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YOUNG INVESTIGATOR PERSPECTIVE

Tanycytes: A Gateway to the Metabolic Hypothalamus

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The central regulation of energy balance relies on the ability of the brain to promptly and efficiently sense variations of metabolic state. To achieve this, circulating hormonal and metabolic signals have to cross the blood–brain interface, where unusual glial cells named tanycytes have been described to play a key role in this process. Tanycytes are specialised polarised ependymoglial cells that line the floor of the third ventricle and send a single process to contact hypothalamic neurones and blood vessels. Although their role in the regulation of energy balance via the modulation of neuronal activity or their chemosensitivity has been already described, recent studies ascribe a new function to tanycytes in the regulation of energy homeostasis as a result of their capacity to regulate the access of metabolic signals to the hypothalamus. This review discusses the peculiar place of tanycytes within the blood–hypothalamus interface, as well as a striking capacity to remodel their own interface to ensure an adaptive metabolic response to energy imbalances.

Key words: blood–hypothalamus interface, arcuate nucleus, metabolic hormones, brain accessibility, brain plasticity, energy balance

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Energy balance and metabolism are carefully regulated by a complex neuronal network connecting the brainstem and the hypothalamus (1). This regulation is based on the central integration and monitoring of peripheral signals circulating in the blood, such as metabolites (glucose, free fatty acids and amino acids) and hormones (mainly leptin, ghrelin and insulin). Produced mainly by the gastrointestinal tract, the pancreas and fat stores, these peripheral signals provide information concerning variations of energy state, and their integration by the brain allows restoration of the energy balance. This integration occurs partly in specific nuclei of the hypothalamus, including the arcuate nucleus (ARC) (2). Two populations of ARC neurones, the anorexigenic neurones, which produce pro-opiomelanocortin (POMC), and orexigenic neurones, which produce neuropeptide Y (NPY) and agouti-related peptide (AgRP), sense circulating signals relevant to metabolic state, and integrate and transmit this information through overlapping projections to other hypothalamic nuclei. The sensing and integration of these signals requires exchanges between the blood and the brain through blood–brain interfaces. At the level of the blood–ARC interface, recent studies have shown that tanycytes, comprising glial cells that have already been described as a component of the hypothalamic neural network controlling energy balance (3), play a crucial role in regulating the access of peripheral metabolic signals to the ARC (4).

This review focuses on the role of these cells as key components of the blood–ARC interface and their participation in energy balance regulation. Tanycytes are useful both to ensure brain homeostasis and to transport metabolic signals into the cerebrospinal fluid (CSF), through which they can be transmitted to the rest of the brain. In addition, tanycytes play a predominant role in the remodelling of their own interface with the blood during an energy imbalance. This plasticity relies on tanycyte/endothelial cell communication, and serves to improve the access of peripheral signals to the ARC to adequately regulate the energy balance. Finally, the review discusses the presence of tanycyte populations with different functions in other brain regions, as well as emerging hypotheses concerning their potential implication in various metabolic disorders, including obesity and diabetes.

The blood–ARC interface: a distinctive organisation as a result of the presence of tanycytes

For the regulation of energy homeostasis, efficient communication between the periphery and the brain, notably the ARC, is necessary. Interestingly, the blood–ARC interface has a unique organisation as a result of the presence of tanycytes (4,5) (Fig. 1). Tanycytes are special polarised ependymoglial cells that line the lateral walls of

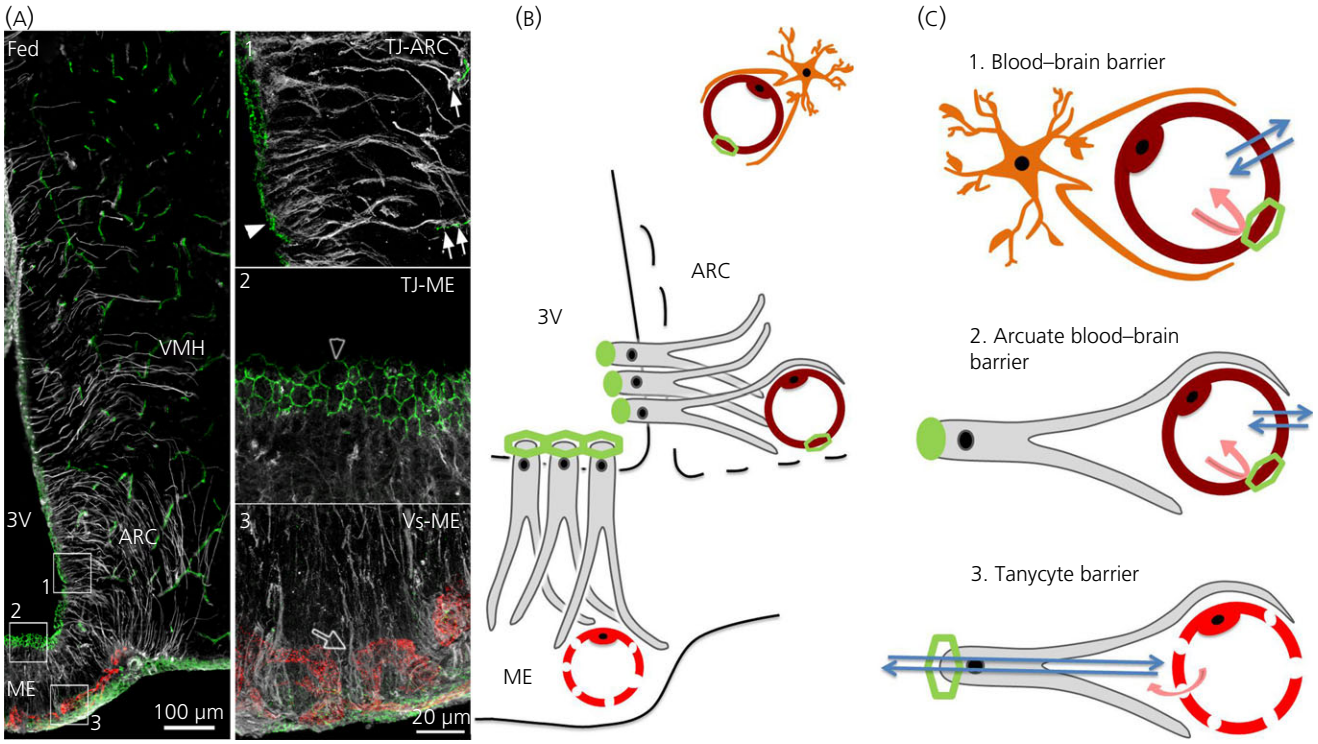

Fig. 1. Organisation of the blood–arcuate nucleus (ARC) interface in the mediobasal hypothalamus. (A) Vimentin (white), zonula occludens-1 (ZO-1; green) and MECA-32 (red) immunoreactivity in coronal sections of the hypothalamic tuberal region in fed animals. Tanycytes exhibit a diffuse pattern of tight junction complexes (arrowheads; inset 1) when interacting with ZO-1-positive blood–brain barrier vessels (arrows; inset 1), whereas they display a honeycomb pattern (empty arrowheads; inset 2) when interacting with MECA-32-positive fenestrated vessels (empty arrows; inset 3). (B) Schematic representation of the hypothalamic tuberal region. (C) Schematic representation of different blood–brain interfaces present in the hypothalamic tuberal region including the blood–brain barrier (1), the blood–ARC barrier (2) and the tanycyte barrier (3). Barrier properties are carried by either endothelial cells (1, 2) or tanycytes (3) to maintain brain homeostasis. Paracellular diffusion cannot take place across these barriers, in contrast to fenestrated vessels (pink arrows); consequently, metabolic signals can only enter the brain by specific transcellular transport (blue arrows). Reprinted with permission from Langlet *et al.* (4). 3V, third ventricle; ME, median eminence; TJ, tight junction; VMH, ventromedial hypothalamus; Vs, vessels.

the infundibular recess and the floor of the third ventricle (6) and play a role in the regulation of numerous physiological functions, such as reproduction (7), energy balance, seasonal adaptations or thermoregulation (3). They are directly in contact with the CSF at their apical surface, and send a single basal process into the brain parenchyma. Tanycytes were first described in the median eminence (ME), a circumventricular organ adjacent to the ARC, where they contact a capillary plexus whose endothelial cells are unique in being fenestrated and highly permeable, allowing the passive and rapid extravasation of bloodborne molecules circulating in the pituitary portal blood (5). Interestingly, we have observed that ME tanycytes, also named β-tanycytes, form a 'tanycyte barrier' by expressing tight junction (TJ) proteins in a continuous belt around their cell bodies (Fig. 1) (4,5). These data demonstrate that, in the ME, barrier properties are delocalised from the vascular wall to the ventricular wall, suggesting that tanycytes ensure brain homeostasis in this 'brain window'. Interestingly, tanycytes also line the ventricular wall of the ARC and send processes that associate closely with blood–brain barrier (BBB) capillaries, whose barrier properties are derived from TJs between their component endothelial cells (5). It has been reported that these ARC tanycytes, which correspond to α-tanycytes, do not possess barrier properties (Fig. 1) (4,5). This phenotypic association between vessels and tanycytes strongly suggests that the organisation of the blood–ARC interface stems from endothelial cell/tanycyte communication. Thus, as a result of their hallmark morphology and localisation at the interface between the blood, the CSF and the metabolic hypothalamus, tanycytes could play a key role in the regulation of blood–ARC exchanges.

Tanycytes as transporters of metabolic hormones

The hallmarks of the blood–ARC interface have prompted a significant amount of interest and debate regarding how circulating metabolic and hormonal signals are able to reach ARC neurones. Based on the presence of microvilli, vesicles and molecules necessary for transcytosis (8), as well as TJ complexes at the apical pole of tanycytes (5), some studies have suggested that these cells, similar to BBB endothelial cells, are capable of transporting macromolecules between the blood and CSF compartments by transcytosis (8). We have confirmed the occurrence of this process in a recent study showing that tanycytes act as a gateway for leptin into the brain (9). Indeed, peripherally administered leptin binds and activates its receptor in ME tanycytes, which internalise, transport and subsequently release it into the CSF by a process requiring tanycytic

extracellular signal-regulated kinase signalling. Once in the CSF, leptin then diffuses into the hypothalamic parenchyma to induce its anorectic effects (9). On a larger scale, tanycyte-transported molecules could be delivered to the rest of the brain through the CSF, as a result of the beating of the cilia of ependymal cells lining the ventricles (10).

Alternatively, some studies have suggested that the fenestrated ME vessels could themselves allow the direct access of signals to the ARC (11). However, the restriction of this capillary fenestration to the ME together with the presence of a barrier composed of ME tanycytes along the ventricular wall suggest the sequestration of these signals within the ME. Indeed, in fed animals, bloodborne molecules are unable to directly reach most ARC neurones (4), which consequently can only sense circulating metabolic signals indirectly, following their active transport through the BBB or the tanycyte barrier (Fig. 1). Nevertheless, we have shown in a recent study that this active but indirect access through the BBB or tanycyte barrier can be replaced by passive but direct access via the 'brain window' during an energy imbalance, through a starvation-induced modification of barrier properties (4). Thus, the hypothesis that fenestrated vessels could allow the free access of metabolic signals to the ARC could also be true, although only under certain conditions.

Regulation of the metabolic hypothalamus by tanycyte barrier plasticity

During an energy imbalance, blood–ARC exchanges are crucial events that allow the restoration of energy homeostasis. We have recently shown that, at the blood–ARC interface, tanycytes are capable of modifying their own barrier properties as described above, leading to the inclusion of the ARC in the 'brain window', initially limited to the ME parenchyma (4) (Fig. 2). After a 24-h fast, a change in the phenotype of pre-existing ME and ARC vessels, namely the appearance of new fenestrations as suggested by the increase in the expression of MECA-32, a fenestral diaphragm protein, leads to an increase in the access of circulating metabolic signals to ARC neurones.

Simultaneous to this vascular plasticity, ME and ARC tanycytes reorganise the TJ proteins at their apical pole, strengthening the tanycyte barrier during fasting (Fig. 2) (4). We hypothesised that this reorganisation could serve to maintain brain homeostasis by preventing the passage of bloodborne substances beyond the ME/ARC (where fenestrated capillaries would allow their free diffusion under fasting conditions) into other brain areas. This hypothesis is reinforced by the timing of fasting-induced ME plasticity: although

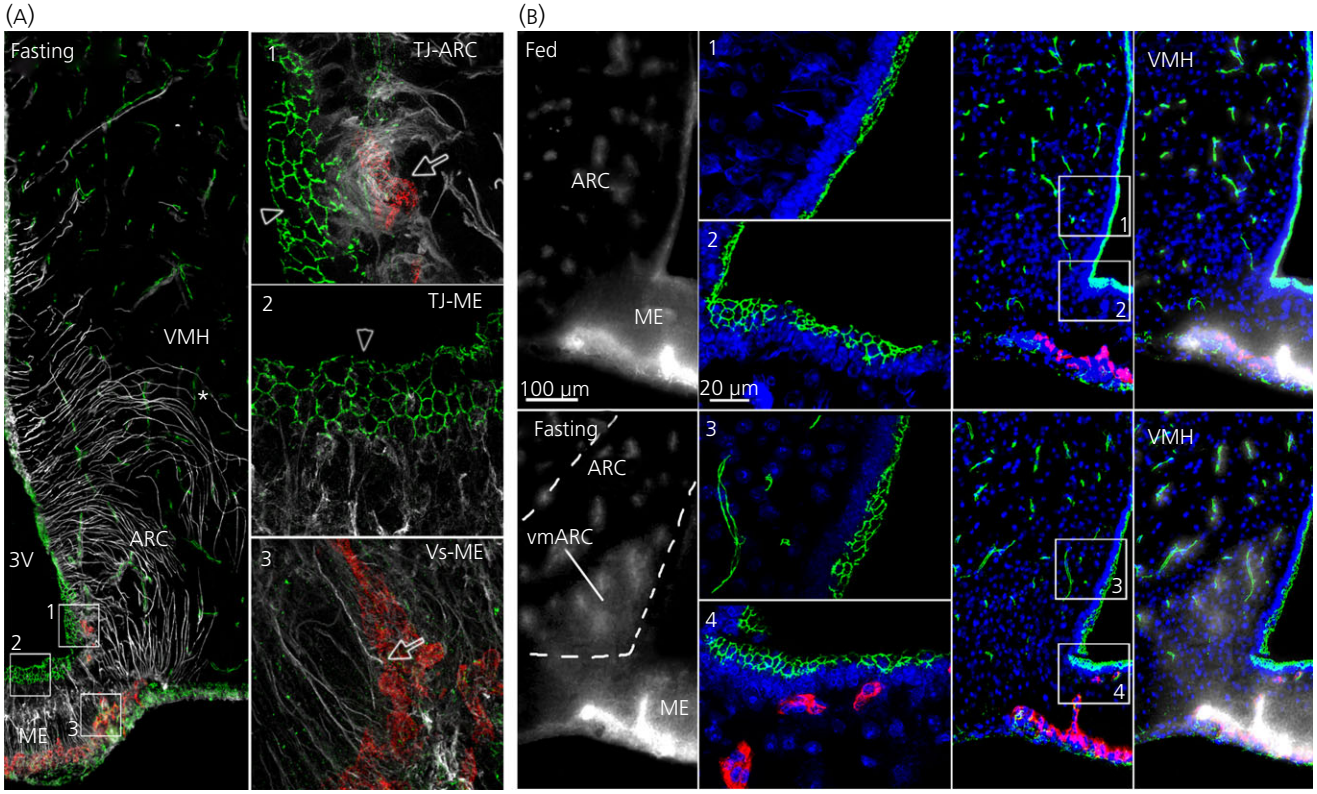

Fig. 2. Plasticity of the blood–arcuate nucleus (ARC) interface and expansion of the 'brain window'. (A) Vimentin (white), zonula occludens-1 (ZO-1; green) and MECA-32 (red) immunoreactivity in coronal sections of the hypothalamic tuberal region in fed animals. During fasting, fenestrated microvessels coming from the median eminence (ME) are observed in the ARC (empty arrows; inset 1) and tight junction complexes are reorganised along the ventricular wall of the ARC (empty arrowheads; inset 1). (B) Evans Blue dye diffusion (grey) and MECA-32 (red) and ZO-1 (green) immunolabelling in the hypothalamic tuberal region in fed and fasting mice. Fasting-induced blood–ARC interface reorganisation is associated with the expansion of the 'brain window' to include the ventromedial ARC (vmARC), making it accessible to bloodborne molecules. Reprinted with permission from Langlet *et al.* (4). 3V, third ventricle; ME, median eminence; TJ, tight junction; VMH, ventromedial hypothalamus; VmARC, ventromedial ARC; Vs, vessels.

vascular plasticity is the first event to occur, as early as 6 h following the initiation of fasting, TJ plasticity appears later (Langlet F., Dehouck B., Prevot V.), suggesting that it is a response to vascular plasticity and serves to confine bloodborne substances to the ME and ARC. Strikingly, the expression and distribution of the transmembrane TJ protein claudin 1 appears to play a key role in TJ plasticity. Indeed, although the TJ proteins occludin and zonula occludens-1 are already present in a diffuse pattern along the ventricular wall lining the ARC under fed conditions (4,5), claudin 1 only appears under fasting conditions (4). Claudin 1 is known to induce the redistribution of TJ proteins within TJ complexes and, consequently, to increase their efficiency (12), and the appearance of this protein along the ARC ventricular wall could be responsible for TJ reorganisation and the plasticity of the tanycyte barrier induced by fasting. Further studies are necessary to determine whether the loss of claudin 1 function could lead to a disruption of the tanycyte barrier and thereby affect neuroendocrine homeostasis.

A consequence of the appearance of newly-fenestrated and permeable capillaries in the ARC combined with the reorganisation of tanycytic TJ complexes sealing the paracellular space between the ARC parenchyma and the CSF is that some ARC neurones are no longer insulated by the BBB and become directly exposed to peripheral metabolic signals (4). This increased accessibility of the ARC to bloodborne molecules during fasting has been observed not only with inert dyes (Fig. 2), but also with metabolic signals such as ghrelin (13), an orexigenic hormone involved in the hyperphagic response during refeeding (14). Moreover, our results also show that fasting-induced tanycyte barrier plasticity enhances the responsiveness of ARC neurones to leptin (4), raising the possibility that the increased access to the ARC induced by tanycyte-endothelial cell reorganisations in the ME is nonspecific and limited only by the size (< 60 kDa) (13) and charge of the molecules crossing the fenestrated endothelium (15). Consequently, in the context of energy balance regulation, we hypothesise that most peripheral metabolic signals, including fasting-induced signals from adipose tissue and the gastrointestinal tract, would be able to reach ARC neurones, accentuating their effects on refeeding and other anabolic processes. Alternatively, we speculate that the reorganisation of the blood–ARC interface could occur in other types of energy imbalance (e.g. following hyperphagia), leading to the increased access of anorectic signals (such as leptin) that are necessary to trigger a suitable response to the imbalance in question. Such a phenomenon could be responsible for the adaptive physiological response, characterised by the diminution of food intake, which takes place 3–5 days after the initiation of a high-fat diet (16).

Glucose as a trigger of tanycyte barrier plasticity

What are the mechanisms underlying this tanycyte barrier plasticity? What nutritional factors trigger these profound morphological changes in fasting mice? In our study, variations in glucose levels were found to be linked to these organisational changes (4). Indeed, the drop of blood glucose levels induced by food deprivation increases the access of metabolic signals to the ARC, whereas the normalisation of glucose levels prevents blood–ARC interface plasticity. Moreover, 2-deoxy-D-glucose (2-DG), a glucose analogue that inhibits glucose metabolism, causes the same pattern of reorganisation of tanycytic TJ complexes and associated fenestrated vessels as those seen in fasting mice. The central detection of glucose level variations thus appears to play a key role in tanycyte barrier reorganisation after fasting.

This detection could be carried out directly by tanycytes. Indeed, an important characteristic of tanycytes with respect to their function of energy balance regulation is their chemosensitivity (3,17). Because their end-feet are in contact with blood, tanycytes are good candidates for sensing variations of metabolic state. In particular, over the last few years, the speculation that these specialised ependymoglial cells could be glucosensors has gained credence with the immunodetection of molecules known to be essential components of glucose metabolism in the pancreatic β-cell paradigm, such as the glucose transporters GLUT1 (18) and GLUT2 (19), glucokinase (20,21) and the K_{ATP} channel subunits SUR Kir6.1 (19,22). The hypothesis that tanycytes are glucosensors has been validated by the recent demonstration that selective glucose puffing onto tanycyte cell bodies induces Ca^{2+} waves in brain slice preparations (23) or in primary cultures of β-tanycytes (24). Interestingly, non-metabolisable glucose analogues such as 2-DG are also capable of evoking these signals in α-tanycytes (23), suggesting that tanycytes do not strictly imitate the β-cell paradigm (3,25).

Although our study shows that glucose level variations play a key role in tanycyte barrier reorganisation during fasting, it only suggests that tanycytes are the cells that detect hypoglycaemia (4). Consequently, it cannot be excluded that other cell types, such as astrocytes, whose population is well developed in the ME (26) and which are known to detect glucose variations (27), could detect hypoglycaemia and then transmit this information to tanycytes. Moreover, because they are in contact with the blood, tanycytes could also sense other signals indicating variations of metabolic state, such as leptin, whose capacity to activate STAT3 in tanycytes has been shown in a recent study from our laboratory (9).

All these findings raise the question: what is the final purpose of tanycyte chemosensitivity? The link between the tanycytic detection of energy state variations and the regulation of energy balance has already been suggested. Indeed, Sanders *et al.* (28) have shown that the i.c.v. injection of alloxan, an inhibitor of glucokinase, destroys tanycytes, leading to a disturbance of food intake behaviour and suggesting that glucose metabolism in tanycytes is very important for the regulation of energy balance. The detection of hypoglycaemia is also linked to changes of gene expression in tanycytes. In our recent study, we have shown that 2DG- or fasting-induced hypoglycaemia induces an increase in vascular endothelrial growth factor (VEGF) expression in tanycytes, thereby triggering blood–ARC interface plasticity (4).

VEGF: the hub of tanycyte/endothelial cell cross-talk

Many growth factors have already been described as being involved in controlling structural plasticity in the brain. In the mediobasal hypothalamus, we have observed that the hypoglycaemia-induced plasticity of the blood–ARC interface is modulated by VEGF, a

growth factor known to induce vascular plasticity (4). Indeed, exogenous VEGF induces capillary changes that mimic those induced by fasting, whereas treatment with VEGF receptor inhibitors such as Axitinib or VEGF receptor (VEGF)R1/2 neutralising antibodies blocks capillary fenestration in fasting animals. Interestingly, using innovative Cre/lox technology, we have demonstrated that tanycytes surrounding the ME and ARC microvessels increase their expression and secretion of VEGF-A during glucopaenia (Fig. 3), resulting in the accumulation of VEGF-A around these vessels and the appearance of new fenestrations via the activation of endothelial VEGFR1/2. In addition, the tanycyte-specific ablation of *vegfa* in adult mice blocks ME plasticity in fasting animals (4). It is now well established that acute hypoglycaemia induces an increase in VEGF levels, by increasing its expression (29), the stabilisation of its RNA (30) and its translation (31,32). Interestingly, although fasting up-regulates VEGF-A mRNA expression in tanycytes, it induces a concomitant increase in the transcript for hypoxia-inducible factor 1α (HIF-1a), known to be involved in hypothalamic glucosensing (33) and to promote VEGF expression (29). HIF-1a could thus be the missing link between hypoglycaemia and VEGF expression in our model. The similar regulation of gene expression in tanycytes according to changes in their environment has also been described in other contexts such as seasonal alterations in daylength and food availability, or torpor (3).

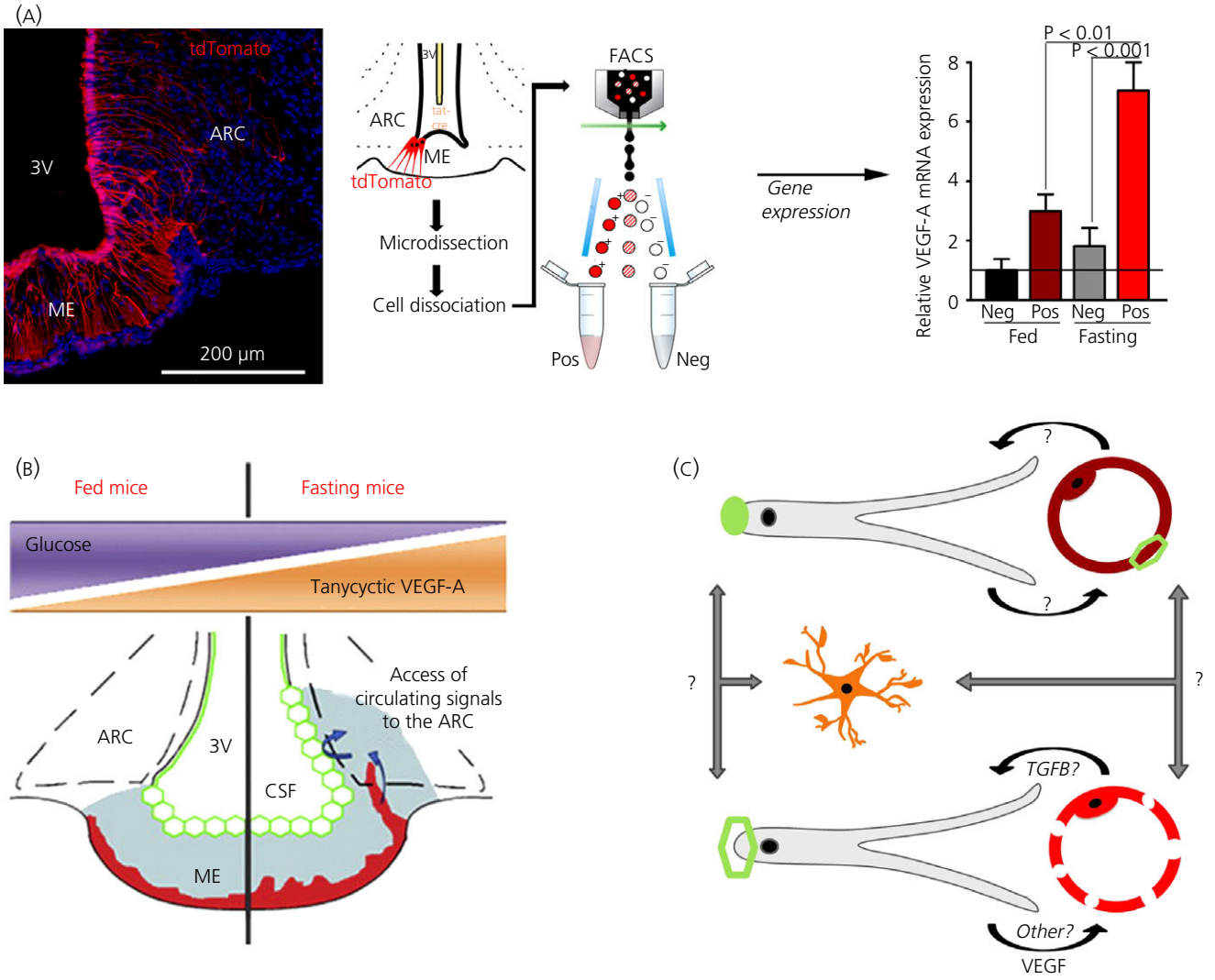

Fig. 3. Blood–arcuate nucleus (ARC) interface plasticity is based on cell–cell communication. (A) Isolation of tdTomato-positive tanycytes by fluorescence activated cell sorting following i.c.v. Tat:Cre injection, and real-time polymerase chain reaction analysis of vascular endothelial growth factor (VEGF)-A mRNA in tdTomato-positive (pos; tanycytes) and -negative cells (neg) in fed and fasting mice. Fasting induces the increase of VEGF expression in tanycytes. (B) Schematic representation of blood–ARC interface reorganisation in fed and fasting mice according to glycaemia, and its effects on the diffusion of bloodborne signals into the brain. (C) Alternative hypotheses concerning cell–cell communications implicated in the organisation of the blood–ARC interface. VEGF secreted by tanycytes induces the fenestration of microvessels contacted by them, although other factors (such as transforming growth factor β) and/or cells (such as astrocytes) could influence the blood–ARC interface plasticity. Reprinted with permission from Langlet *et al.* (4). 3V, third ventricle; CSF, cerebrospinal fluid; FACS, fluorescence activated cell sorting; ME, median eminence; Neg, negative; Pos, positive; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

The plasticity of the tanycyte barrier is based on tanycyte/endothelial cell communication (Fig. 3). In the past two decades, compelling evidence has emerged that cell–cell communication involving tanycytes, astrocytes and endothelial cells plays a key role in ME plasticity (7). In our model, we have described cross-talk between tanycytes and endothelial cells via VEGF secretion. However, other signalling mechanisms that mediate blood–ARC interface plasticity also have to be considered (Fig 3), notably with regard to TJ reorganisation along the ventricular wall. At the blood-ARC interface, tanycytes that contact fenestrated vessels always display a honeycomb pattern of TJ protein organisation, which is responsible for their barrier properties (4,5). We hypothesised that tanycytes could receive information from fenestrated and BBB vessels that dictates whether or not these barrier properties are necessary, through soluble factors such as transforming growth factor β, which is already known to be expressed in the ME (34), implicated in ME plasticity (35) and involved in the establishment of barrier properties (36,37). Finally, possible cross-talk among tanycytes, or between tanycytes and another cell type such as astrocytes, mediated by gap junctions or functional hemichannels (24), could be implicated in ME plasticity.

Tanycytes as modulators of the metabolic hypothalamus

During the last decade, several studies have revealed an unsuspected aspect of tanycyte function: their identity as neural stem cells. Their morphology and lineage, which parallel those of radial glial cells, their peculiar gene expression profile typical of neural stem cell populations, and their capacity to proliferate and differentiate into both neurones and glia, including astrocytes and other tanycytes, are hallmarks of these cells (38,39).

A relationship between this proliferative capacity and energy balance, based on the hypothesis that tanycytes could contribute to the plasticity and remodelling of hypothalamic neural networks controlling energy balance, has been proposed in some studies. The first evidence in favour of a metabolic role for hypothalamic cell proliferation is that newborn cells migrate from the ependymal layer into the hypothalamic parenchyma, and are integrated into hypothalamic neuronal networks via synapse formation (40). These new neurones express neuropeptides involved in energy-balance regulation, such as orexin, POMC, AgRP and NPY, and are responsive to metabolic inputs such as leptin (41,42) or fasting (42). Moreover, the manipulation of hypothalamic neurogenesis has shown that this process plays a critical role in the regulation of food intake and body weight: the specific inhibition of neurogenesis using computed tomography-guided focal irradiation leads to reduced body weight and fat mass in animals fed a high-fat diet by increasing oxygen consumption, energy expenditure and total activity (42). Finally, a promising link between hypothalamic cell proliferation and the control of energy homeostasis has been provided by the recent finding that the neurocytokine ciliary neurotrophic factor (CNTF). Already known to decrease food intake and to cause weight loss via the activation of leptin-like pathways (43), CNTF strongly stimulates neurogenesis in both mice that are normally fed and those with diet-induced obesity, yielding leptin-responsive NPY and POMC neurones (44). Interestingly, in the hypothalamus, CNTF (45) and the CNTF receptor (44) are both observed in tanycytes, and CNTF treatment induces pSTAT3 signalling in these cells (45), suggesting that tanycytes could be involved in CNTF-induced neurogenesis in the adult mouse hypothalamus and its effect on energy balance regulation. Taken together, these data show that modulating hypothalamic neurogenesis could have an impact on feeding and energy metabolism, and vice versa.

Based on these studies, it is tempting to speculate that the plasticity of the blood–ARC interface described in our study could be a result of the proliferative capacity of tanycytes. Although the lack of an increase in the proliferation marker Ki67 in the mediobasal hypothalamus in our animals (Langlet F., Dehouck B., Prevot V.) suggests that this event is likely not linked to cell proliferation, we cannot exclude the possibility that fasting modulates neurogenesis in the hypothalamus, in particular from tanycytic precursors, to allow long-term adaptations to energy imbalances. Indeed, Gouaze *et al.* (16) have reported a transient increase in cell proliferation in the hypothalamus within 3 days of an energy imbalance induced by high-fat diet administration.

Other tanycytes in the brain

Although tanycytes were first described at the level of the ME, we have also observed the presence of tanycyte-like cells in other circumventricular organs (CVOs), atypical brain structures that line the third and fourth ventricles and play a role in regulating body homeostasis based on blood–brain communication (46). As described previously for the ME, the CVOs harbour specialised blood–brain interfaces characterised by a dense capillary plexus with a fenestrated endothelium (11,26) and lacking TJ complexes (26). This peculiar structure allows the two-way exchange of metabolic information: the delivery of neurohormones into the bloodstream by secretory organs such as the ME, and the sensing of bloodborne molecules by neurones located within sensory organs such as the organum vasculosum of the lamina terminalis, the subfornical organ and the area postrema. Interestingly, we have shown that, in these sensory organs, ependymal cells bordering the ventricles possess long processes that project into the brain parenchyma to reach the fenestrated capillary network (26). Remarkably, these tanycyte-like cells also display well-organised TJs around their cell bodies, associated with diffusion barrier properties (26). Moreover, the presence of effective TJs together with neuroanatomical studies showing the presence of microvilli (47), bulbous protrusions at the ependymal surface of the CVOs (48), and vesicles within ependymal cells bordering the CVOs (6,8,49) suggest that, as for ME tanycytes, these tanycyte-like cells could be also capable of transporting macromolecules between the blood and CSF compartments via transcytosis. CVOs are also a site for neurogenesis as a result of the favourable environment for proliferation (42,50,51). This raises several intriguing questions: are tanycyte-like cells a characteristic feature of all CVOs, and are they potentially involved in regulating exchanges between the blood, brain and CSF within these 'brain windows'? Similar to ME tanycytes, are they chemosensitive? What is their role in the control of other physiological functions such as

osmoregulation, for example? Do they also undergo plastic changes in order to increase or decrease the area within the 'brain window'?

Pathological perspectives

Because the hypothalamus plays a role in the regulation of numerous physiological functions, and putative tanycytes are present in other brain regions that regulate their own functions, tanycyte dysfunctions could be implicated in numerous disorders, as we have shown in the case of neuroendocrine perturbations (52). New knowledge of tanycyte functions and their deregulation could allow us to improve our understanding of various metabolic diseases and develop new strategies to counteract the rising global incidence of obesity and related illnesses. These pathologies are often a result of the incapacity of peripheral signals to induce a central neuronal response. One mechanism responsible for this hormone resistance is the alteration of the access of peripheral molecules to the CNS, in particular to the ARC (53), although the status of tanycyte barrier reorganisation and endothelial fenestration under these pathological conditions remains to be explored. Our preliminary results suggest that the tanycyte/endothelial cell interface in the ME is disorganised in mice with diet-induced obesity (Langlet F., Dehouck B., Prevot V.). Even more interestingly, leptin is no longer transported by tanycytes and released into the CSF but accumulates in the ME and, consequently, fails to reach the mediobasal hypothalamus, resulting in leptin resistance (9). What is the cause of this alteration of the blood–ARC interface? Is it a result of the alteration of tanycyte chemosensitivity or/and gene expression? Is there a dysfunction of endothelial cell/tanycyte communication? Could molecules such as VEGF, which control blood–hypothalamus barrier plasticity, hold therapeutic potential for treating dysfunctions of the neuroendocrine control of energy homeostasis in hormone-resistant individuals or in other pathological states involving the ARC? The answers to these and other questions could provide new insight into the mechanisms and treatment of metabolic diseases.

Conclusions

The privileged position of tanycytes between the CSF and the blood allows them to sense the composition of these two physiological liquids, and thus to participate in the regulation of metabolic states. Our recent studies have established a new physiological concept in this regulation by showing that tanycytes, by means of their plastic barrier properties, control the access of metabolic signals to neurones of the hypothalamus. This newly-discovered function of tanycytes as gatekeepers to the metabolic hypothalamus and regulators of the adaptive response to energy imbalances makes these intriguing cells a new and potentially promising target for therapeutic approaches.

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