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PERSPECTIVE

Gastrocytes and GLUttony – astrocyte regulation of calorie intake via glutamatergic modulation of gastric activity in rats

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The brain dorsal vagal complex (DVC) is a bi-directional relay between the brain and gastrointestinal tract controlling satiety, the feeling of fullness after consumption of a meal. Understanding the physiological mechanisms underlying satiety may aid development of new therapeutic approaches for disordered eating, particularly in relation to consumption of calorie-dense foods implicated in the development of obesity. Focusing on a class of cells in the central nervous system called astrocytes, a new comprehensive study by Clyburn and colleagues provides mechanistic insights into the early-stage molecular and cellular adaptations within the DVC following consumption of a calorie-rich refined high-fat diet (HFD) (Clyburn et al., 2023).

Astrocytes are highly adaptive glial cells which work in concert with neurons serving structural and functional roles in the brain. Numerous studies now show that modulation of astrocyte function can impact a variety of aspects of physiology, pathology and behaviour. Modulation of food intake and body weight in rodents is sufficient to impact astrocyte function and, in turn, modulation of a variety of facets of astrocyte signalling can change feeding behaviour (García-Cáceres et al., 2019).

DVC astrocytes are involved in the regulation of food intake, glucose homeostasis, cardiovascular function and breathing (MacDonald & Ellacott, 2020). Common mechanistic threads in these studies include astrocytic regulation of glutamatergic neurotransmission and release of the gliotransmitter ATP. The following brain regions constitute the DVC: the area postrema (AP), a circumventricular site where hormones and circulating factors can more readily enter the brain and exert endocrine actions; the nucleus of the solitary tract (NTS), site of termination of vagal inputs from the periphery and integration of inputs from higher brain centres such as the hypothalamus; and the dorsal motor nucleus of the vagus (DMV), the origin of parasympathetic output to the periphery, including motor signals controlling gastrointestinal function. A direct neuronal relay between the NTS and DMV provides a neural regulatory feedback loop. Prior work by Clyburn and colleagues revealed increases in NTS–DMV glutamatergic transmission via NMDA receptors during homeostatic adaptions in caloric intake following introduction of a HFD in rats (Clyburn & Browning, 2021). Consolidating and extending evidence from this and other published studies, Clyburn and colleagues herein explored the role of DVC astrocytes in this process.

When laboratory rodents first have access to a HFD they undergo a period of 'binge-like' eating, consuming up to twice their normal daily caloric intake in the first 24−48 h. Over the next 5−7 days homeostatic mechanisms work to restore caloric intake closer to the normal iso-caloric level. Despite these adaptations, with continued consumption of the HFD caloric intake typically remains elevated leading to weight gain and obesity. This experimental paradigm is used to study physiological adaptations to changes in caloric density. In their 2012 study using this paradigm, Thaler and colleagues first described changes in inflammation and glial reactivity in the hypothalamus that temporally mirror the pattern of food intake during the homeostatic adjustments (Thaler et al., 2012). Using a histology approach in rats, Clyburn and colleagues observed increased expression of an astrocyte marker in the NTS and DMV from days 3−5 after introduction of the HFD. Using both pharmacological and chemogenetic approaches they subsequently show that inhibiting astrocyte activity in the rat DMV during this phase is sufficient to prevent the homeostatic reduction in food intake seen; thus, they implicate DMV astrocytes in the homeostatic feeding adaptation to a HFD.

In addition to changing the amount of food consumed, introduction of a HFD impacts patterns of food intake and gastric function, leading to a delay in gastric emptying and reduced gastric tone and motility. Clyburn and colleagues demonstrate here for the first time that chemogenetic inhibition of astrocyte activity is sufficient to prevent the HFD-induced modifications in gastric activity observed on the 4th day after the diet switch. In a series of comprehensive electrophysiological studies, the authors identify astrocyte-mediated modulation of glutamatergic and purinergic signalling in the NTS→DMV→gastric neuron pathway as the underlying molecular mechanism. Together, these studies elegantly provide a mechanistic basis by which astrocytes act as key components of the physiological adaptation of brainstem neurocircuits controlling gastric function following introduction of a HFD.

This study advances our understanding of how brainstem astrocytes mediate early physiological adaptations to a HFD challenge (Clyburn et al., 2023), with many interesting angles still to pursue. This study focuses on changes in NTS→DMV→gastric neuron circuits, but as significant gastric distention occurs during the hyperphagia immediately following introduction of a HFD, it would be fascinating to examine changes at the vagal-NTS synapse in this paradigm. Furthermore, even though astrocytes express hormone receptors and have direct nutrient-sensing capabilities, how these cells integrate hormonal, neuropeptide and nutrient sensing during normal feeding and dietary challenge remains unclear. This may be particularly pertinent for astrocytes in the NTS at the level of the AP which are more readily exposed to both hormonal and nutritional flux. Multiple brain regions, including the DVC, show changes in astrocyte morphology in obese rodents, with evidence in some areas for region-specific functional impacts of these astrocyte changes (García-Cáceres et al., 2019). Increasingly, astrocytes are also being implicated in weight loss and anorexia associated with disease. More regional mechanistic studies, like the work of Clyburn and colleagues, are needed to advance understanding of astrocytic contribution to feeding regulation in

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different physiological and pathological contexts.

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Additional information

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Keywords

astrocyte, brainstem, feeding, gastric emptying, glutamate, nucleus tractus solitarii, vagus nerve

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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