and ghrelin. Leptin, produced by adipose tissue, provides long-term adiposity feedback. Both insulin, released by the pancreas, and ghrelin, produced by the stomach, provide short-term feedback to the hypothalamus based on daily energy intake and expenditure. It is not clear whether other gut hormones involved in the regulation of food intake via hypothalamic mechanisms, such as GLP-1, mediate short-term or the long-term feedback.

Of all the hypothalamic nuclei, the arcuate nucleus (ARC) is the most important metabolic feedback center. Localized in the mediobasal hypothalamus, the ARC senses signals from the circulation more directly than other brain regions due its juxtaposition to the median eminence, where the blood brain barrier (BBB) is permeable to blood-borne factors, including nearly all known circulating metabolic active hormones, such as leptin, insulin, glucocorticoids, estrogen, ghrelin and GLP-1 in the ARC [4–7]. In addition to these endogenous factors, pharmacologically modified hormones such as pegylated recombinant leptin can also act in the ARC, specifically by inducing phospho-signal transducer and activator of transcription 3 (pSTAT3) [8], which is activated in response to various cytokines as well as leptin. Taken together, this indicates that the ARC is vulnerable to diverse metabolic inputs.

Two major populations of neurons in the ARC regulate metabolic sensing. One population of neurons produces the anorexigenic peptides alpha-melanocytes-stimulating hormone (αMSH), derived from the pro-opiomelanocortin (POMC) precursor, and cocaine- and amphetamine-regulated transcript (CART). The other population of neurons produces the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) [9]. Genetic deletion of POMC AgRP or NPY in the ARC may result in mild or severe metabolic disorders [10–14]. Moreover, the AgRP projections to other parts