


Feature Review

Tanycytes: bloodhounds of the metabolic brain

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Constant monitoring and fine-tuning of internal body status to maintain energy homeostasis despite changing physiological needs and environmental conditions are essential brain functions. Hypothalamic tanycytes – specialized ependymogial cells at the interface between the blood and the brain – play crucial roles in this regulation through mechanisms as diverse as sensing and responding to circulating nutrients and metabolic hormones, gating their access or shuttling them into the brain, modulating hypothalamic neuronal function and neuroendocrine communication with peripheral organs, and generating new regulatory neurons. We summarize these mechanisms and emphasize striking recent discoveries that extend beyond energy balance to reproduction and even cognitive aging. These highlight the need for a deeper understanding of the physiological and pathological roles of these unique cells.

Neuroanatomy and classification of tanycytes

To maintain whole-body and energy homeostasis, the mammalian brain, in particular the hypothalamus, has several regulatory circuits that sense and integrate peripheral signals to generate a physiologically relevant response, and which incorporate positive and/or negative feedback information to fine-tune this response. However, most hypothalamic neurons, like the rest of the brain, are not exposed to real-time fluctuations in blood composition due to the presence of the blood–brain barrier (BBB). Glial cells that contact either blood vessels or the cerebrospinal fluid (CSF), which mirrors circulating levels of several metabolic hormones and signals generated by peripheral organs and pathways, thus play an especially important role in detecting this information and transmitting it to the appropriate neurons. Growing evidence has revealed that tanycytes of the hypothalamus occupy a unique position in this regard.

Tanycytes (etymologically: ‘stretched cells’) are elongated and polarized ependymogial cells with a striking morphology consisting of cell bodies lining the walls of the third (3V) and fourth ventricles and long processes that enter the parenchyma of various nuclei to contact neurons, astrocytes, and blood vessels, either *en passant* or by means of specialized ‘endfeet’ (Figure 1) [1,2]. In mammals, tanycytes are particularly abundant in the circumventricular organs, such as the median eminence (ME) of the hypothalamus, which are typically devoid of a canonical BBB, and instead possess fenestrated capillaries that allow extravasation of blood-borne hormonal and metabolic signals into adjacent regions [3,4]. In addition, tanycytes also border other regulatory nuclei that are mostly irrigated by vessels of the canonical BBB, such as the arcuate, dorsomedial, and ventromedial nuclei of the hypothalamus (ARH, DMH, and VMH, respectively) [1,2]. Importantly, because of their radial glial lineage, tanycytes, along with the subventricular zone and the hippocampal dentate gyrus, constitute one of the few neurogenic niches that persist in the adult brain, and comprise both pluripotent neural stem cells (NSCs) and neuronal progenitors [5].

The consensus nomenclature for tanycytes until recently has been based on their dorsoventral position along the ventricular wall. Thus, at the rostrocaudal level of the ME/ARH, α_1 tanycytes

Highlights

Tanycytes, particularly those of the mediobasal hypothalamus, occupy a privileged position at the interface between the peripheral circulation and the brain circuits that regulate energy homeostasis.

A growing number of receptors and transporters for nutrients, metabolic signals, and hormones of several hypothalamic–pituitary axes have been detected in tanycytes.

Tanycytes use these receptors and transporters in a variety of mechanisms that extend beyond nutrient sensing and shuttling of hormones to the regulation of neuronal responses and adult neurogenesis.

A key emerging function of tanycytes is regulating the crosstalk between various hormonal axes (e.g., reproduction, growth, stress, metabolism) and physiological functions controlled by the hypothalamus.

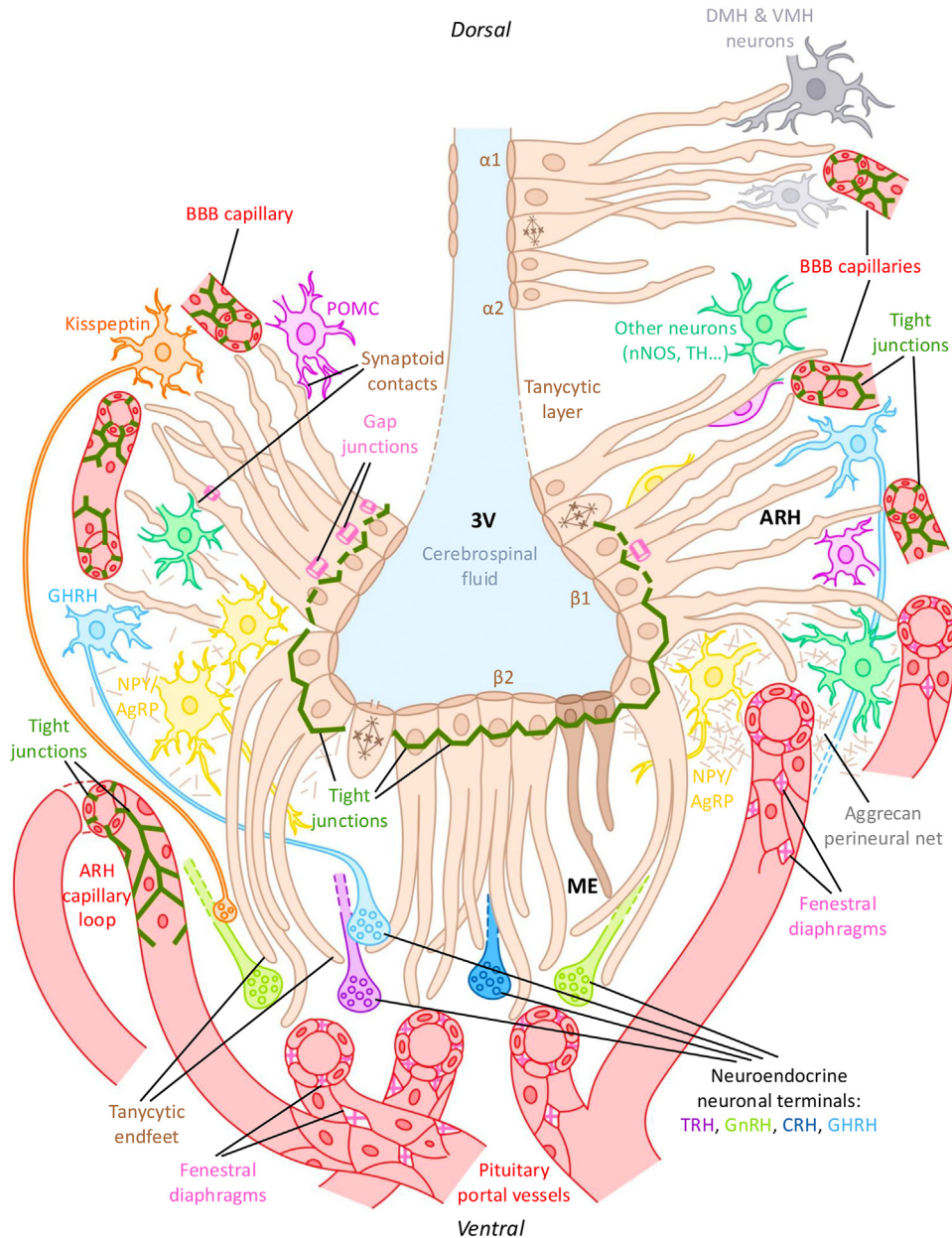
The link between tanycytic dysfunction and energy balance not only in metabolic disorders but also in disorders of reproduction and cognitive aging may provide new insights of diagnostic and therapeutic value.

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Figure 1. Schematic illustration of tancytic neuroanatomy and cellular interactions in the mediobasal hypothalamus (MBH). Interactions between different classes of tancytes surrounding the third ventricle (3V) at the level of the median eminence (ME) and arcuate nucleus of the hypothalamus (ARH) with blood–brain barrier (BBB) and fenestrated capillaries of the pituitary portal circulation, neurons of the ARH, and neuroendocrine neuronal terminals in the ME. Note the presence of tight junctions (dark-green bands) surrounding the endothelial cells of the BBB and ME tancytes, as well as ARH tancytes in contact with fenestrated capillaries, including capillary loops penetrating the ARH which become fenestrated depending on peripheral energy status (fenestral diaphragms indicated by pink windows). The boundary between the ME and ARH is also composed of a plastic perineural net of aggrecan deposits. Figure not to scale. Abbreviations: $\alpha_1/\alpha_2/\beta_1/\beta_2$ indicate α_1 , α_2 , β_1 , and β_2 tancytes; DMH, dorsomedial nucleus of the hypothalamus; POMC, proopiomelanocortin; VMH, ventromedial dorsomedial nucleus of the hypothalamus.

comprise the population that extends processes into the DMH and VMH, and α_2 into the dorsal ARH, while β_1 and β_2 tanycytes, which line the ventral regions and the floor of the 3V, extend their processes into the ventral ARH and the ME, respectively (Figure 1). However, growing evidence has revealed that tanycytes display molecular and functional diversity and specialization, as well as plasticity under different physiological and pathological conditions [6]. The tanycytes of the ME and the ARH, with which the ME forms an anatomical complex in the mediobasal hypothalamus (MBH), are the best studied, principally in rodents and seasonal species [1,7], and correspond to those found in the anterior and middle regions of the infundibulum (equivalent to the ARH) and ME in humans [2,8]. Indeed, these tanycytes, whose endfeet contact the fenestrated capillary bed of the pituitary portal circulation, are ideally positioned to detect both peripheral signals passing through these blood vessels and hypothalamic hormones and neuropeptides secreted into them for delivery to the anterior pituitary (Figure 1). Accordingly, the various subpopulations of these tanycytes express a large number of receptors or transporters not only for nutrients (e.g., glucose) and metabolic hormones (e.g., leptin or insulin) but also for hormones of the hypothalamic–pituitary axes that influence metabolism based on biological rhythms or reproductive status, as well as other molecules and signals (Table 1), and these provide a solid basis for a more relevant and nuanced classification in the future.

Thanks to their anatomical localization and these structural and molecular characteristics, tanycytes act as ‘bloodhounds of the metabolic brain’ through an astounding range of mechanisms that are not mutually exclusive: (i) sniffing out and transmitting information about circulating nutrients and metabolic signals to hypothalamic regulatory circuits, (ii) transporting them into the hypothalamus so that they can act on these circuits, (iii) modulating the neuroendocrine control of metabolic processes by the brain, including through feedback, and (iv) generating new hypothalamic neurons.

Nutrient and metabolite sensing by tanycytes

Both *in vivo* and *in vitro*, tanycytes react to different molecules, including glucose [9,10], fatty acids [11,12], amino acids [13], and various hormones [14–18] (Table 1), by generating calcium (Ca^{2+}) waves that are often mediated by ATP (Figure 2). In addition, tanycytes also respond to physiological or pathological stimuli by secreting gliotransmitters and other signaling molecules, for example VEGF-A or prostaglandin E2 (PGE2), which influence neuronal function [19–22]. Tanycytes are also intimately associated with various populations of neurons. The anatomical proximity and interactions of ME tanycytic endfeet with neuronal terminals secreting gonadotropin-releasing hormone (GnRH) or thyrotropin-releasing hormone (TRH) have been extensively described [1]. Tanycytes bordering the ARH, on the other hand, have numerous protrusions along their processes that contact both glial and various ARH neuronal populations (Figure 1) including neurons that express AgRP/neuropeptide Y (NPY), proopiomelanocortin (POMC), and to a lesser extent kisspeptin/neurokinin B/dynorphin (KNDy) and tyrosine hydroxylase (TH). In some cases, tanycytes appear to encapsulate synapses with their endfeet [23] and in others receive synaptoid inputs [23,24]. These protrusions are equipped with mitochondria and ribosomes, which indicates that they are active communication domains [23] that possibly underlie the ability of tanycytic activation to trigger depolarization in some ARH neurons [10,25]. Conversely, these protrusions may enable neurons to modulate the activity of tanycytes, including signal sensing/transmission, through synaptoid communication [21]. For example, ablation of the suprachiasmatic nucleus (SCN), the circadian clock of the brain which sends vasopressinergic fibers to innervate tanycytes, leads to changes in tanycytic morphology, gene expression, and ME/ARH barrier permeability (further detailed below) depending on the time of day, suggesting that these neurons modulate tanycytic sensitivity to peripheral molecules in a time-specific manner [26]. Similar interactions may be present between tanycytes and neurons of other hypothalamic regions such as the DMH and VMH.

Table 1. Tanycytic expression of receptors/transporters for nutrients, metabolic signals, and hormones involved in regulating energy homeostasis

Gene ^a	Protein ^a	Tanycyte type				Notes, methods, and findings	Refs
		β2	β1	α2	α1		
Glucose, lipid, and amino acid receptors and transporters							
<i>Slc2a1</i>	GLUT1	+	+++	+++	+++	Immunohistochemistry and <i>in situ</i> hybridization; the mRNA seems to be expressed in all tanycytes but β2 tanycytes appear to be negative for the protein	[209]
<i>Slc2a2</i>	GLUT2	+++	+++	+	+	Immunohistochemistry and <i>in situ</i> hybridization; only mRNA was shown for β2 tanycytes	[30,210]
<i>Slc2a6</i>	GLUT6	++	++			Immunohistochemistry; expressed by β tanycytes during fasting	[29]
<i>Slc16a1</i>	MCT1	+	+++	+		Principal glucose transporter, as shown by immunohistochemistry; transcripts were shown by RNA-seq and qPCR in tanycytes isolated by fluorescence-activated cell sorting (FACS)	[17,25,211]
<i>Slc16a3</i>	MCT4		+++			Immunohistochemistry; strong labeling in dorsal β1 tanycytic processes contacting ARH neurons that are known to transfer lactate to POMC neurons (e.g., [25]); transcripts were shown by qPCR in tanycytes isolated by FACS	[25,211]
<i>Slc1a2</i>	GLT1		+	+++	+++	Glutamate transporter 1; shown by immunohistochemistry and <i>in situ</i> hybridization	[212]
<i>Glast</i>	GLAST	+++	+++	++		Glutamate/aspartate transporter, the protein was originally shown in β tanycytes by Berger and Hediger [212]; by contrast, mRNA distribution using reporter mice describes expression in a tanycytic stem cell-rich α population	[171,212]
<i>Grm4</i>	mGluR4					Glutamate transporter; localization not shown (receptor antagonist and activity studies)	[13]
<i>Tas1r1</i>	TAS1R1	++	++	++		Umami taste receptor (as a heterodimer with TAS1R3); localization not shown (activity studies and reporter gene localization)	[13]
<i>Tas1r2</i>	TAS1R2					Sweet taste receptor (as a heterodimer with TAS1R3); localization not shown, possibly β tanycytes (activity studies)	[44]
<i>Tas1r3</i>	TAS1R3					Component of both sweet and umami taste receptor heterodimers (see above); localization not shown (activity studies)	[44]
<i>Tas2r</i>	TAS2R	+++	+++			Multiple subtypes; bitter taste receptors possibly involved in glucosensing; RNA-seq results	[17]
<i>Fabp7</i>	BLBP	+++				Shown by immunohistochemistry, brain lipid-binding protein is a marker of stem cells that labels adult neurogenic niches	[48]
Metabolic hormone receptors and transporters							
<i>Glp1r</i>	GLP1R	+	++	+++		Shown by immunochemistry and electron microscopy, <i>in situ</i> hybridization, and qPCR in isolated tanycytes by FACS	[100,101]
<i>Lepr</i>	LEPR	++	++	++	++	mRNA is expressed at low levels throughout the tanycytic layer, as shown by <i>in situ</i> hybridization using RNAscope technology and FACS-isolated tanycytes; protein localization shown by allosteric antibody (XPA) binding, ligand-binding studies (<i>in vitro</i> [15] and <i>in vivo</i> [64]), functional assay <i>ex vivo</i> , and knockout studies <i>in vivo</i>	[15]
<i>Insr</i>	INSR	+++	+++	+++	+	<i>In situ</i> hybridization shows <i>Insr</i> in all tanycytes; functional INSR protein shown by knockout studies	[16]
<i>Ghsr</i>	GHSR	+				ME tanycytes express low levels of mRNA for the ghrelin receptor GHSR, and ghrelin transport by tanycytes may predominantly involve other mechanisms	[80]
<i>Fgfr1</i>	FGFR1	+++	+			<i>In situ</i> hybridization; FGF21, itself also produced by tanycytes [11,89], binds to a heterodimer consisting of FGFR1C, FGFR2C, or FGFR3 and β-KLOTHO, while FGF23 binds to a heterodimer of FGFR isoforms with α-KLOTHO. However, α tanycytes of the neurogenic niche are responsive to FGF1 and could thus be expected to express FGFR1	[91,93]
<i>Adipor1</i>	ADIPOR1	+++	+++	++		Immunohistochemistry; high expression in β and α2 tanycytes	[104]
<i>Adipor2</i>	ADIPOR2	+++	+++			Immunohistochemistry; high expression at the level of the ARH and ME, tapering off dorsally; single cell (sc) RNA-seq data suggest high expression in all ventricular cells	[104]
<i>Tlr4</i>	TLR4	++	+++			Strong protein expression in β1 tanycytes, but appears to be activated by inflammatory stimuli in tanycytic stem cells. TLR4 can detect a plethora of ligands, including resistin, an adipokine	[108]

Table 1. (continued)

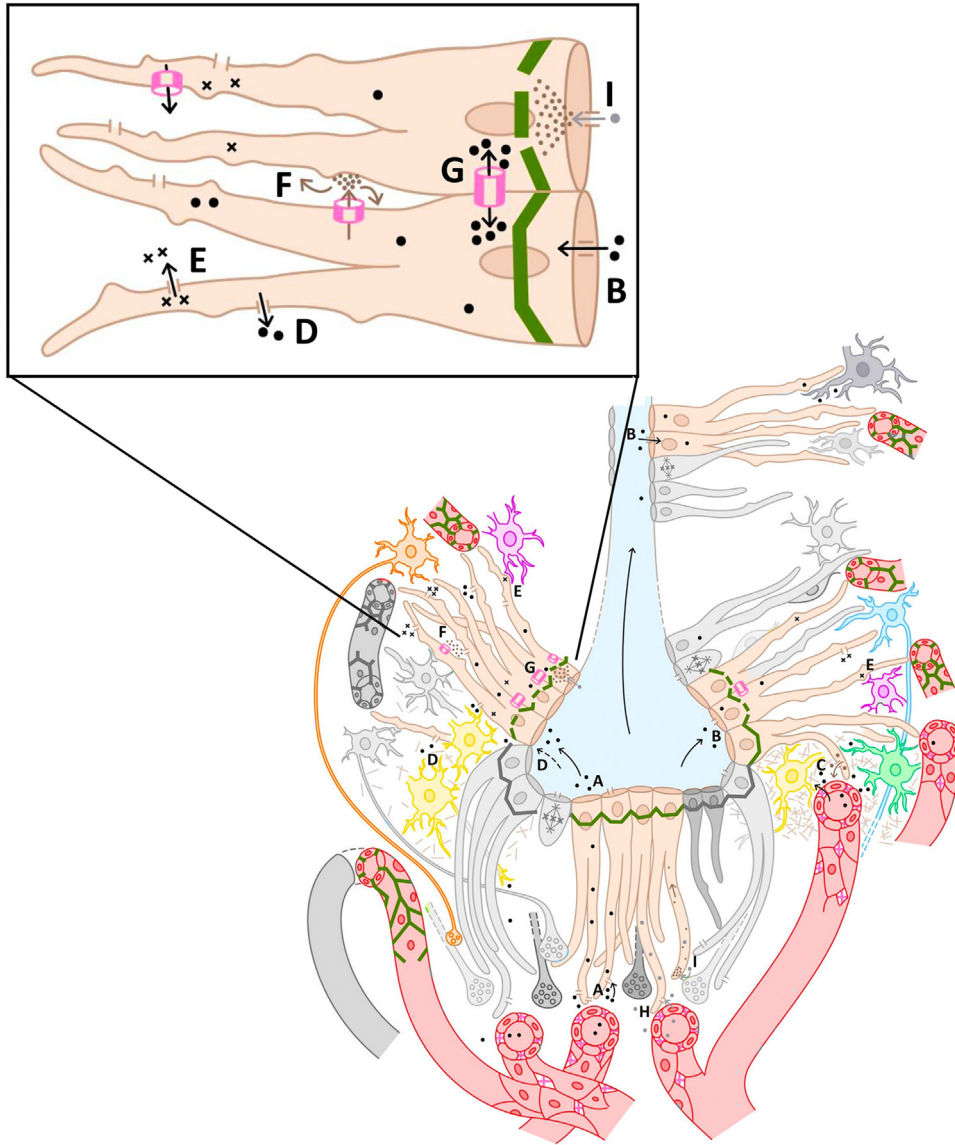
Gene ^a	Protein ^a	Tanycyte type				Notes, methods, and findings	Refs
		β2	β1	α2	α1		
Hypothalamic–pituitary axis hormone receptors and transporters							
<i>Trhr</i>	TRHR1	++	++			Shown mainly in β tanycytes by PCR, scRNA-seq, and <i>in situ</i> hybridization	[14,213,214]
<i>Tshr</i>	TSHR	+++	+++			<i>In situ</i> hybridization; functional TSHR shown in primary cultured tanycytes using antagonist studies	[18,215]
<i>Thra1</i>	TRHα2	+++	+++	+++	+	Principal thyroid hormone receptor widely expressed in tanycytes, as shown by <i>in situ</i> hybridization	[18]
<i>Thrb</i>	TRHβ	+	+	+		Very low expression shown by <i>in situ</i> hybridization	[18]
<i>Slco1c1</i>	OATP1C	+	+			A thyroid hormone transporter that is expressed in low levels, as shown by <i>in situ</i> hybridization, in TSHR-expressing tanycytes	[18]
<i>Slc16a2</i>	MCT8	+++	+++	+++	+++	A thyroid hormone transporter and specific marker for tanycytes; shown by <i>in situ</i> hybridization and immunohistochemistry	[18]
<i>Slc15a2</i>	PEPT2		+++	+++	+++	PEPT2 acts as a transporter for melatonin in addition to various other functions [216], and is expressed in tanycytes (shown by <i>in situ</i> hybridization)	[217]
<i>Esr1</i>	ERα	+++	+++	++		Estrogen receptor α (ERα) shown by <i>in situ</i> hybridization, immunolabeling, and qPCR of FACS-sorted tanycytes, as well as selective knockout studies	[137]
<i>Crhbp</i>	CRHBP	+++	+++			Immunohistochemistry; distribution in α tanycytes was not shown	[152]
<i>Igf1r</i>	IGF1R	?	+++			mRNA by scRNA-seq in tanycytes (subpopulation not indicated); protein localization shown by immunohistochemistry at the level of the ARH	[160,218]
<i>Ghr</i>	GHR	++	++	++		scRNA-seq data from Steuermagel <i>et al.</i> [219], interpreted by Menezes <i>et al.</i> , together with activation studies [161]	[161]
<i>Egfr</i>	EGFR	+++	+++	+++	+++	Involved in leptin transport by tanycytes; shown by immunohistochemistry and proximity ligation assay with LEPR	[15,220]
Receptors involved in neurogenesis							
<i>Fgfr1</i>	FGFR1	+++	+			<i>In situ</i> hybridization; FGF21, itself also produced by tanycytes [11,89], binds to a heterodimer consisting of FGFR1C, FGFR2C, or FGFR3 with β-KLTHO, while FGF23 binds to a heterodimer of FGFR isoforms with α-KLTHO. However, α tanycytes of the neurogenic niche are responsive to FGF1 and could thus be expected to express FGFR1	[91,93]
<i>Fgfr2</i>	FGFR2	+++	+++				
<i>Fgfr3</i>	FGFR3	+	+	++	+++		
<i>Cntfr</i>	CNTFRα	++	++	+++	+++	Tanycytes also express CNTF, the first molecule that was shown to stimulate tanycytic neurogenesis	[221]
Other receptors							
<i>Gpr50</i>	GPR50	+++	+++	+++	+++	An orphan receptor and member of the melatonin receptor family that is strongly expressed in all tanycytes, as shown by immunohistochemistry; GPR50 heterodimerizes with various GPCRs and tyrosine kinase receptors	[222,128]

^aBold font indicates demonstrated mRNA and/or protein expression.

Glucose

Glucose is not simply a fuel molecule. It informs the brain about energy availability and acts as a regulator of metabolic status by controlling the activity of neuronal circuits that influence multiple parameters regulating energy balance and glucose metabolism. Given its importance for cellular metabolism, physiological concentrations of glucose are kept within a very narrow range by several overlapping but complementary mechanisms, including feedback from the above processes [27].

Glucose access to the hypothalamus is region-dependent, and takes place via active transport across barriers by glucose transporters (GLUTs), as in the rest of the brain, as well as by passive diffusion through fenestrated capillaries, or a combination of both [27,28]. This is the case in the ME, where blood-borne glucose extravasates from fenestrated capillaries of the pituitary portal



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Figure 2. Nutrient and metabolite sensing by tanycytes. The active transport of glucose (black dots) into the hypothalamus from the blood takes place in two steps: (A) GLUT-dependent uptake of glucose liberated by extravasation from fenestrated capillaries of the median eminence (ME) by ME tanycytes, which release it into the cerebrospinal fluid (CSF), and (B) uptake of CSF glucose by arcuate nucleus of the hypothalamus (ARH) and more dorsal tanycytes for transfer to neurons. (C) Passive diffusion of glucose through capillary loops penetrating the ARH that become fenestrated in response to tanycytic signals such as VEGF-A (brown dots). (D) Glucose transported by tanycytes or diffusing into the ARH is perceived by NPY/AgRP neurons (yellow). (E) By contrast, ARH proopiomelanocortin (POMC) neurons (magenta) can only perceive glucose that is converted into lactate by tanycytes (black crosses). (F) ATP generated in response to the glucose signal can also exit the cell via connexin 43 hemichannels and exerts autocrine/paracrine effects on tanycytes themselves. (G) The transfer and amplification of lactate and synchronous activation of POMC neurons is mediated by connexin 43 gap junctions (pink and white tubes) which connect ARH tanycytes. (H) Tanycytes also take up saturated and unsaturated fatty acids (gray dots) from the circulation to store them in lipid droplets or metabolize them. (I) Some amino acids (gray crosses), and possibly also fatty acids, trigger intracellular signaling cascades when taken up by tanycytes (brown sprays). (Inset) Detailed view of glucose and lactate transfer by ARH tanycytes. Figure not to scale.

circulation, and seems to be picked up and transported by ME tanycytes that release it into the CSF at the ventricular wall [29]. This glucose is then carried by the CSF to adjoining regions such as the ARH and VMH, which it enters either through passive diffusion or through tanycytic transport in the reverse direction.

The various GLUT isoforms involved in this multistep transport are expressed by different populations of 3V tanycytes and may perform different functions. The expression and subcellular localization of GLUT1 and GLUT2 in tanycytes have been extensively described [28]. Glucose transport into the CSF at the ME is most likely mediated by the high-affinity GLUT1 that is expressed by the endfeet of β_2 tanycytes, and may additionally involve the low-affinity GLUT2 as well as GLUT6 during hyperglycemia or refeeding after fasting (Figure 2A) [29,30]. Similarly, the concentration of glucose in the interstitial fluid of downstream hypothalamic nuclei such as the VMH is about four times lower than that observed in the ARH [19] in fasting but not fed rats. This suggests that GLUT1 expressed by β_1 and α tanycytic cell bodies is the major contributor to glucose uptake from the CSF and release into these regions (Figure 2B), but that ARH values may additionally reflect glucose entry through other routes (discussed below). Moreover, in rats, circadian variations in glucose access to the ARH also appear to be correlated with tanycytic GLUT1 expression [26]. However, *in vivo* studies on inhibition of tanycytic glucose transport, including by GLUT2, demonstrated impaired neuronal responses to fasting and glucose administration, accompanied by altered expression of orexigenic and anorexigenic neuropeptides, changes in feeding behavior, and metabolic syndrome [30,31], which indicates that multiple tanycytic GLUT species are involved in glucose transport depending on physiological conditions.

The passive GLUT-independent diffusion of glucose into the ME and the adjacent ARH is also not a static process, and is instead highly modulatable, in part as a function of energy status. It has long been known that, during fasting in mice, glucose concentrations in the ARH double, mediated by a tanycytic vascular endothelial growth factor A (VEGF-A)-induced increase in the fenestration of local BBB vessels which allows glucose to extravasate directly into the ARH instead of being transported from the ME or CSF (Figure 2C) [19]. The local accumulation of glucose is aided by simultaneous reinforcement of tight junctions between tanycytic cell bodies bordering the ARH (Figure 1) [19] and increased deposition of aggrecan, which constitutes a diffusion barrier, around these ARH capillaries (Figure 1) [32]. This repositioning and remodeling of diffusion barriers could promote the local entry or accumulation of glucose, thereby allowing it to act on orexigenic ARH neurons expressing neuropeptide Y and agouti-related peptide (NPY/AgRP neurons).

Tanycytes not only control glucose access but also act as 'translators' of the glucose signal. While glucose is conveyed as-is to NPY/AgRP neurons of the ARH (Figure 2D) [33], anorexigenic ARH neurons expressing POMC, that were long thought to be glucosensors, in fact only perceive and respond to the glucose metabolite lactate which is provided to them by ARH tanycytes that take up glucose from the CSF and convert it to lactate (Figure 2E) [25]. The formation of a functional syncytium because of the presence of connexin 43 (CX43)-mediated gap junctions between tanycytes (Figure 2F) [34,35], in particular those that terminate on vessels of the BBB, could facilitate the rapid propagation and amplification of the glucose signal throughout the tanycytic population, and thus lead to coordinated activation of their target neurons [25]. Glucose entry into β_1 and α tanycytes triggers the release of ATP, possibly through hemichannels formed by CX43 (Figure 2G) [9,36], leading to paracrine signaling in tanycytes themselves as well as the activation of NPY neurons through P2Y1 purinergic receptors and the propagation of a tanycytic Ca^{2+} wave [9,10]. Interestingly, the CX43-mediated release of ATP and the resulting signal transduction pathways may also be involved in fibroblast growth factor 2 (FGF2)-induced tanycytic proliferation and, presumably, neurogenesis [37].

In addition to the machinery necessary for glucose transport (GLUTs), its conversion to pyruvate and/or lactate, and the cellular influx or efflux of these metabolites through monocarboxylate transporters (MCTs) [25,38], tanycytes express other enzymes involved in glucose metabolism and modulation which determine the cellular and physiological response to it. These include glucokinase (GK), a hexokinase that phosphorylates glucose and inhibits its release from the cell, as well as K_{ATP} channels, which are also used for glucosensing by pancreatic β cells [2,28]. Tanycytes also employ the glucose 6 phosphatase (G6PT) system, that is used both by hepatocytes to release glucose under hypoglycemic conditions [39] and by pancreatic β cells [40], suggesting similarities between the glucoregulatory mechanisms in these different cell types. Furthermore, GK regulatory protein (GKRP), which binds to GK and sequesters it in the cell nucleus, thus modulating glucose uptake, is expressed in tanycytes where it influences both lactate production under hyperglycemic conditions and the production of ketone bodies such as β -hydroxybutyrate (β HB) under hypoglycemic conditions, as well as ARH orexigenic/anorexigenic neuropeptide expression in response to varying glucose levels [41]. Adenovirus-mediated downregulation of GK in tanycytes alters the expression of ARH neuropeptides (POMC, AgRP, NPY, and the cocaine- and amphetamine-regulated transcript CART) in response to glucose injection directly into the 3V, and induces higher food intake [42]. More dramatically, attenuation of GK expression in tanycytes induces caspase-mediated death of β tanycytes and perturbs their communication with ARH NPY neurons and the function of these neurons, at least under fasting conditions, leading to a general metabolic syndrome phenotype characterized by increased food intake, fat mass accumulation, and central leptin resistance [43]. These changes are also accompanied by a reduction in the extracellular matrix surrounding NPY neurons [43], which implicates tanycytic signaling in the fasting-induced increase in aggrecan deposits by these neurons [32]. Similarly, knockdown of G6PT specifically in tanycytes results in decreased body weight, fat mass, and food intake, as well as decreased FOS protein expression and *Npy* mRNA expression in the ARH of fasting mice [39].

Tanycytes may also employ other molecules and mechanisms to respond to glucose. For instance, tanycytes express the TAS1R2/TAS1R3 sweet taste receptor that may be involved in glucose signaling, and the proportion of tanycytes responding to glucose significantly decreases from ~53% in wild-type mice to ~22% in mice lacking TAS1R2, implying that more than half of glucosensitive tanycytes utilize TAS1R2 heterodimers, while the rest rely on other as yet unspecified mechanisms [44,45]. A small subpopulation (~5%) of ME/ARH tanycytes that express a gustatory Ca^{2+} -activated monovalent cation channel, TRPM5, together with high levels of GLUT1, also express bitter taste receptors of the TAS2R family [17]. These tanycytes, which are closely associated with fenestrated capillaries of the ME, show transcriptomic reprogramming under fasting conditions, and their specific ablation impairs glycemic control, indicating their importance for brain glucosensing and response. The wealth of information provided by these recent studies suggests that much remains to be discovered concerning these glucose-sensing and regulatory mechanisms, including the interactions between the various receptors and transporters.

Lipids

In keeping with the important role of the hypothalamus in regulating lipid metabolism, it has long been known that some hypothalamic neurons can sense and respond to fatty acids (Figure 2H) [46]. Surprisingly, however, although the presence of lipid droplets in tanycytes was described almost half a century ago [47], the first molecular indication that hypothalamic tanycytes could sense or take up lipids comes not from their now well-accepted role in the regulation of metabolism but from the fact that they give rise to new hypothalamic neurons in adulthood that also play a role in energy homeostasis [2]. Indeed, a subpopulation of ME/ARH tanycytes expresses brain lipid-binding protein (BLBP), a marker of NSCs during development and in brain regions involved in adult neurogenesis [48]. Much of the available information on lipid and fatty acid sensing and

uptake by tanycytes has been reviewed elsewhere [1,49–51], although their function and underlying mechanisms have been relatively poorly studied. Ablation of ME/ARH tanycytes in mice leads to an increase in body fat mass in addition to several other effects, suggesting that tanycytes may play a role in brain lipid sensing and the control of peripheral lipid metabolism, although it is difficult to tease apart their specific effects given the likely alteration of hypothalamic integrity [52].

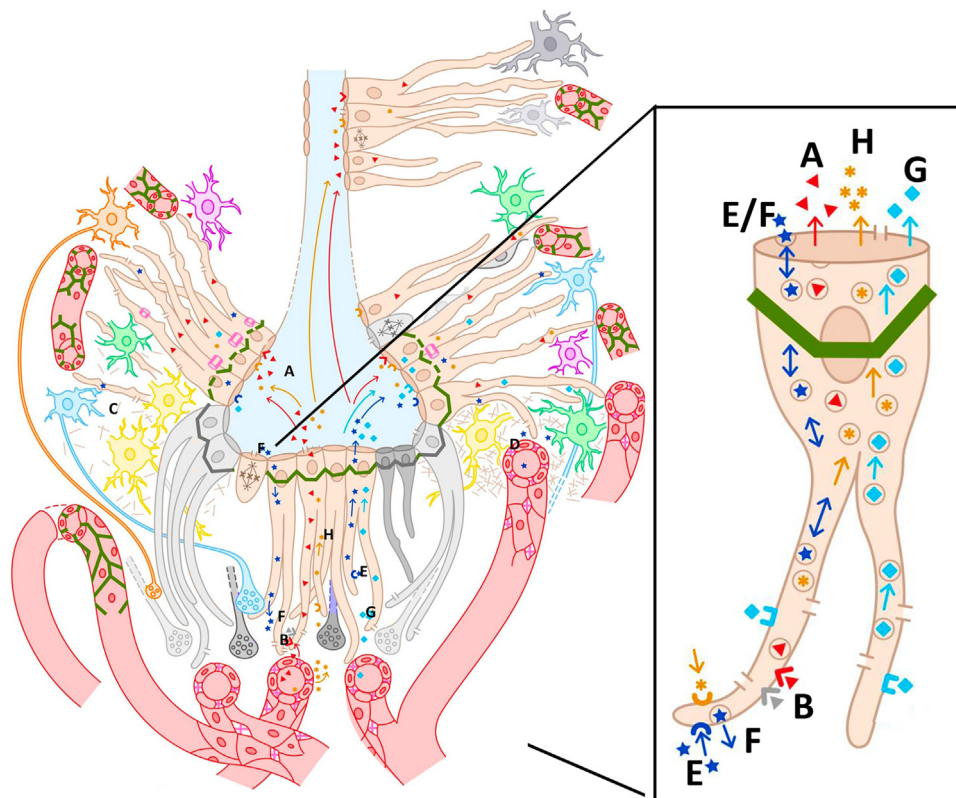
Unlike astrocytes, which only take up unsaturated fatty acids, tanycytes can take up and distribute both saturated and poly-unsaturated fatty acids. Furthermore, the fatty acids studied differ both in terms of their content and their subcellular (or extracellular) localization in tanycytes, and lipid droplets are increased following a high-fat diet (HFD) [12]. Dietary fatty acids may also alter the expression of multiple cytokines and growth factors by tanycytes, with downstream effects on metabolic and physiological pathways [22]. For instance, depending on the exposure of tanycytes to high circulating dietary fatty acids or fasting, tanycytes secrete the hepatokine FGF21. This is mediated by oxidation of the long-chain saturated fatty acid, palmitate, which is predominantly found in tanycytic lipid droplets [12], but not of oleate, leading to activation of a reactive oxygen species (ROS)/p38-MAPK signaling pathway [11]. Tanycytic FGF21 is thought to inhibit neurons in the hypothalamus that promote peripheral lipolysis, and its targeted deletion alters energy homeostasis by increasing expenditure and reducing fat mass [11]. Tanycytes have also been shown to express the catalytic subunit of the serine/threonine phosphatase protein phosphatase 2A, which is activated in response to HFD *in vivo* and by the saturated fatty acid palmitic acid *in vitro*; this activation is AMPK-dependent, and may also activate the hypoxia-inducible factor HIF1 α , leading to the production of several other factors including VEGF-A [22]. Tanycytic expression of VEGF-A, a key regulator of energy status-dependent hypothalamic barrier plasticity [19], additionally mediates the effects of a glucagon-like peptide 1 receptor (GLP-1R) agonist on glycemic control and downstream lipid metabolism [53], and favors the anorexigenic output of ARH neurons in response to heat exposure [21]. The translocase TSPO, a mitochondrial outer-membrane protein that is expressed in peripheral organs involved in lipid storage and metabolism [54], is also highly expressed in tanycytes and elicits AMPK-dependent lipophagy and altered energy balance in response to overnutrition, and protects mice from diet-induced obesity (DIO) [55]. Intriguingly, fasting induces large-scale transcriptomic shifts or switches in tanycytic subpopulations, including in several other genes involved in lipid biosynthesis and metabolism [6]. More research is thus necessary to understand the precise mechanisms and role of tanycytes in lipid sensing and metabolic control by the brain.

Amino acids

Amino acids are important satiety signals. In addition to fatty acids, it has been known for decades that the brain can respond to circulating amino acids (not counting excitatory amino acids important for neurotransmission) [56]. However, the involvement of hypothalamic tanycytes in amino acid sensing only emerged recently with the finding that the TAS1R1/TAS1R3 heterodimeric umami taste receptor and the metabotropic glutamate receptor mGluR4 are expressed by tanycytes and are involved in the detection of CSF-borne amino acids [13], similar to the involvement of the TAS1R2/TAS1R3 sweet taste receptor in glucose sensing [44,45]. Specifically, tanycytes respond differentially to several essential amino acids (Ala, Arg, Ser, Lys, and to a lesser extent Pro). Ala, Arg, and Ser all evoke robust ATP release through pannexin 1 hemichannels (PANX1) and the calcium homeostasis modulator 1 (CaLHM1) which amplifies the Ca²⁺ response through a mechanism involving P2 purinergic receptor signaling (Figure 2). Interestingly, the response to Arg and Lys depends on TAS1R1 expression, whereas mGluR4 mediates the response to both Ala and Lys [13]. Further *in vivo* investigations will be necessary to explore whether and how tanycytes sense other dietary amino acids under different physiological conditions and the involvement of this sensing in metabolic homeostasis.

The tanyctic hormonal shuttle

While the idea that some ME ependymal cells could serve as conduits for tracer molecules dates back almost half a century, it is only in the past decade that proof of a physiologically relevant blood–CSF shuttling by tanyocytes has emerged, thanks largely to studies on the mechanism of entry into the brain of the peripheral adipocyte-derived hormone leptin that is essential for the regulation of energy balance. Indeed, tanyocytes, like other cells, possess molecules and structures involved in endocytosis and transcytosis. In keeping with their polarized morphology, this molecular machinery also appears to be polarized, suggesting a preferred directionality of transport [3,57]. These ultrastructural features, as well as the large number and variety of receptors identified in tanyocytes to date (Table 1), play essential roles in tanyctic detection and trafficking of blood-borne or CSF-borne metabolic signals and hormones across brain barriers, including the blood–CSF barrier that is composed of tanyctic cell bodies sealed by tight junctions at the ME (Figure 3). Furthermore,



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Figure 3. The tanyctic shuttle for peripheral metabolic signals and hormones. (A) Median eminence (ME) tanyocytes take up leptin (red triangles) liberated by extravasation from fenestrated capillaries from where it is transported in clathrin-coated vesicles (see inset) into the cerebrospinal fluid (CSF) of the third ventricle (3V). (B) This uptake is a two-step process that requires both leptin binding to the long form of the leptin receptor, LEPRb (red V), and the binding of epidermal growth factor, EGF, or related peptides (gray triangle) to its receptor, EGFR (gray V), with which LEPRb forms a complex. (C) Ghrelin (navy-blue stars) transported into the arcuate nucleus of the hypothalamus (ARH) stimulates growth hormone-releasing hormone (GHRH) neurons (light blue). (D) Ghrelin can also extravasate from fenestrated capillary loops in the ARH in the vicinity of NPY/AgRP neurons (yellow) under fasting conditions. (E) Ghrelin can both be transported from the blood to the CSF in clathrin-coated vesicles by ME tanyocytes expressing its receptor (navy-blue semicircles) or (F) is transported in the reverse direction from the CSF to the blood. (G) ME tanyocytes express the insulin receptor (turquoise-blue brackets) and can transport insulin (turquoise-blue squares) from the circulation into the hypothalamus. (H) Similarly, ME tanyocytes express fibroblast growth factor receptor 1 (FGFR1; ocher semicircles) which binds to the hepatokine fibroblast growth factor 21 (FGF21; ocher asterisks) and transports it into the hypothalamus. (Inset) Detailed view of receptor complex formation and vesicular transport of metabolic signals. Figure not to scale.

the transport of many of these hormones and metabolic signals is interdependent, suggesting a complex system of checks and balances.

Leptin

Leptin, an anorexigenic adipokine secreted by white adipose tissue (WAT), informs the brain, particularly but not exclusively ARH neurons that regulate food intake and metabolism, about peripheral energy status. Leptin injections in animals or humans with a functional leptin receptor (LEPR) decrease appetite and increase energy expenditure, while a genetic deficiency of leptin or LEPR leads to obesity and type 2 diabetes. Paradoxically, many obese individuals have high circulating leptin but disproportionately low CSF leptin levels, leading to the concept of central leptin resistance – namely the inability of circulating leptin to access its target neuronal circuits, and consequently dysregulation of food intake and obesity [58–60]. Interestingly, leptin, insulin, and the orexigenic peptide ghrelin are all involved in the developmental programming of hypothalamic metabolic circuits [61–63].

Under physiological conditions, ME tanycytes, which express LEPR, are the first and main port of entry for leptin into the brain, and take up this hormone from the pituitary portal circulation and transfer it to the CSF to reach its target neuronal circuits in the ARH and more distant brain regions (Figure 3A) [15,64,65]. Leptin enters ME tanycytes as early as a few seconds after its peripheral administration and activates them, as indicated by STAT3 phosphorylation, within 5 min [15,64]. This leptin uptake occurs through clathrin-coated vesicles in the endfeet of ME tanycytes in a process that requires sequential activation of both a signaling-competent form of its receptor, most likely LEPRb, by leptin, and of the epidermal growth factor receptor (EGFR, which forms a complex with LEPRb) by EGF or EGF-related peptides (Figure 3B) [15,64,66]. The subsequent downstream signaling of the extracellular signal-regulated kinase (ERK) pathway is essential for leptin release from early endosomes [15,64]. In DIO mice following prolonged HFD, this mechanism breaks down, and even high circulating levels of leptin fail to trigger its LEPR–EGFR-mediated transport, while boosting ERK signaling restores leptin shuttling and its physiological effects [64]. While other routes for leptin entry into the brain are known or suspected, notably through the choroid plexus [67,68], although this only expresses the short form of LEPR, LEPRa [69], that lacks the intracellular signaling domain, or by directly crossing the BBB [68,70]. However, targeted downregulation of LEPR or EGFR in tanycytes [15], as well as expression of the botulinum neurotoxin light chain B (BoNT/B) selectively in tanycytes to block their vesicular transport [65], both mimic the physiological and molecular effects of leptin resistance, and lead not only to obesity but also to insulin resistance [65] or type-2 diabetes [15]. These observations confirm that tanycytic leptin transport is a key mechanism in wider metabolic sensing and regulation, but that other routes may play complementary or regulatory roles, especially given the propensity of LEPR to form a complex with other receptors. Interestingly, EGF enhances the effects of leptin on ERK activation without affecting STAT3 activation [15].

The involvement of other receptors and signaling pathways in tanycytic leptin transport cannot be ruled out. For instance, the subpopulation of ARH and ME tanycytes that express TRPM5 and GLUT1 also responds to specific hormones, leptin included, by Ca^{2+} release and STAT5 phosphorylation (pSTAT5). Interestingly, specific ablation of tanycytes expressing TRPM5 disrupts leptin signaling in the ME (with the loss of pSTAT5 immunoreactivity in all tanycytes) [17]. In addition, in DIO mice in which the tanycytic shuttle is compromised, ARH neurons show low levels of constitutive STAT3 phosphorylation [64,71,72]. Further investigations are thus necessary to better understand how tanycytes mediate the effects of leptin on the neuronal circuits that control energy metabolism, and whether and how alternative routes for the entry of circulating leptin into the hypothalamus are activated as DIO progresses.

Ghrelin

Ghrelin, the 'hunger hormone', is a small orexigenic peptide produced principally by the stomach and other peripheral tissues that acts on the brain, in particular on hypothalamic feeding circuits, to regulate food intake, glucose metabolism, and body weight in the opposite direction to the anorexigenic leptin [73,74]. However, recent research has revealed more complex functions of this peptide, such as activation of reward and motivation centers [75]. It is also a potent stimulus for the secretion of growth hormone-releasing hormone (GHRH) (Figure 3C) [73].

Ghrelin can extravasate from fenestrated capillary loops originating in the ME to reach and activate ARH neurons under some physiological conditions such as fasting (Figure 3D) [19,76]. However, diffusion of ghrelin liberated by extravasation into the ARH parenchyma and its access to ARH neurons is strictly limited to the vicinity of the fenestrated capillary loops [76] because of the presence of aggrecan deposits around these neurons (Figure 1) [32]. Concurrently, tanycytic transport of ghrelin from the peripheral circulation to the CSF, where it exhibits a pulsatile pattern, at least in sheep [77], has been inferred from the fact that these cells take up peripherally administered fluorescent ghrelin (Figure 3E) [78]. Surprisingly, however, when this hormone is injected directly into the CSF, ghrelin is abundantly internalized by the cell bodies of β tanycytes and released at their endfeet via a clathrin-dependent mechanism (Figure 3F) [79], although the functional significance of this reverse tanycytic shuttle or clearance remains speculative. While the influx of circulating ghrelin into the CSF appears to require the expression of the ghrelin or growth hormone secretagogue receptor, GHSR, its efflux from the CSF may be GHSR-independent [80].

Interestingly, like leptin, ghrelin transported into the hypothalamus during the neonatal period is involved in the organization and programming of ARH feeding circuits [81]. This phenomenon is likely of key physiological importance because neonatal overfeeding, which blocks blood-borne ghrelin entry into the ARH during the development of ARH neuronal circuits, can have life-long neurodevelopmental consequences for energy homeostasis [62,78].

Insulin

Insulin is secreted by pancreatic β cells in response to high circulating glucose levels, a process that may itself depend on leptin and/or glucose sensing by the brain (e.g., [15,82]), and must also be perceived by target neurons in the hypothalamus and elsewhere to exert glycemic control [83]. The widespread and nonselective ablation of ME/ARH tanycytes decreases insulin sensitivity, suggesting a role for tanycytes in the access of insulin to hypothalamic targets [52]. However, lesions of this key glial population appear to have no effect on glucose tolerance, which implies a compensatory increase in insulin secretion, and the lack of specificity of this experimental strategy would likely impact on multiple pathways and processes, making the results difficult to interpret. According to a meticulous recent study, ME tanycytes also express the insulin receptor (INSR) and are essential for insulin access to ARH neuronal circuits that must respond to it (Figure 3G) [16], in keeping with the insulin resistance shown by mice in which the tanycytic shuttle is inactivated [65]. Furthermore, inactivating only ~30% of *Insr* mRNA specifically in tanycytes results in a halving of tanycytic AKT phosphorylation (pAKT) in response to peripheral insulin injection, which resembles the extent of insulin resistance induced by HFD [16]. The reduction of INSR expression in tanycytes is accompanied by a decrease in tanycytic insulin uptake and transport, an even more marked decrease in pAKT in the ARH, and activation of AgRP neurons (but not POMC neurons), as well as decreased and delayed ability of insulin to lower systemic glycemia and a reduction in hepatic gluconeogenesis. Furthermore, the ability of leptin and ghrelin to influence food intake and leptin-induced STAT3 phosphorylation in ARH neurons is impaired in these mice [16]. However, although this reduction in insulin signaling in the ARH is very similar to that observed in DIO mice upon peripheral insulin administration, mice lacking INSR in tanycytes,

unlike DIO mice, show minimal or no alterations in body weight, basal glucose concentration, energy expenditure, or basal locomotor activity, suggesting the differential control of these metabolic parameters by hypothalamic circuits, in keeping with the differential activation of ARH neurons by tanycyte-shuttled insulin [16]. In addition, there are probably other routes of entry of insulin into the hypothalamus, as indicated by the fact that suppression of INSR in ME tanycytes has a limited radius of action [16].

FGF21

FGF family proteins are implicated in cell proliferation, including in tanycytes, and angiogenesis. While most FGFs are produced locally and act in a paracrine manner, some FGFs are secreted into the bloodstream. One such endocrine FGF, FGF21, that is principally secreted by the liver, has evoked considerable interest for its therapeutic potential in metabolic disorders [84]. Hepatic FGF21 production follows a circadian rhythm and is regulated by and reciprocally regulates both the hypothalamic–pituitary–adrenal (HPA) and the hypothalamic–pituitary thyroid (HPT) axes ([85]; reviewed in [86,87]). FGF21 has diverse effects on metabolism, in particular under stressful metabolic conditions such as fasting or dietary imbalance [88,89], including energy expenditure/brown adipose tissue (BAT) thermogenesis, body weight regulation, insulin sensitivity, and glycemic control [88,89]. Some of these effects may involve early-life programming of metabolic functions [89]. While some metabolic effects of FGF21 are mediated directly by peripheral tissues such as WAT or the liver, many require brain signaling through FGF receptor 1 (FGFR1) and its coreceptor β -KLOTHO (KLB) [90]. Interestingly, β tanycytes, which appear to be necessary for shuttling hepatic FGF21 into the hypothalamus to reach its target neurons in the lateral hypothalamic area and zona incerta and thus exert its BAT thermogenesis and anti-obesity effects [89], not only express FGFR1 (Figure 3H) [89,91] but also FGF21 itself [11,88,89]. However, the effects of tanycytic FGF21 may be different from or even contrary to those of hepatic or peripheral FGF21 [11], suggesting that one could act as a competitive inhibitor or regulator of the signaling of the other. In this regard, it is important to note that KLB,

thought to be essential for FGF21 actions based on its role in adipocytes and hepatocytes, has only rarely been demonstrated in tanycytes until now [91–94], and FGF21 may signal through other FGFR1 receptor complexes [95]. In addition, FGF21 is known to trigger ERK phosphorylation [95,96], which is involved in the tanycytic shuttle and is necessary to release leptin into the CSF [64], suggesting that some transcytotic machinery may be common across several metabolic hormones.

GLP-1

Glucagon-like peptide 1 (GLP-1; 7–36 amide) is an incretin hormone that is primarily secreted by intestinal L-cells in response to ingested nutrients such as glucose [97]. Despite a short half-life in the circulation, it is necessary for glucose regulation because it enhances glucose-induced insulin secretion from pancreatic β cells, promotes satiety, and reduces body weight, activities that make GLP-1 and its agonists of great therapeutic value for the treatment of obesity and type 2 diabetes [98]. Interestingly, while GLP-1 has been known for >20 years to be produced by neurons of the caudal part of the nucleus of the solitary tract (NTS), which project to several hypothalamic nuclei [99], its G protein-coupled receptor (GLP1R), that is also present on other target cells including pancreatic β cells and various hypothalamic neurons, is expressed by both α and β tanycytes of the MBH [100]. This tanycytic GLP1R binds to and is activated by the GLP1R agonist semaglutide, which is then taken up and released by tanycytes [100], setting the stage for the involvement of the tanycytic shuttle in GLP-1 actions. Indeed, GLP1R-expressing ME/ARH tanycytes appear to play an essential role in transporting another GLP-1 agonist, liraglutide, to target hypothalamic regions that control energy metabolism [101]. Blocking

this GLP1R-mediated transport by expressing BoNT/B selectively in these tanycytes is sufficient to block the anti-obesity actions of liraglutide, including decreased food intake, changes in body weight and fat mass, and fatty acid oxidation [101], suggesting that GLP-1, like leptin, insulin, and FGF21, depends on hypothalamic regulatory circuits to exert its peripheral metabolic actions. Surprisingly, while GLP-1 has long been known to potentiate the glycemia-reducing effects of insulin, a recent study shows that insulin-induced hypoglycemia also has a reciprocal effect on GLP1R-mediated central effects [53]. Peripheral coadministration of insulin with exendin-4 (Ex-4), another GLP1R agonist, potentiates the expression of GLP1R and the uptake of Ex-4 by ME tanycytes, and consequently enables access of Ex-4 to target cells in the ME/ARH and NTS/area postrema [53]. This entry, which is not mediated by insulin *per se* but by the insulin-induced decrease in circulating glucose levels and tanycytic VEGF-A expression, both activates insulin signaling, as measured via the phosphorylation of AKT in target regions, and paradoxically, given the lipogenic effects of insulin, shifts peripheral fuel metabolism from glucose to fatty acid oxidation [53]. The complexity of GLP-1 actions is shown by a recent connectomics study that identified a large number of afferents to orexigenic AgRP neurons of the ARH and paraventricular nucleus of the hypothalamus (PVN), several of which express GLP1R [102]. Further investigations will be necessary to identify which among these are targets for tanycyte-shuttled GLP-1 or its agonists.

Other metabolic hormones

The effects of adiponectin, another adipokine involved in regulating energy metabolism and for which tanycytes express receptors, are mainly contrary to those of leptin [103]. Indeed, both ADIPOR1 and ADIPOR2 have recently been observed in β tanycytes [104], although their presence may have been masked in some other studies by their high expression in neighboring ARH neurons. Adiponectin is also present in the CSF, including in humans [105,106], raising the possibility of tanycytic shuttling similar to that of other metabolic hormones. Interestingly, adiponectin restores insulin sensitivity in obese or diabetic mice through an AMPK-mediated mechanism [107], although it is not known whether these effects are mediated or facilitated by tanycytic transport or signal transduction. Tanycytes also express Toll-like receptor 4 (TLR4) [108], a molecule that, in addition to its role in autophagy and pathogen-induced inflammation, is a receptor for resistin – another adipokine with effects opposite to those of adiponectin. Resistin contributes to obesity-induced inflammation and central insulin resistance, possibly through or in addition to downregulating the expression of adiponectin receptors as well as FGF21 and its receptors [109]. Both adiponectin and resistin also regulate brain glucose metabolism [110].

Whether tanycytes also respond to or transport other peripheral metabolic hormones is not known at present, but this appears likely, given our growing knowledge of their molecular diversity. Numerous examples of both the specificity and the cooperation of tanycytic actions with respect to these hormones have been demonstrated; for example, the interaction of insulin transport with ghrelin signaling [16], the coupling of EGF and leptin receptor activation [15], and the potentiation of leptin effects by FGF21 [89], often through converging downstream signaling pathways such as ERK or AKT phosphorylation. These findings reinforce not only the view of tanycytes as gatekeepers that control the access of various metabolic hormones and signals to regulatory brain circuits but also their emerging role in the fine-tuning the response of the brain to these overlapping and contradictory signals.

Tanycytes as effectors of metabolic adaptations to biological rhythms

Biological rhythms dictated by the environment determine both the survival of the individual and the propagation of the species. Most, if not all, metabolic functions and signals are subject to circadian regulation [111], and in seasonal species, for example sheep and hamsters, these

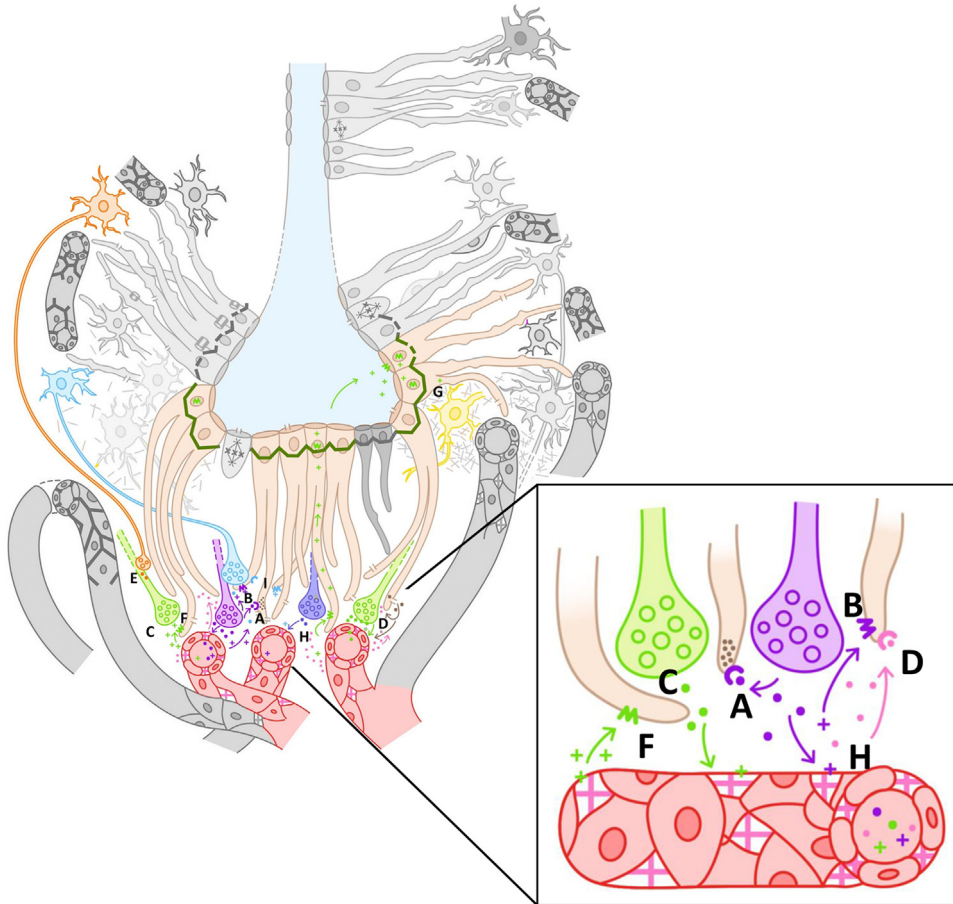
functions and signals correspond to differences in the breeding season and length of gestation that are optimized to lead to the birth of young during the spring or summer when food availability is high [7,112]. Interestingly, the cellular and molecular machinery underlying seasonal changes also persists in nonseasonal laboratory animals [113]. Many of the effects of environmental cues or biological rhythms on physiological processes are mediated by hormones of several hypothalamic–pituitary neuroendocrine axes whose dysregulation (i.e., excess or deficiency) or untimely release leads to adverse effects and disorders. These neuroendocrine axes follow a common blueprint that can be greatly simplified as follows: hypothalamic neurons that produce peptide-releasing hormones (and some inhibiting hormones) such as GnRH, TRH, corticotropin-releasing hormone (CRH), and GHRH project to the ME, where they intermingle with tanycytic processes and secrete their neurohormone into the pituitary portal circulation (Figure 4). Once in the anterior pituitary, these hormones stimulate specific cells (gonadotropes, thyrotropes, etc.) to produce the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as thyroid-stimulating hormone or thyrotropin (TSH), adrenocorticotropic hormone (ACTH), and growth hormone/somatotropin (GH). These then act on target organs to elicit the further secretion of steroid and thyroid hormones in the first three cases. ME tanycytes, which express receptors for many of these hormones (Table 1), are essential regulatory components of many of these hormonal axes and are thus ideally placed to impact metabolic function and adaptations.

The HPT axis, melatonin, and seasonality

The HPT axis plays a central role in regulating the function of peripheral metabolic organs/tissues and the adaptation of the organism to environmental factors. Its effects are mediated by thyroxine (T4), a prohormone which is converted to its bioactive form, triiodothyronine (T3) by the selenoprotein iodothyronine deiodinase type II (DIO2), or is inactivated by DIO3 (which also inactivates T3). All hormones of the axis also exert feedback control at different levels, including the hypothalamus, where tanycytes play a key role [114,115].

Tanycytes have long been known to express both DIO2 (for which they have the highest expression among brain cells) and DIO3, as well as pyroglutamyl peptidase II (PPII), an ectoenzyme that cleaves TRH, and several thyroid hormone transporters [116–120]. The endfeet of β_2 tanycytes, which control the access of PVN neuronal terminals that secrete TRH into the pituitary portal circulation, also express the TRH receptor (TRHR1) (Figure 4A). In response to locally released TRH, tanycytic TRHR1 is activated, which induces Ca^{2+} signaling through a G α q/11 protein-mediated pathway and triggers the extension of tanycytic endfeet to block access to TRH neuronal terminals, thus limiting the further release of TRH [14]. In addition, TRH terminals release glutamate concomitantly with TRH, which also leads to Ca^{2+} signaling and depolarization of β_2 tanycytes [121]. This activates the tanycytic diacylglycerol lipase α (DAGL α)-dependent presynaptic-like release of endocannabinoids from tanycytic endfeet, and also inhibits the release of TRH and prevents TSH-induced hyperthyroidism [121,122]. In addition, tanycytes respond to both circulating T4 and probably also TRHR1 activation by increasing the expression of PPII [14,119]. The TSH receptor (TSHR) is also expressed by tanycytes (Figure 4B), and its activation in different tanycytic subpopulations increases the expression of *Dio2* and *Dio3* as well as the thyroid hormone transporter gene *Sico1c1* through at least two different pathways: a TSHR/G α q/protein kinase C (PKC) pathway and a TSHR/G α s/cAMP response element-binding protein (CREB) pathway [18]. Physiological challenges such as fasting also increase *Dio2* expression in tanycytes and activate the DIO2/T3/PPII pathway [123,124].

In mammalian and non-mammalian species, adaptations to seasonal changes are mechanistically coordinated by melatonin secretion by the pineal gland, which is directly correlated with



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Figure 4. Tanycytic regulation of hypothalamic–pituitary neuroendocrine axes. Median eminence (ME) tanycytic processes intermingle with axons and terminals from multiple hypothalamic neuroendocrine neuronal populations that secrete their peptide hormone into the pituitary portal circulation. (A) Thyrotropin-releasing hormone (TRH; violet dots) released by TRH-expressing neuronal terminals (violet) in the vicinity of fenestrated vessels both enters the pituitary portal circulation for delivery to the anterior pituitary and exerts feedback on ME tanycytes which express the TRH receptor, TRHR1 (violet semicircle), and triggers a signaling cascade in these cells (brown spray). (B) Tanycytes also express the receptor for thyroid-stimulating hormone (TSH; violet crosses), thyroid-stimulating hormone receptor (TSHR; violet M shape), as well as several thyroid hormone transporters and converting enzymes including iodothyronine deiodinase type II (DIO2, not shown). (C,D) Extension or retraction of ME tanycytic endfeet controls the access of GnRH (and other) neuronal terminals (lime green) to fenestrated pituitary portal capillaries, into which they release GnRH (lime-green dots). (E) The release of GnRH is stimulated by arcuate nucleus of the hypothalamus (ARH) neurons that produce kisspeptin (orange). (F) ME tanycytes also express the estrogen receptor ER α (lime-green M shape) which allows the estrogen signal from the periphery (lime-green crosses) to exert feedback on hypothalamic circuits. (G) In particular, this estrogen signal is transmitted to NPY/AgRP neurons (yellow) to control energy metabolism. (H) Retraction of ME tanycytes and access of CRH-expressing neuronal terminals (similarly to TRH and GnRH terminals) to the fenestrated capillaries is mediated by, among other signals, nitric oxide (pink dots) from endothelial cells. (I) Tanycytes express both the receptor (light-blue semicircles) for growth hormone-releasing hormone (GHRH, light-blue dots) and the receptor (IGFR1; light-blue M shape) for insulin-like growth factor 1 (IGF1; light-blue crosses) which is secreted in response to growth hormone by the liver. (Inset) Detailed view of the dynamic interaction between representative neuroendocrine terminals (lime-green and violet) and ME tanycytic endfeet, and feedback from hypothalamic–pituitary hormonal axes. Figure not to scale.

the duration of the dark phase, and is itself regulated by the SCN, the biological clock of all vertebrates [7]. In seasonal species, prolonged melatonin production in winter (prolonged dark phase or short days, SD) reduces TSH expression, which causes tanycytes to decrease *Dio2*

expression and increase *Dio3*, while the opposite takes place during spring/summer (decreasing dark phase or long days, LD); seasonal changes are also observed in hundreds of other genes, including many considered to be specific to tanycytes [2,125]. For example, neutralizing FGFR1c, the receptor for FGF21, in the tanycytes of hamsters under LD, but not under SD, leads to reduced food intake and body weight accompanied by *DIO2* expression, namely an SD-like phenotype [126].

In the context of seasonal changes, tanycytes are also implicated in the induction of and cyclic arousal from torpor, a strategy by which metabolism and thermogenesis are brought to a quasi-complete halt to achieve energy homeostasis during SD. Mice deficient in GPR50, an orphan G protein-coupled receptor of the melatonin receptor family that can heterodimerize with the two functional mammalian melatonin receptors, and which is both highly expressed in tanycytes and seasonally regulated, present a paradoxical metabolic phenotype – increased metabolic rate and locomotor activity, resistance to body weight gain with HFD, and lower fasting glycemia than wild-type mice, but reduced body temperature and a lack of leptin-induced thermogenesis. Intriguingly, these GPR50-deficient animals also exhibit the spontaneous induction of torpor upon fasting or glucopenia, that is reversible by TRH treatment, and display both higher levels of tanycytic *Dio2* expression and lower *Trh* expression in the PVN [127,128]. Some of the metabolic phenotype of GPR50-deficient mice and species exhibiting natural torpor, such as the Siberian hamster, may stem from its induction of thioredoxin-interacting protein (TXNIP), a protein expressed by tanycytes, as well as by pancreatic β cells and various hypothalamic neurons, that is involved in cellular glucose and lipid metabolism [129]. Surprisingly, α tanycytes, and to a lesser extent β tanycytes, are among the cell types that show the highest expression of FOS, a marker of cellular activity, immediately before cyclic arousal periods during torpor [130], suggesting a role for tanycytes in restarting dormant metabolic processes. In this regard, the variability in the expression of other genes in adult rat tanycytes has been suggested to reflect oscillatory activity, a mechanism that is also displayed by neural stem/progenitor cells and could contribute to the rhythmic or cyclic functions of tanycytes [131].

Intriguingly, seasonal changes in the HPT axis of Siberian hamster dams during gestation and lactation influence the density and morphology of ME tanycytes in the pups, suggesting that early-life programming plays a role in tanycyte-mediated metabolic adaptation [132,133]. In addition, the density of tanycytic processes in Djungarian hamsters varies depending on their responsiveness to SD [134], which further confirms that tanycytic morphological plasticity and possibly adult neurogenesis [112], in addition to functional plasticity, could play a role in their translation of biological rhythms into metabolic signaling. This modulation has important repercussions for feeding behavior and energy metabolism, and consequently for reproduction [112,135], as detailed below.

The hypothalamic–pituitary–gonadal (HPG) axis and metabolic–reproductive coupling

To ensure that puberty and breeding take place under optimal conditions, namely when food availability and energy stores can be mobilized to prioritize mating, gestation, parturition, and lactation over feeding, the reproductive axis and metabolic status must be coupled. GnRH neurons, that are principally located in the median preoptic area of the hypothalamus, release GnRH at the ME in a rhythmic pattern mediated by a pulse-generating neuronal network in the ARH, as well as by sustained retraction of tanycytic endfeet in proestrus, to facilitate the preovulatory surge of GnRH that is necessary to stimulate gonadal growth, gametogenesis, and the synthesis and release of gonadal steroid hormones [136]. Each hormone of the axis also exerts feedback control at different levels to fine-tune its function. GnRH neurons themselves do not express receptors for most of these hormones, while tanycytes are well positioned both structurally and

functionally to play a key role in metabolic–reproductive coupling in the hypothalamus [1,137]. In particular, $\beta 1$ and $\beta 2$ tanycytes, which control the release of GnRH (similarly to TRH) by neuronal terminals (Figure 4C,D), are the same tanycytes that act as shuttles for circulating metabolic signals and hormones into the hypothalamus and that constitute the blood–CSF barrier in the ME (discussed in previous sections). Interestingly, the morphology of tanycytic endfeet and the interactions between GnRH neuronal terminals, tanycytic endfeet, and fenestrated portal capillaries in the ME are modulated by seasonal cues and feeding status [138,139].

In addition to the reproductive changes mediated by the differential effects of the TSH/DIO2/T3 system in tanycytes in LD and SD breeders, information on daylength is relayed to GnRH neurons through two neuropeptidergic neuronal populations in the ARH – those producing kisspeptin, a potent stimulator of GnRH production (Figure 4E), which act as the pulse generator for GnRH release, and those producing RFamide-related peptide 3 (RFRP3) [135]. The circadian regulation of RFRP3 expression in the ARH in response to melatonin is also mediated by activation of the thyroid hormone receptor TR α in tanycytes [140], and kisspeptin neurons respond to estrogenic feedback and, either directly or indirectly, metabolic hormones, such as leptin and insulin, which are shuttled into the hypothalamus by tanycytes (discussed in previous sections). Interestingly, in female mice, the expression of estrogen receptor α (ER α) by ME and ARH tanycytes (Figure 4F) links reproductive function to metabolic status in a two-pronged manner – while ME tanycytes mediate the estrogen positive feedback that stimulates the retraction of their endfeet and thus facilitates GnRH secretion, ARH tanycytes appear to transmit the estrogen feedback signal to hunger-sensing NPY/AgRP neurons (Figure 4G) and mediate estrogen-induced suppression of their activity; these neurons, in turn, are known to inhibit reproductive function through downregulation of GnRH/LH pulsatile release [137]. In the absence of tanycytic ER α activation by estrogens, *Npy* expression and food intake are increased, while energy expenditure and fatty acid oxidation are decreased [137]. Intriguingly, in juvenile female mice, the activity of these hypothalamic NPY/AgRP neurons in the run-up to puberty, that is itself controlled by food availability and body weight, dictates the maturation of the rhythmic activity of ARH kisspeptin neurons, and thus gates the activation of GnRH neurons and the timing of puberty [141,142]. Anorexigenic ARH POMC neurons, that are themselves activated by tanycytic lactate signaling [25], have also been implicated in the regulation of puberty by translating the leptin signal into their principal neuropeptide product, α melanocyte-stimulating hormone (α MSH), which stimulates kisspeptin neurons and thus GnRH production [143]. This α MSH-mediated POMC neuron/kisspeptin neuron communication may be modulated by energy status, and thus influences GnRH release [144,145]. Various other mechanisms and metabolic signals, many of which are sensed, transported, or regulated by tanycytes (discussed earlier), have also been shown to influence the maturation and function of the HPG axis and GnRH neurons [146–148].

The HPA axis and metabolic signaling

ME tanycytes also associate with the axons of CRH neurons of the PVN, the apex neurons of the HPA axis. Glucocorticoids and mineralocorticoids secreted by the adrenal cortex at the other end of the axis regulate or modify a variety of processes, including energy balance and lipid and glucose metabolism, both under physiological conditions and to prioritize survival in response to external or internal stressors. Tanycytes may modulate CRH release in a similar manner to GnRH or TRH: tanycytic endfeet retract to allow direct neurohemal contacts between CRH-positive neuronal terminals and pituitary portal capillaries [149], a process that, as shown for GnRH neurons [150], may be mediated by nitric oxide (NO) (Figure 4H) [151]. Rat tanycytes express CRH-binding protein, which suggests that there may be tanycytic feedback mechanisms [152], although CRH neuronal terminals also appear to be capable of directly responding to corticosterone and noradrenaline feedback [153]. Since the HPA axis is subject to circadian

regulation [111], and the surge in adrenal glucocorticoid secretion that precedes the daily active phase (diurnal or nocturnal) is mediated by the SCN and melatonin, one could expect ME tanycytes to transmit metabolic information to regulate both circadian feeding activity and stress-induced physiological or pathological adaptations of food intake through mechanisms similar to those seen above. Indeed, some effects of fasting or hypoglycemia-induced leptin on ARH AgRP neurons are mediated by the HPA axis [154], which evokes the idea that glucocorticoids might potentiate tanycytic leptin transport (even if the converse might also be true). Indeed, selective knockout of *Lep^r* in tanycytes suppresses the leptin-mediated normalization of corticosterone levels during fasting [15] (Table 1). These studies, while sparse, certainly indicate the need for further investigations to elucidate the potential involvement of tanycytes in circadian and stress hormone-mediated changes in metabolic signaling.

The hypothalamic–pituitary–somatotropic (HPS) axis at the intersection of growth and metabolic stress

Finally, the HPS or growth axis, as its name suggests, controls body growth, an energy-intensive process that also is a prerequisite for puberty, and therefore interacts closely with several aspects of both metabolic homeostasis and reproduction. In addition, it is involved in the maintenance of energy homeostasis, as well as in tissue repair and the response to metabolic stress in adulthood [155,156]. While GH release is stimulated by GHRH neurons of the ARH, it is inhibited by another hypothalamic neuropeptide, somatostatin or GH inhibitory hormone, that is produced by neurons of the periventricular nucleus of the hypothalamus (PVH). GH, which is released in a pulsatile fashion that peaks during the dark phase and plateaus at puberty, then acts on various peripheral organs and systems, notably by stimulating the production of insulin-like growth factor 1 (IGF1) by the liver, which provides feedback to hypothalamic neurons [157]. Both GHRH and somatostatin are expressed by other hypothalamic neuronal populations which may have different functions, including regulation of the HPS axis. In keeping with its roles throughout life, several hypothalamic neuronal populations, in particular AgRP neurons of the ARH, continue to express the growth hormone receptor (GHR) even in adulthood [158,159].

Tanycytes express the IGF1 receptor IGFR1 [160] as well as GHR (Figure 4) [161]. However, tanycytic GHR expression does not appear to be necessary for GH entry into the brain [161], suggesting that its feedback and transport mechanisms are different. In addition, IGF1 stimulates tanycytic proliferation and the generation of new GHRH neurons [162], in keeping with the postulated homeostatic function of hypothalamic neurogenesis in the adult brain (next section). However, while the neuronal terminals of ARH GHRH neurons are found in the same zone as those of other neuroendocrine neurons, where they are surrounded by abundant ME tanycytic processes, whether tanycytes control the release of GHRH through the outgrowth or retraction of their endfeet is not known, and other mechanisms have been proposed for the regulation of its release [163,164].

Cross-axes functions of tanycytes

Tanycytes may also mediate the interaction between the different hypothalamic–pituitary axes. For example, T4 has been shown in rats to trigger rapid expression of retinaldehyde dehydrogenase 1 (RALDH1) and the synthesis of retinoic acid by tanycytes, which in turn could increase the hypothalamic expression of metabolism-related genes (e.g., *Ghrh*, *Agrp*) [165]. In addition, both leptin and ghrelin, which act on GHRH neurons as well as on other ARH and hypothalamic neuronal populations [155,157], are transported into the hypothalamus by tanycytes, as previously discussed.

In addition to the above hypothalamic–pituitary axes, the hypothalamus harbors or receives projections from several other neurons that synthesize and release a variety of neuropeptides and

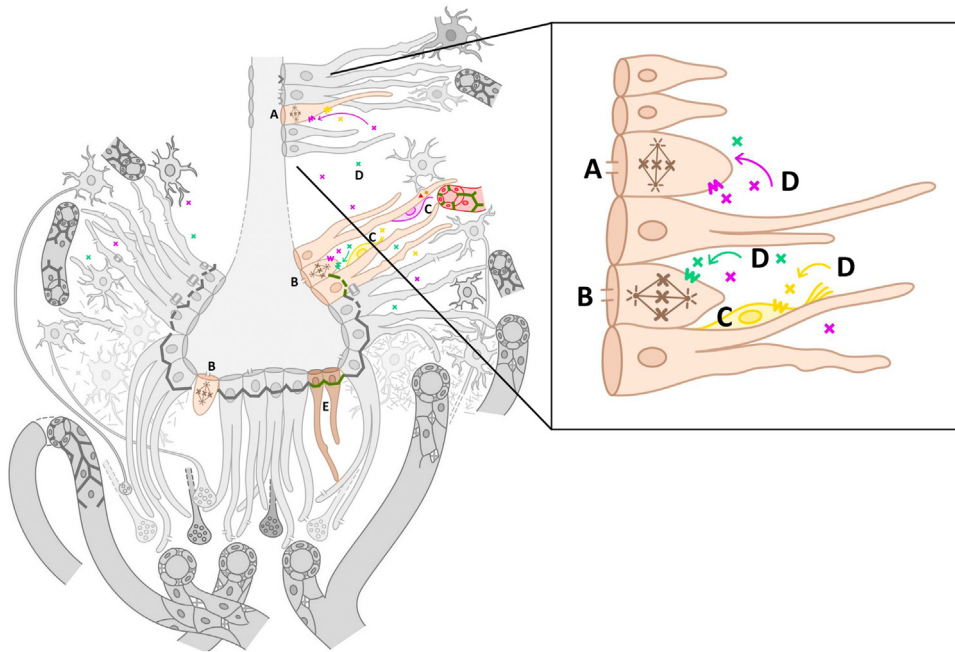
neurotransmitters. Some of these, for example tuberoinfundibular dopaminergic neurons, also appear to interact with ME tanycytes [1]. While most studies on these other regulatory circuits or of axes such as the HPA and HPS do not currently take into consideration a role for tanycytes, these cells are ideally placed to act as a hub for metabolic signaling and communication between these various circuits and axes.

Tanycytic neurogenesis and metabolic regulation

Reflecting the pleiotropic role of tanycytes, neurogenesis by tanycytic NSCs (mainly α tanycytes along the dorsal reaches of the ventricular wall) and neuronal progenitors (principally β tanycytes at the level of the ME/ARH) (Figure 5A,B), which constitute the third neurogenic niche of the adult mammalian brain after the subventricular zone of the lateral ventricles and the hippocampal subgranular zone [5], has also been associated for several years with metabolic function [166–170]. While most of these stem/progenitor cells are thought to remain quiescent, their proliferation under physiological conditions is regulated by the autocrine actions of several growth factors and cell proliferation pathways, including many that are also active in other neurogenic niches or during development [171–173] (Table 1). The progeny of these proliferating cells differentiate into diverse hypothalamic neurons, including several that are implicated in the maintenance of body weight and energy homeostasis (Figure 5C). This suggests that the phenomenon of adult hypothalamic neurogenesis by a tanycytic subpopulation may serve to promote homeostatic mechanisms, for instance by generating POMC neurons in response to HFD [174] or their congenital deficiency [175], or conversely to compensate for a loss of AgRP/NPY neurons [168], rather than having a purely orexigenic or anorexigenic effect (Figure 5D).

Importantly, this neurogenic niche appears both to be involved in the etiology of metabolic imbalances such as obesity and to be influenced by these imbalances [5,176]. For example, early studies show that the mitogen ciliary neurotrophic factor (CNTF), which promotes hypothalamic neurogenesis in adult mice, leads to weight loss [166], while elimination of proliferating ME tanycytes increases body weight [169]. Similarly, HFD in mice leads to a decrease in tanycytic neurogenesis and an apoptosis-mediated decrease in the generation of newborn neurons destined to be integrated into ARH regulatory circuits, which can be reversed by food restriction [177]. The HFD-induced decrease in neurogenesis appears to involve activation of the inflammatory NF- κ B pathway, which induces apoptosis and alters NOTCH signaling, and is implicated in the development of obesity and diabetes [167]. In this context, FGF2-induced tanycytic neurogenesis requires tanycytic CX43 expression [34,35] and CX43–P2Y1 signaling [37], both of which are involved in tanycytic glucosensing and transmission [10,25], as discussed above.

In terms of the growing number of factors that potentially regulate and are expressed by these progenitors, two homeobox genes recently linked to human obesity and to influence metabolic parameters in mice, *lrx3* and *lrx5*, appear to be expressed by a population of tanycytic precursors in mice [178]. These genes regulate adult hypothalamic neurogenesis, specifically the generation of POMC and NPY/AgRP neurons in the ARH, and thus the response to leptin [179]. Similarly, the endozepine diazepam-binding inhibitor/acyl-CoA-binding protein (DBI/ACBP), an endogenous ligand of benzodiazepine receptors, has been shown not only to be expressed and released by tanycytes, a process that is glucose/insulin-sensitive, but also to reverse DIO by potentiating the effects of leptin [180]. Intriguingly, DBI/ACBP, which is also involved in adult neurogenesis in the subventricular and subgranular zones [181], is coexpressed with nestin (and possibly SOX2) in the tanycytic neurogenic niche [182]. In this context, although hypothalamic neurogenesis has previously been shown to protect against obesity, tanycytes are also known to mediate inflammation-induced anorexia/cachexia [20], and DBI/ACBP has recently been suggested as a treatment for anorexia [183]. How the constitution and proliferation of this neurogenic



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Figure 5. Tanycytic neurogenesis associated with arcuate metabolic circuits. Hypothalamic tanycytes include both (A) neural stem cells (NSCs, and dorsal α tanycytes undergoing symmetric cell division), and (B) neuronal progenitors [arcuate nucleus of the hypothalamus (ARH) and median eminence (ME) tanycytes undergoing asymmetric cell division]. (C) Tanycytic neurogenesis gives rise to several neuronal cell types, including ARH neurons involved in controlling energy metabolism [flattened neuroblasts destined to give rise to NPY/AgRP neurons (yellow) and POMC neurons (magenta); the corresponding receptors are shown by M/W symbols]. (D) The types of neurons generated may vary depending on the metabolic conditions (physiological and pathological cues are represented by yellow, magenta, and blue-green crosses) to reestablish energy homeostasis. (E) Age-related loss of tanycytic processes (as seen in older women); dramatic changes in tanycytic gene expression with age also suggest that tanycytic morphology and/or function may be affected by normal aging or in metabolic or age-related cognitive disorders. (Inset) Detailed view of two types of proliferating tanycytes and the generation of new ARH neurons. Figure not to scale.

niche and the identity of the new neurons (or glia, including tanycytes) generated are adapted to the metabolic context remains to be further studied.

Pathological implications of tanycytic metabolic sensing and regulation

The ability of tanycytes to sense, translate, or transport diverse metabolic hormones and signals to mediate energy homeostasis, while primarily investigated in animal models, also implies that dysfunctions in these mechanisms could be involved in a wide spectrum of human disease processes ranging from metabolic and developmental disorders, to the consequences of hypothalamic inflammation or infection, to normal and pathological brain aging, which all influence or are influenced by metabolic status. While direct evidence for the involvement of tanycytes in the pathogenesis of human metabolic disorders is still woefully inadequate, much indirect evidence and several studies in animal models point to such mechanisms. Conversely, the elucidation of tanycytic mechanisms may lead to the identification of new disorders or breakthroughs in the study of known disorders.

Tanycytes and metabolic dysfunction

Metabolic disorders in humans are often associated with resistance to or CSF deficiency of key metabolic hormones (e.g., leptin, insulin, FGF21). This is in keeping with the wealth of studies in

animal models discussed above which have demonstrated the important role of tanycytes in sensing, transporting, or transmitting peripheral metabolic signals to ARH neurons and more distant regulatory circuits, as well as obesity- or HFD-mediated changes in metabolic sensing, the tanycytic shuttle, the function of hypothalamic–pituitary axes, and tanycytic neurogenesis [1,2,51]. Further emphasizing the potential role of tanycytes in the pathogenesis of metabolic disorders, a recent single-cell transcriptomic study in the hypothalamus of macaques that develop DIO and type 2 diabetes revealed that α and β tanycytes of the infundibulum display among the largest number of pathology-specific changes in gene expression, including those involved in morphological changes linked to their barrier properties and the sensing and transport of metabolic hormones, as well as changes in their connections with hypothalamic neurons regulating metabolism [184]. Which of these changes are causal and which are the consequence of the metabolic imbalance is a valid question. Interestingly, β tanycytes in diabetic macaques may undergo autophagy and apoptosis which further disrupt tanycytic function [184]. Whether similar changes occur in the hypothalamus of human subjects with metabolic disorders is not known.

Tanycytes and age-related or pathological cognitive decline

A recent brain-wide single-cell transcriptomic study in mice indicates that hypothalamic tanycytes, including those of the neurogenic niche, and ARH neuronal populations involved in energy homeostasis, are among the cell types of the brain that display the most striking changes in gene expression during physiological aging [185]. In the hypothalamus of elderly women, the number of tanycytic processes, but not of tanycytic cell bodies, appears to decrease, supporting the loss of some tanycytic functions across the lifespan [186] (Figure 5E). Interestingly, selective blockade of the tanycytic shuttle in adult mice has recently been shown to impair spatial working memory [65]. Together, these observations raise the question of the role of tanycytes in age-related cognitive decline and disorders such as Alzheimer's disease (AD) which are also accompanied by metabolic comorbidities.

Indeed, several metabolic hormones that act through the hypothalamus are perturbed in AD [187], and more continue to be added to the list. Obesity, which disrupts tanycytic leptin transport, is a known risk factor for dementia [188], as is type 2 diabetes and insulin resistance [189], although a recent machine-learning based study of mental health in 20 000 patients with prediabetes and a similar number of control patients suggests that the mechanisms linking these conditions to the two metabolic disorders may diverge [190]. Obesity also disrupts GnRH pulsatility [191], a hallmark of AD, supporting a role for GnRH pulsatile release in cognitive function [192]. Since tanycytes also mediate inflammation-induced anorexia by secreting PGE2 [20], a signal that triggers both tanycytic endfoot retraction and increased GnRH neuron access to pituitary portal vessels [66,193], and astrocyte-mediated GnRH secretion [194,195], obesity or AD-mediated inflammation, by triggering sustained tanycytic retraction, could further deregulate GnRH pulsatility and thus worsen cognitive decline [196]. The deregulated HPG axis, together with the loss of tanycytic processes, would then disrupt estrogen feedback to ARH metabolic regulatory circuits [21]. Tanycytes may also be involved in clearing Tau, and possibly other pathogenic peptides, from the CSF through transcytosis in the reverse direction to that seen for most metabolic hormones, and Tau-containing tanycytes in the infundibulum of patients with AD are fragmented [197]. This observation, the first to directly pinpoint a tanycytic defect in a human disease, potentially provides an additional, neuroanatomical, explanation for both the metabolic dysregulation and altered GnRH pulsatility in AD. Together, these pathological changes would likely set up a vicious cycle of reproductive, metabolic, and cognitive dysfunctions, a triad that is seen especially in postmenopausal women with AD, with tanycytes at its hub. Whether hypothalamic neurogenesis also plays a role in these mechanisms is a good, but so far unanswered, question [198]. Interestingly, SARS-CoV-2 virus, that was responsible for the recent COVID-19

pandemic, appears to be capable of neuroinvasion, and both infects tanycytes and depletes GnRH neurons in patient brains, leading to a dramatic loss of GnRH and a long-lasting disruption of the HPG axis, as well as cognitive impairments seen in men [199,200]. Some of these patients also display changes in body weight, suggestive of altered tanycytic metabolic function. Longitudinal studies of COVID-19 patient cohorts may thus shed further light on the interplay between GnRH neuronal function, cognition, and tanycytic metabolic regulation.

Other pathogenic mechanisms involving tanycytes

The involvement of tanycytic mechanisms or injury in other conditions with a metabolic component deserves further investigation. For instance, GPR50 (Table 1), whose expression in the adult brain is highest in tanycytes, has surprisingly been shown to suppress neurite outgrowth and cell migration both in mouse embryonic neuronal precursors and in postnatal tanycytes *in vitro* [201]. Polymorphisms in *GPR50*, whose ligand remains unknown, have long been identified in patients with obesity as well as in those with neurodevelopmental (autism spectrum disorder) and neuropsychiatric disorders (depression, bipolar disorder, attention-deficit hyperactivity disorder, seasonal affective disorder) [202–206]. The relative contribution to these disorders of a developmental deficit or perturbation of GPR50 versus adult tanycytic expression of the receptor remains to be determined. With regard to tanycytic injury, the expression of tight junction proteins, and thus the organization of the blood–CSF barrier at the ME, is disrupted in tanycytes following cortical injury, leading to delayed pituitary dysfunction [207]. Both mechanical and ischemic injury of the hypothalamus also trigger increased tanycytic proliferation as a compensatory mechanism [160,208].

Concluding remarks and future perspectives

The enormous wealth of information emerging regarding the diverse mechanisms through which tanycytes are involved in detecting, communicating, and controlling metabolic signals and processes, together with their strategic location at the interphase between the brain and the periphery, suggest that these cells play a unique physiological role. Several outstanding questions remain, for instance regarding the number, subtype, specificity or plasticity, and functions of different tanycytic subtypes, as well as the interaction between the various mechanisms described here. The now widespread use of single-cell transcriptomics and other multiomic techniques should help to better define tanycytic subtypes, and investigating disorders of brain metabolic regulation, keeping in mind the putative involvement of tanycytes, may provide novel insights into human physiology and pathology (see Outstanding questions). These insights may also be important from a therapeutic point of view if the tanycytic shuttle can be leveraged to deliver drugs to hypothalamic or more distant circuits, or their feedback mechanisms can be manipulated to correct imbalances in metabolic hormones. The next few decades will hopefully continue to yield fascinating discoveries regarding these 'bloodhounds of the metabolic brain'.

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Declaration of interests

The authors declare no competing interests.

Outstanding questions

Given the plethora of receptors, transporters, and signaling pathways expressed by tanycytes, are tanycytic populations plastic or transcriptionally and functionally distinct?

How does the structural organization of tanycytes, that is essential for their barrier, shuttling, and regulatory properties, accommodate such a large variety of mechanisms?

Could 'tanycytopathies' or tanycytic dysfunctions explain metabolic comorbidities in a variety of disorders involving altered brain function, both non-communicable and infectious?

How does the development, establishment, and aging of the various HPG axes impact on tanycytic function and vice versa?

Given their role as a brain interface, could pharmacological or genetic targeting of tanycytes be a viable therapeutic option for diseases that impact on metabolic function or other physiological processes?

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