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Astrocytes in neural circuits controlling appetite and food intake.

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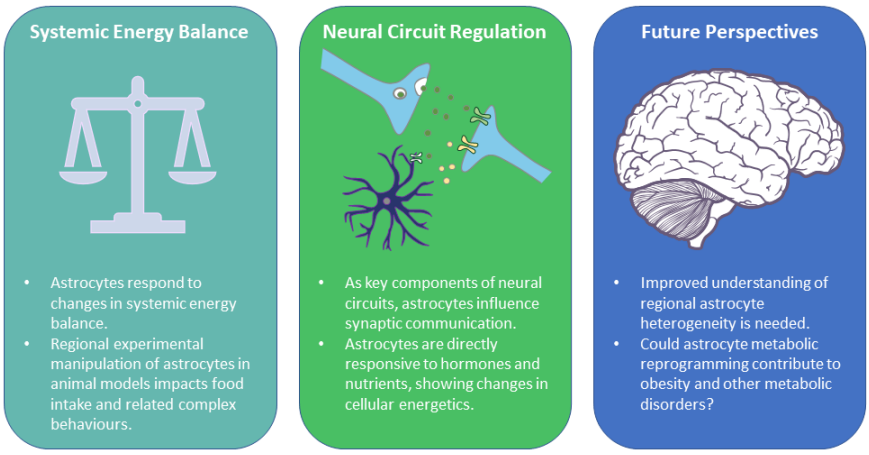
Abstract (100-120 words)

The regulation of feeding behaviour is a complex process controlled by neural circuits in the brain. In addition to neurons, genetic and pharmacological studies in animal models are revealing that glia, including astrocytes, are important components in these neural circuits. This review incorporates the latest evidence (published since 2019) from different brain regions for a contribution of astrocytes in regulating neural circuits controlling appetite and food intake, which encompasses eating when hungry to meet energetic need (homeostatic feeding) and hedonic eating for pleasure in the absence of energetic need (non-homeostatic feeding). The brain regions examined include the hypothalamus, dorsal vagal complex of the hindbrain, and the mesolimbic and cortico-striatal systems. The emerging theme of a potential astrocyte energetic model of neural circuit regulation in the context of feeding behaviour is evaluated.

Graphical Abstract



Keywords:

astrocyte, feeding, appetite, hypothalamus, dorsal vagal complex

Highlights

- Astrocytes respond to changes in systemic energy balance.
- Experimental manipulation of astrocytes in animals impacts food intake.
- Astrocytes are directly responsive to hormones, showing changes in energetics.
- Improved understanding of regional astrocyte heterogeneity is needed.
- Could astrocyte metabolic reprogramming contribute to obesity?

Introduction

Over the last 25 years technological advances have revolutionised our understanding of the neural networks regulating appetite. Genetic and physiological studies in animal models have identified numerous hormones, neuropeptides, and receptors that contribute to the regulation of food intake by the central nervous system (CNS), including those that drive hunger and satiety. Concomitant studies have revealed that many of these are also essential appetite regulators in humans. The importance of the CNS in orchestrating feeding behaviour is underscored by studies integrating mouse single-cell RNA sequencing data with human genome wide association studies (GWAS); these have revealed that genetic variants associated with obesity are enriched in genes encoding proteins expressed in the brain [1–3]. Advances in single-cell genetic mapping technologies are now enabling characterisation, in mouse tissue, of the heterogeneity within, and between, neural cell populations in different brain regions in distinct states of energy availability e.g., fed *vs*. fasted [4] and lean *vs.* obese [5]. While these studies revealed changes in neurons, they also observed transcriptional regulation within glial cells in response to changes in energy availability, underscoring the necessity to understand the contribution of non-neuronal populations in the regulation of eating behaviour.

Astrocytes are key components of neural networks. Unlike neurons, these glial cells do not send extended long-range projections within or between brain regions. Despite this, astrocytes have key modulatory roles with respect to neuronal activity and communication (for review see [6]). Astrocytes are directly responsive to neurotransmitters, are essential for their recycling, and maintain ionic balance within the brain. Through altering their morphology, astrocytes also physically modulate synaptic contacts (for review see [6]). The roles of astrocytes in maintaining the tissue environment and energy availability within the brain mean that they have a broad and dynamic influence on central nervous system function. Increasingly, studies are observing that specifically modulating astrocyte activity is sufficient to change different aspects of physiology and behaviour (for recent reviews see [7,8]), cementing their importance in neural network function.

This review will incorporate the latest evidence from different brain regions for a contribution of astrocytes in regulating neural networks controlling appetite, which encompasses eating when hungry to meet energetic need and hedonic eating for pleasure. Critically, the brain regions implicated in these “homeostatic” and “non-homeostatic” aspects of feeding behaviour, and the underlying neurochemical mechanisms, can overlap (for review see [9]). To provide the most up-to-date picture, studies published since 2019 will be the focus, but seminal older studies will also be highlighted where appropriate.

Hypothalamic and dorsal vagal complex astrocytes

Nuclei within the hypothalamus and dorsal vagal complex (DVC) are the principal brain sites implicated in the homeostatic regulation of food intake, classified here as the consumption of food to meet energetic need. The location of the hypothalamus centrally on the ventral surface of the brain means that it is ideally positioned to integrate peripheral and central information. Similarly, the DVC of the hindbrain is a key integratory hub. Within the DVC, the nucleus of the solitary tract (NTS) is the termination site of inputs from the vagus nerves so is critical for receiving interoceptive cues. Reciprocally, the dorsal motor nucleus of the vagus (DMX), also within the DVC, sends neural projections out of the brain, via the vagus nerves, to modulate the activity of peripheral organs. Both the hypothalamus and the DVC contain circumventricular sites, namely the organum vasculosum of the lamina terminalis (OVLT; rostral hypothalamus), median eminence (medial hypothalamus), and area postrema (DVC), areas of the brain in which the blood-brain barrier (BBB) vascular endothelial

cells lack barrier properties, providing direct exposure of these brain areas to circulating factors including hormones, cytokines, and nutrients (for review see [10]). In the hypothalamus, glial cells called tanycytes which line the third ventricle take on many of these regulatory barrier functions, including hormone transport into the brain (for review see [11]). Importantly, a proportion of tanycytes express glial-fibrillary acidic protein (GFAP), an intermediate filament protein commonly used experimentally as a marker of astrocytes. As such, a contribution of tanycytes cannot always be excluded in studies which assess hypothalamic GFAP expression (either on the protein or mRNA level) or use the GFAP promotor to genetically manipulate astrocyte function either locally in the hypothalamus or in all GFAP-expressing cells. This is an important caveat to be aware of when considering some of the studies discussed below. Furthermore, while extensively used as an astrocyte marker, it should be noted that not all astrocytes express detectable levels of GFAP and even in astrocytes that do have detectable GFAP, because it is a cytoskeletal protein it does not reliably reflect the complete morphology or the full extent of the individual domain of an astrocyte within the brain. Many of the studies cited here, including work from my own group, use GFAP as an astrocyte marker, but we still know little about the underlying mechanisms by which it is regulated in the context of energy homeostasis studies where it is typically used as a generic marker of "astrocyte activation". There are risks with over-reliance and over-interpretation of studies using GFAP as an experimental astrocyte marker, and the strengths and limitations have been recently reviewed elsewhere [12,13].

As important components of the neurovascular unit, astrocytes influence BBB permeability (for review see [6]). By virtue of this, and the fact that astrocytes express receptors for key hormones and cytokines as well as having direct nutrient sensing capacity (reviewed in [14]), astrocytes are among the first neural cells to respond to changes in circulating factors in the course of normal physiology and during disease. Indeed, building on earlier studies demonstrating changes in hypothalamic GFAP-expression 24-hours after feeding mice a calorific high-fat diet [15,16], recent work provides evidence of rapid post-prandial changes in this parameter and also astrocyte coverage of POMC-neuronal soma in mice as early as 1-hour after eating [17,18]. Post-prandial retraction of astrocyte processes observed within the hypothalamic arcuate nucleus has been linked to increased firing activity of proopiomelanocortin (POMC) neurons critical for reducing food intake [17]. This post-prandial reduction in astrocytic coverage of POMC neurons was not observed 1-hour after eating a high-fat diet. However, in agreement with Cansell et al, who in a related study looked at GFAP gene expression, when the effects of both diets are compared in the post-prandial state there was a relative increase in astrocyte coverage of POMC-neuronal soma in the high-fat diet fed animals compared to the standard chow fed animals [17,18]. It is tempting to speculate whether differences in post-prandial astrocytic plasticity between the diets could be a mechanism contributing to acute high-fat diet-induced hyperphagia. There is experimental evidence that hypothalamic glial responses following dietary changes may vary with the specific dietary components and nutrient combinations [19].

Within the arcuate nucleus, astrocytes are also implicated in modulating the activity of the other arm of the hypothalamic melanocortin system, the agouti-related protein (AgRP) neurons which promote food-seeking. Overnight fasting of mice causes increased medial basal hypothalamus (MBH) GFAP levels [20,21], increased GFAP-immunoreactive process coverage of AgRP neurons, and a reduction in inhibitory neuronal inputs to these cells [21]; these effects can be phenocopied by treatment of the animals with the appetite-stimulating hormone ghrelin. The effects of ghrelin appear to be downstream of the action of ghrelin on AgRP neurons; although hypothalamic astrocytes have been reported to express the ghrelin receptor [GHS-R1a][22], synaptic blockers prevented ghrelin-induced astrocyte depolarization and specific chemogenetic inhibition of AgRP neurons prevented ghrelin-induced increases in MBH GFAP [21].

Together these studies build on earlier work [23–25] and reinforce the dynamic contribution of astrocytes to modulating plasticity of hypothalamic melanocortin circuits controlling food intake. Nuzzaci and colleagues propose that astrocytic regulation of hypothalamic melanocortinergic synaptic connectivity across the day according to prandial state, and one could also possibly include a circadian influence [26], represents a more energetically efficient and rapidly responsive system than neuronal synaptic remodelling [17]. However, it is unlikely structural remodelling is the only astrocytic contribution, and rapid adaptive changes in astrocyte metabolism (see below) leading to alterations in neuronal energy supply and local ion and neurotransmitter homeostasis are probably important. Astrocyte derived-transmitters including ATP/adenosine [25], Acyl-CoA binding protein (ACBP [27]), and prostaglandins [21] are also implicated in this process. Limiting longer-range astrocyte-astrocyte communication by pharmacological blockade of connexin 43 hemichannels is also sufficient to acutely reduce food intake in mice [28], but the neural circuits impacted have yet to be identified.

Although to date most of the work looking at the influence of astrocytes on neural circuits controlling appetite has focused on the hypothalamus, evidence is emerging for a contribution to key circuits within the DVC. Increased number and morphological complexity of DVC GFAP-immunoreactive astrocytes is associated with excess calorie intake following 12-hours of access to a high-fat diet in mice [29], and is also observed in obese Zucker diabetic fatty rats [30] (increased GFAP-immunoreactivity only). However, Stein and colleagues found that maintenance of rats on a high-fat diet for 8 weeks reduced DVC GFAP-immunoreactivity and had no observable impact on this parameter in the arcuate nucleus of the hypothalamus of the same animals [30]. These findings further support the work of Thaler and colleagues which indicate that the impact of high-fat feeding in rodents on hypothalamic astrocytes changes over time [15], but also suggests that these effects may differ across brain regions. As such, further work examining the impact of the duration of an obesogenic diet on astrocyte function across brain regions is warranted. Because of the key role of the DVC in regulating satiety, it will be important to examine whether the post-prandial differences seen in hypothalamic astrocytes [17,18] are also observed in the DVC, and whether these are associated with altered astrocytic coverage of key-neuronal populations in this region, particularly those which receive direct vagal innervation.

Recently, circadian regulation of the glio-vascular interface in the DVC (area postrema-NTS border) has been identified, with increased BBB permeability in this region at the onset of the dark-phase (ZT13). This correlates with increased responsiveness of local NTS neurons to glucose and hormones (cholecystokinin, ghrelin, and orexin A) in an *ex vivo* brain slice multi-electrode array study [31], presumably in preparation for the active nocturnal feeding period. How circadian regulation of the DVC glio-vascular unit influences feeding behaviour and whether disruption of the normal pattern of feeding e.g., by fasting or time-restricted feeding, influences the activity of this novel circadian oscillator remains to be determined. Work from our group has shown that chemogenetic activation of DVC GFAP-expressing cells is sufficient to reduce normal nocturnal food intake as well as fast-induced refeeding [29], although it is likely that the magnitude of the attenuation of food intake seen is partially related to potential supraphysiological effects associated with chemogenetic activation of these cells. However, there is good evidence from a range of electrophysiological and *in vivo* studies examining different aspects of physiology, including breathing and cardiovascular parameters, that DVC astrocytes are key components of neural circuits regulating physiology (recently reviewed elsewhere [32]).

Astrocytes of the mesolimbic and cortico-striatal systems

The mesolimbic dopamine system regulates motivation and rewarding aspects of feeding behaviour and is linked to hedonic food intake: eating for pleasure, even in the absence of energetic need (for a recent review see [33]). Of relevance here, recent data has added a new dimension by demonstrating further inputs to the midbrain dopamine neurons originating from the gut vagal afferents via the hindbrain (DVC and parabrachial nucleus)[34]. This provides a novel mechanism linking feeding and reward. Subsequently, a subpopulation of parabrachial nucleus projecting dopamine neurons of the caudal ventral tegmental area (VTA), anatomically distinct from those projecting to the nucleus accumbens (NAcc) of the striatum, were implicated in meal-termination[35].

To date, much of the data on the role of astrocytes in regulating neural circuits within the mesolimbic system comes from studies examining other goal-directed behaviours and substance use disorders (for review see [36]), but are relevant here as finding and consuming food are goal-directed behaviours (for review see [37]). Differential astrocyte dopamine receptor (D_1R - D_5R) expression is reported in various brain regions which may underlie heterogeneity in astrocyte dopamine responsiveness between brain nuclei (reviewed in [38]). Through the activity of the glutamate transporter GLT-1, astrocytes within the VTA regulate glutamatergic excitation of GABA neurons, thus controlling GABAergic inhibition of dopamine neurons [39]. Behaviourally in mice, optogenetic activation of VTA astrocytes induces avoidance of the associated location in real-time and following conditioning, suggestive of active and learned negative salience, an effect that could be eliminated by GLT-1 deletion from VTA astrocytes [39]. In addition to GLT-1, astrocytes also express metabotropic glutamate receptors, $GABA_B$ receptors, and GABA transporters (for review see [6]), meaning that there are likely other regulatory nodes within VTA astrocytes that could impact that activity of the local dopamine neurons. For example, within the prefrontal cortex, astrocyte $GABA_B$ receptors are implicated in regulating inhibition within cortical circuits which impact goal-directed behaviours [40].

VTA dopamine neurons project to the NAcc, a ventral striatal brain region implicated in the liking and wanting of food, with consumption of palatable food increasing NAcc dopamine levels (for review see [37]). NAcc astrocytes are directly responsive to dopamine leading to the release of the gliotransmitters ATP/adenosine and the depressing of local glutamatergic neurotransmission [41]. In a related study, chemogenetic activation of GFAP-expressing cells in the dorsal striatum resulted in differential regulation of the excitatory inputs to the direct (reduced frequency) and indirect (increased frequency) pathway medium spiny neurons [42]. Behaviourally, chemogenetic activation of these dorsal striatum GFAP-expressing cells reduced habitual reward seeking and promoted goal-directed reward behaviour, again mediated through an adenosine-signalling mechanism [42]. With respect to feeding, the dorsal striatum is postulated to be involved in habitual feeding and food anticipatory activity [43], with changes in functional activity of both the dorsal and ventral striatum reported in people living with obesity [44]. Supporting changes in astrocyte function in these brain regions in obesity, increases in GFAP-immunoreactivity have been observed in the substantia nigra and striatum of mice fed a high-fat diet for 20-weeks, compared to standard chow fed age-matched controls [45]. Given the links between changes in reward processing and behaviour associated with obesity and substance use disorders, there is potential relevance to the understanding of astrocyte involvement in feeding to also consider the emerging literature from the substance use field [36].

The orbitofrontal cortex (OFC) is reciprocally connected to the VTA, striatum, and amygdala, and is implicated in decision-making in relation to feeding behaviour and the rewarding value of food by integrating information from a variety of senses (for review see [46]). In obese rats, astrogliosis is observed in the OFC where it is associated with altered glutamate homeostasis, leading to increased extra-synaptic glutamate, and reduced GABAergic transmission [47]. These diet-induced changes were

not observed in the primary motor cortex or the prelimbic cortex, suggesting relative specificity to the OFC and potentially providing evidence of region-specific impacts of obesity on astrocyte function. This is proposed to impact the balance between excitatory and inhibitory transmission in the OFC, which may contribute to alterations in feeding behaviour in obesity [47].

Mechanisms of astrocytic regulation of feeding circuits

While hypothalamic astrocytes are undoubtedly fundamentally influenced by the activity of neurons and neuronal projections within their immediate territory [17,21], astrocytes are also directly responsive to hormones (for review see [14]). In the context of the neuroendocrine regulation of energy homeostasis, what could be the potential purpose for neurons and astrocytes within the same neural circuit being (simultaneously) directly sensitive to the same hormones via receptors expressed on their surface? A consistent theme emerging from the published data is the impact of alterations in hormone signalling on astrocyte energetics (**Table 1**) and mitochondrial dynamics. Overnight fasting in mice increases mitochondrial density in hypothalamic astrocytes, suggesting a dynamic response of astrocytic mitochondria to nutritional stress and/or the associated hormonal changes, such as an increase in circulating ghrelin; indeed, exogenous ghrelin administration to mice recapitulates the fasting-associated increased in astrocyte mitochondrial density [21]. Furthermore, inhibition of mitochondrial fission in DVC astrocytes following overexpression of a dominant-negative form of dynamin-related protein 1 (Drp-1) is sufficient to attenuate food intake, body weight gain, and the development of insulin resistance in high-fat diet fed rats [48]. Together, these studies reinforce the potential importance of astrocyte mitochondrial dynamics in the regulation of neuronal networks controlling feeding; however, further work in this area is needed.

Table 1: Examples of how hormone/neuropeptides involved in energy homeostasis impact astrocyte energetics

Signalling pathway	*Observed impact on astrocyte energetics*	*References*
Adiponectin	Adiponectin treatment enhances glucose uptake and glycolysis in primary cultured mouse astrocytes. Also increases lactate and ketone body production.	[49]
Ghrelin	Systemic ghrelin treatment increases mitochondrial density in mouse hypothalamic astrocytes.	[21]
	30mins of acyl-ghrelin treatment decreases glucose uptake in rat primary astrocytes (effect not seen after 24h treatment)	[22]
Glucagon-like peptide-1 (GLP-1)	GLP-1R-deficient mouse primary astrocytes in culture show attenuated mitochondrial respiration, increased glucose uptake and glycolytic flux and, altered astrocyte mitochondrial dynamics.	[50]
Insulin	Insulin-receptor deficient mouse primary astrocytes in culture show decreased glucose-stimulated glucose uptake, reduced glycolytic rate, and higher basal mitochondrial respiration.	[51]

Leptin	24h leptin treatment increases glucose uptake in rat hypothalamic astrocytes in culture	[20]

Based on these combined observations, one answer to the above question is that the direct action of hormones involved in energy homeostasis promotes appropriate metabolic adaptations in astrocytes, for example changes in expression or activity of glucose transporters or components of the astrocyte-neuron lactate shuttle, readying them to rapidly respond to corresponding changes in the activity of local neuronal networks which are responding to the same hormones. Any experimental disruption of this energetic adaptation by astrocytes impacts neural circuit activity, by reducing the astrocyte capacity to rapidly support changes in neuronal activity. This is reinforced by evidence that manipulating astrocyte energy sensing through adult-inducible global overexpression or deletion of Sirtuin 1 (Sirt1) in mouse GFAP-expressing cells changes systemic energy homeostasis: increases in food intake and body weight following astrocyte overexpression of Sirt1, and reductions in the same parameters following Sirt1 deletion [52]. Recently, Clyburn and Browning elegantly reviewed the evidence that astrocytes are key to improving synaptic efficacy in metabolic circuitry and how this is influenced by energy excess associated with high-fat diet feeding [53]. Currently, it remains unknown whether astrocyte hormone and neuropeptide receptor expression is limited to brain regions where local neurons also express receptors for those hormones, or if hormone receptor expression on astrocytes can potentially alter neural circuit activity independently of the action of that hormone on local neurons. Any potential (regional) expression of homeostatic regulatory neuropeptides by astrocytes is also relatively underexplored.

For focus, the studies highlighted above are largely limited to the contribution of astrocytes to the neural circuits controlling feeding during normal physiology and have not typically extended to maladaptive changes during anorexia, diabetes, or obesity. Conceptually it is noteworthy that changes in astrocyte activity, including astrogliosis during chronic imbalance, are apparent in response to changes in energy availability, specifically in states of acute and chronic energy excess (e.g., a single big fatty-sugary meal [16–18,29] or chronic consumption of a high-fat high-sucrose diet [15,23,54]) or reduced energy availability (e.g., fasting [20,21] and acute weight-loss [55]). This is likely partly because differential activity of components of the same neural circuits, e.g., neurons of the central melanocortin system, are integral in restoring homeostasis in the face of energy perturbations in both directions and as well as determining the adaptive energetic thresholds for the animal (for recent review of the central melanocortin system see [56]). In the context of high-fat high-sucrose diet feeding studies, acutely astrocyte changes are likely part of a protective homeostatic response to deviations in energy availability [16–18,29] but when they persist, resulting in astrogliosis, can contribute to obesity pathology [15,23,54].

Supporting a contribution of the astrocyte energetic model of neural circuit regulation postulated above, chronic states of whole organism energy imbalance e.g., obesity (chronic energy excess) or anorexia (chronic energy insufficiency) attenuate metabolic flexibility in astrocytes critical for rapid homeostatic adaptations. For example, maternal high-fructose diet consumption, which causes metabolic perturbations in the offspring, negatively impacts mitochondria number and attenuates cellular metabolism (both glycolysis and oxidative phosphorylation) in hippocampal astrocytes [57]. Disruption of astrocyte lipid-uptake by deletion of lipoprotein lipase in mouse GFAP-expressing cells from 6-weeks onwards has little impact on body weight in animals when maintained on standard laboratory diet, but results in exaggerated weight gain when the animals were on a high-fat diet [58]. This may be due to reduced metabolic flexibility in these cells: an inability to utilize and store lipids,

and thus an increased reliance on glycolysis for energy [58]. In a mouse streptozotocin (STZ)-induced model of type 1 diabetes, genetic-deletion of the enzyme pyruvate dehydrogenase kinase-2 in hypothalamic astrocytes was sufficient to attenuate the diabetes-associated increase in hypothalamic inflammation and food intake, likely by altering astrocyte metabolic responses [59]. Recently the chromatin remodelling factor HMG20A, suggested to be an important factor in mediating astrocyte metabolic adaptation to stress, was shown to be upregulated in the hypothalamus following chronic high-fat feeding in mice [60]. It is tempting to speculate whether reduced metabolic flexibility in astrocytes contributes to changes in neural circuit dynamics in the face of chronic energy imbalance or potentially contributes to aging-related changes in energy homeostasis. Changes in astrocyte metabolic flexibility are already implicated in the pathophysiology of aging and neurodegeneration (for review see [61]).

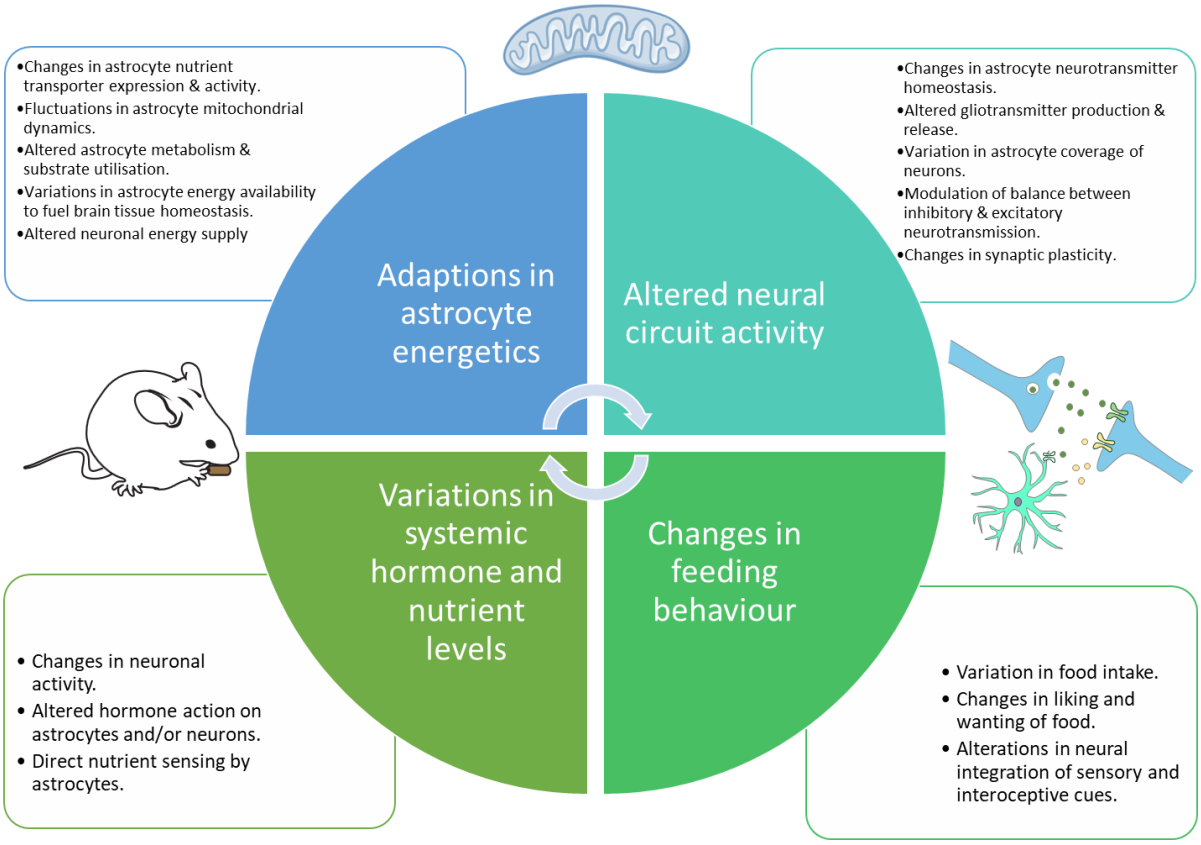
Conclusions

The recent studies described above demonstrate that modulating astrocyte activity through opto- or chemo-genetic manipulation [29,39,41,42], or specifically modulating astrocyte expression of different hormone/neuropeptide receptors [50,51] or factors involved in in cellular energetics [48,52], is sufficient to impact feeding and other related complex behaviours in animals (summarised in **Figure 1**). The nature and extent of astrocyte responses to changes in systemic energy homeostasis are likely dynamic and determined by the type and duration of the homeostatic deviation experienced by the animal. During normal physiology, adaptive dynamic adjustments to astrocyte cellular metabolism necessary to enable the cells to respond to changes in neuronal activity are probable. Given the energetic costs to the cell, major structural remodelling of astrocytes and extensive changes in mitochondrial dynamics may predominantly be reserved for more significant and/or chronic deviations in systemic homeostasis. Arguably, in a mouse overnight fasting or exposure to a calorically dense diet (either acutely or chronically) could represent examples of such events.

Astrocyte responses under different states of energy availability, and likely during normal physiological feeding patterns, are undoubtedly regionally distinct. As such, further work is required to understand these, and to reveal how these may be differentially altered in maladaptive states such as obesity or anorexia. This will be facilitated by improvements and increased diversity in the experimental tools available to study astrocytes, particularly in the intact animal where their contextual interactions with other cells are maintained. Sophisticated studies of this nature are already being carried out in the study of neurodegeneration, where regional astrocyte metabolic reprogramming has been identified and is associated with neuronal vulnerability [62,63].

Better understanding of regional astrocyte responses, including hormone and neurotransmitter responsivity, will also improve understanding of how astrocytes integrate different facets of feeding behaviour, as well as potentially elucidating the relationship between energy homeostasis and other neuroendocrine axes e.g., reproduction and stress - where the roles of astrocytes in the regulation of the latter, via the regulation of synaptic plasticity by astrocyte energetics, is already implicated [64]. Astrocytes are responsive to sex-hormones, and sex-differences in astrocyte responses have been reported but need to be further explored, including in the context of energy homeostasis[65,66]. While much remains to be understood, astrocytes are clearly key players in the neural circuitry regulating appetite and other complex behaviours.

Figure 1: A summary of how changes in astrocyte energetics may impact neural circuits regulating food intake and appetite



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Using a combination of histological, electrophysiological, and in vivo behavioural approaches in mice, the authors demonstrate rapid post-prandial morphological changes in hypothalamic astrocytes, and implicate these in synaptic plasticity of POMC neurons which inhibit feeding. Provide mechanistic evidence of an important role for hypothalamic astrocytes in short-term regulation of food intake.

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Using a combination of histological, electrophysiological and molecular biology approaches in mice, the authors demonstrate that fasting, the appetite-stimulating hormone ghrelin, and chemogentic activation of AgRP neurons each increase expression of the astrocyte marker GFAP in the hypothalamus. This is accompanied by increased astrocyte mitochondrial density and astrocyte coverage of feeding-promoting AgRP neurons. Decreased inhibitory tone to these to AgRP neurons is mediated in part by hypothalamic astrocytes responding to GABA. This provides mechanistic evidence of astrocytic involvement in regulating AgRP neuron activity in response to changes in systemic energy.

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