MINI-REVIEW

Obesity, Diabetes and Energy Homeostasis

What is the physiological role of hypothalamic tanycytes in metabolism?

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Abstract

In vertebrates, the energy balance process is tightly controlled by complex neural circuits that sense metabolic signals and adjust food intake and energy expenditure in line with the physiological requirements of optimal conditions. Within neural networks controlling energy balance, tanycytes are peculiar ependymoglial cells that are nowadays recognized as multifunctional players in the metabolic hypothalamus. However, the physiological function of hypothalamic tanycytes remains unclear, creating a number of ambiguities in the field. Here, we review data accumulated over the years that demonstrate the physiological function of tanycytes in the maintenance of metabolic homeostasis, opening up new research avenues. The presumed involvement of tanycytes in the pathophysiology of metabolic disorders and age-related neurodegenerative diseases will be finally discussed.

energy balance; glia-neuron communication; glucose homeostasis; hypothalamus; tanycyte

INTRODUCTION

Although cells can sense the systemic cues of their immediate environment to maintain energetic and cellular stability, the central nervous system is often considered the conductor orchestrating the metabolic response necessary to maintain the balance between energy intake and expenditure (1, 2). Distinct neural cell populations, including neurons and glia present in the hypothalamus and the brainstem, are interconnected in elaborate and dynamic networks that ensure the maintenance of energy balance (3, 4). These cells integrate a range of metabolic information through humoral, hormonal, and nervous signals to modulate different aspects of metabolism and behavior, such as food intake, thermoregulation, metabolism, physical activity, insulin and glucagon secretion, hepatic glucose production, and glucose/fatty acid metabolism in adipose tissue and skeletal muscle (5, 6). A coordinated dialogue between the brain and periphery is, therefore, required for the system to work properly.

Among the cells involved in the regulation of energy balance and glucose homeostasis, tanycytes have begun to attract considerable attention (7–10). Hypothalamic tanycytes are elongated glial cells lining the walls and floor of the third ventricle (11, 12). Their cell bodies form the ventricular layer, and their processes extend into the hypothalamic parenchyma to connect with neurons, glial cells, and vessels located in key metabolic centers, including the arcuate nucleus (ARH), the ventromedial nucleus (VMH), and the dorsomedial nucleus (DMH) (Fig. 1) (13, 14). In addition, tanycytes present a diverse and dynamic gene expression profile allowing them to display multiple functions, ranging from neural stem cells to neuronal modulators (10), and to adapt these functions to the physiological state to ensure metabolic homeostasis (15). Its peculiar biology along with its key position within the hypothalamus has earned the tanycyte the label of “metabolic integrator” with its three-way exchange interface (10): tanycytes are potentially able to receive metabolic information from the cerebrospinal fluid (CSF) and the blood, to then modulate neural responses and ensure physiological changes in energy balance.

Different models are currently available to study how tanycytes impact body weight and glucose homeostasis. One of them is the use of pharmacological agents and/or specific genetic manipulations. These models allow us to modulate tanycyte functions and measure the physiological consequences for energy balance (16, 17). Seasonal animals also constitute a powerful model to study tanycyte functions (18, 19). Indeed, these animals, including hamsters, sheep, F344 rats, and birds, naturally integrate the light/dark cycle throughout the year to adapt their physiology to ensure optimal long-term control of energy and, subsequently, to maximize reproduction. Over a long photoperiod (i.e., spring and summer), animals increase their food intake and body weight with maximum anabolism, whereas during a short photoperiod (i.e., autumn and winter), these individuals decrease their food intake and body weight, catabolizing their energy stores. These seasonal variations in the light/dark cycles encoded by
melatonin are integrated by tanycytes through the detection of the β subunit of the thyroid-stimulating hormone (βTSH) (20, 21) secreted from the pars tuberalis. Thus, tanycytes are considered the gateway to the brain for photoperiodic information.

However, the global physiological function of hypothalamic tanycytes identified through these different models remains unclear, as different studies have led to contradictory effects. This review will summarize what we know so far about the role played by tanycytes in metabolic physiology while illuminating possible avenues for future research. The different studies related to the tanycyte's physiological functions will be compared while keeping in mind the glial nature of these cells. Finally, the putative link between alterations in tanycyte function and the development of metabolic diseases will be discussed.

**TANCYTES REGULATE FOOD INTAKE**

“Tanycyte ablation” studies were initially used by different groups to evaluate the global impact of tanycytes on food intake. Sanders et al. (17) reported that the suppression of the tanycyte layer following alloxan injection induces hyperphagia during refeeding in response to an overnight fast. More recently, hyperphagia was also reported in mice in which median eminence (ME) and ARH tanycytes were conditionally ablated through tamoxifen treatment (22). In this study, male mice displayed, after 8 wk of treatment, an increase in food intake, particularly in response to food deprivation, associated with fat mass accumulation (22). Whereas these two studies suggest a global anorexigenic role for tanycytes, others using genetic manipulations revealed that the tanycyte impact on food intake is subtler. Indeed, the alteration of tanycyte glucose metabolism through the deletion of monocarboxylate transporter 1 (MCT1), glucose transporter 2 (GLUT2), or glucokinase (GCK) in the tanycyte layer also resulted in hyperphagia during refeeding (16, 23, 24), whereas an alteration in tanycyte mitochondrial machinery through the deletion of Tspo decreased food intake in high-fat diet conditions (25). Recently, Bolborea et al. (26) also showed using an optogenetic approach that tanycyte activation acutely increases food intake.

The mechanisms underlying these physiological effects mainly rely on modulation of hypothalamic neurons (Fig. 2), in particular NPY/AgRP and POMC/CART neurons, by
Increasing or decreasing neuropeptide gene expression (16, 17, 23–25), by regulating neuronal cell signaling (27, 28), and/or by altering membrane potential (26). This neuronal modulation by tanycytes occurs in indirect and direct ways. First, tanycytes constitute the blood-brain interface in the basal hypothalamus, which controls the access of nutrients and hormones to hypothalamic neurons (27, 29–31). During fasting, the tanycyte interface is reshaped to improve the access of metabolic signals to the ARH and to induce meal initiation (30). This reorganization could be induced by tanycytes themselves through metabolic sensing (30) as well as by neurons (32). Second, tanycytes are also able to modulate neuronal functions by releasing both orexigenic and anorexigenic molecules, what we will call “tanykines,” into the hypothalamic parenchyma such as diazepam-binding inhibitor (DBI) (33, 34), purines (26, 28, 35, 36), triiodothyronine (T3) (37), chemerin (38), and prostaglandin E2 (PGE2) (39) (Fig. 2).

To date, the mechanisms underlying the local action of tanykines on hypothalamic neurons remain poorly understood. The diazepam-binding inhibitor (DBI) mainly acts through the melanocortin pathway: DBI increases the firing rate of POMC neurons through a GABA-independent pathway (40, 41), and the pharmacological blockade of the MC4R blocks its anorexigenic effects (34).

Extracellular purines, especially ATP, have also been said to act on feeding neurons, such as NPY and POMC neurons. Purinergic receptors such as P2X4 are expressed by NPY neurons, and their activation increases spontaneous GABA release on anorexigenic POMC neurons (42). Nutrients are able to induce ATP release by tanycytes within the hypothalamus (35, 43, 44), resulting in the depolarization of both POMC and NPY neurons (26). P2 receptor antagonists completely abolish this depolarization, suggesting that tanyctic ATP mediates presynaptic inputs on both NPY and POMC neurons (26). Interestingly, in vivo induction of tanyctic ATP release by a short optostimulation induces acute hyperphagia, demonstrating that the balance between NPY and POMC neuron activation shifts toward the orexigenic pathway in these experimental conditions. Furthermore, tanycytes express ecto-ATPase NTDDase2 that allows for the conversion of ATP into adenosine (45), which could then mediate NPY neuron inactivation through adenosine A1 receptors (46). More studies are still needed to determine how the tanyctic purinergic signal is decoded by the different ARH neuronal populations.

Triiodothyronine (T3), of which hypothalamic levels are regulated by the deiodinase 2/deiodinase 3 balance in tanycytes in seasonal animals, is able to regulate mitochondrial proliferation in NPY/AgRP neurons and to increase the

**Figure 2.** Tanycytes are modulators of energy balance. By interacting with both neurons and vessels—locally in the mediobasal hypothalamus and globally through the cerebrospinal fluid—tanycytes modulate both orexigenic and anorexigenic pathways and participate in the regulation of glucose homeostasis and energy balance. This neuronal modulation by tanycytes occurs through indirect (i.e., regulation of blood/brain exchanges) and direct (i.e., secretion of tanykines) pathways. DBI, diazepam-binding inhibitor; NPY, neuropeptide Y; PGE2, prostaglandin E2; POMC, proopiomelanocortin; PVN, paraventricular nucleus; T3, triiodothyronine; 3v, third ventricle.
excitability of these neurons in C57Bl/6 (37). The physiological consequences of the T3 tanyctic release after severe fasting (24-h) is thus a faster refeeding. A large panel of genes have also been described to be transcriptionally regulated by T3, which has been extensively reviewed (47), but no clear physiological functionality has emerged so far. Another possible route of action for hypothalamic T3 in energy balance could be via the thyrotropin-releasing hormone (TRH) neurons located in the paraventricular nucleus (PVN). Their terminals end in close relationship with tanyctye endfeet, which control both TRH neurosecretion and the negative feedback of this axis (48, 49). However, this neuroendocrine loop in the thyroid hormone axis was found to be completely insensitive to photoperiodic alterations in Siberian hamsters or F344 rats, suggesting the independence of these two systems (50). Finally, the last possible route for hypothalamic T3 action is through the retinoic acid pathway (51). T3 administration increases the expression of Raldh1 enzyme (retinaldehyde dehydrogenase 1) in tanyctyes (52). Interestingly, this retinoic acid pathway is known to increase Agrp and Pomec gene expression ex vivo in hypothalamic explants (53).

As described above, tanykines released by tanyctyes are both orexigenic and anorexigenic. This dual action is well illustrated by the role of chemerin or retinoic acid receptor responder protein 2 (Rarrres2) (38). This inflammatory signal is highly expressed in tanyctyes and controlled by the βTSH signal. Its role is highly complex, as it would act on tanyctyes and ependymal cells themselves and may have both orexigenic and orexigenic effects according to the chronicity of its injection and to the photoperiod (38). Indeed, intracerebroventricular injections of chemerin in F344 rats during a short photoperiod induce an increase in food intake without affecting the reproductive state (38). Interestingly, similar injections in rats during a long photoperiod induce a bodyweight redistribution along with a decrease in food intake and an increase in thermogenesis (38). Similarly, acute chemerin injections during a short photoperiod produce a short-term reduction in Pomc and Agrp gene expression, whereas chronic injections sustainably increase Pomc gene expression (38), supporting the hypothesis that tanyctyes are able to modulate both orexigenic and anorexigenic pathways (26).

Therefore, the multiple and opposing effects of hypothalamic tanyctyes on mice physiology make their classification as a stimulator or inhibitor of food intake somewhat difficult. These opposing effects rely on the glial nature of these cells, which display multiple and adaptive metabolic functions (10, 15), and integrate both orexigenic and anorexigenic neural circuits (14, 26). Considering tanyctyes as modulators rather than regulators of food intake will advance our understanding of their physiological functions. It is, therefore, crucial to decipher how tanyctyes specifically communicate with orexigenic versus anorexigenic neural populations, as well as systematically consider the physiological state of the individual (e.g., circadian rhythm, catabolic/anabolic state).

TANYCYTES REGULATE ENERGY EXPENDITURE

Based on the laws of thermodynamics, an equilibrium between energy intake and expenditure is required to regulate body weight. The brain is able to modulate the three main processes that dissipate energy, which are locomotor activity, fatty acid oxidation, and thermogenesis (6). Unfortunately, energy expenditure has not been systematically analyzed in research focusing on tanyctye biology, but a few studies have documented this matter recently.

Yoo et al. (22) noted that, in their tanyctye ablation model, visceral white fat accumulation occurs in the early phase, before the appearance of hyperphagia, suggesting an initial impact on energy expenditure. However, although the respiratory exchange ratio (RER; i.e., decrease in fatty acid oxidation) increases at thermoneutrality in this model, no change in energy expenditure has been observed (22). In contrast, tanyctye-specific ablation of Tspos stimulates energy expenditure in high-fat-diet mice (25). In this particular case, body temperature was increased (without affecting locomotion), resulting in increased energy expenditure via an AMPK-dependent lipophagy of lipid droplets in tanyctyes, permitting an elevation of ATP release (25). Recently, Geller et al. (54) showed that tanyctyes secrete Fgf21. Although the central effect of FGF21 is to increase energy expenditure (55), its deletion in tanyctyes alters lipid sensing and induces an increase in O2 consumption and energy expenditure during the active/dark phase (54). This increase results from extensive fatty acid oxidation in subcutaneous white adipose tissue, alongside unchanged locomotor activity (54). Tanyctic Fgf21 deletion would, therefore, promote lipid mobilization and browning, resulting in an increase in energy expenditure and a decrease in fat accumulation (54). Interestingly, the decrease in fat accumulation in this model occurs without affecting food intake (54), suggesting that tanyctyes regulate the specific energy expenditure of regulatory neural networks. Mechanistically, Geller et al. (54) proposed regulation through paracrine action on hypothalamic neurons. Indeed, alteration of tanyctye lipid sensing through Fgf21 deletion increases Avp, Ghrh, and Trh expression in the hypothalamus (54). These neuropeptides are known to be involved in the regulation of cellular metabolism, energy expenditure, and lipid utilization through hypothalamic-pituitary axes and the sympathetic nervous system. However, other pathways are not excluded, as an anatomical link between dorsal-medial ARH neurons, and white adipose tissue has been described in the Siberian hamster (56, 57). This pathway would be directly controlled by histamine levels in summer conditions (i.e., anabolic state) (56, 57).

In seasonal animals, environmental challenges (seasons or exceptional harsh conditions) can induce an adaptive physiological response called torpor (short/daily) or hibernation (long periods) to limit energy expenditure. Torpor is characterized by a reduction in body temperature rheostat close to ambient values, thus decreased physiological activity (hypoxia, hypoglycemia, cardiac functions alteration) and metabolic rate. Although this state can be naturally observed in adaptive responses to photoperiodic changes, it can also be induced by fasting, caloric restriction, or acute cold exposure in mammals. GPR50 is an orphan G protein-coupled receptor (homolog to melanin receptors but unable to bind this hormone), expressed in many parts of the hypothalamus and, in particular, in the tanyctic layer (58, 59), that has been shown to play a role in torpor. In the Siberian hamster, which uses daily torpor as an adaptive response to winter
conditions, GPR50 gene expression decreases in tanycytes during a short photoperiod (60–62). GPR50 null mice are resistant to diet-induced obesity and are less sensitive to weight loss during fasting challenges. In these animals, during the active/dark phase, body temperature is lower with an increased locomotor activity compared with that seen in wild-type mice (63, 64). Not surprisingly, when fasted, these animals experience severe hypometabolism (low circulating glucose, etc.) and rapidly enter a torpor state (63). These mice also lack thyroid hormone availability in the hypothalamus (63). Furthermore, GRP50 in the hypothalamus is fundamental to leptin signaling and energy expenditure through thermogenesis (63). Finally, microarray analysis by Hand et al. (65) pinpointed an unexplored route downstream the GRP50 pathway through thioredoxin-interacting protein (TXNIP). Indeed, TXNIP is tightly linked to the cellular redox balance and is key in β-pancreatic cells, acting as an energy sensor (66). Interestingly, Tnixip is enriched in tanycytes, and its expression is upregulated in GRP50 null mice, in seasonal torpor in the Siberian hamster, and in fasting- and cold-induced torpor (65). TXNIP null mice lost their ability to enter torpor under harsh conditions (65), suggesting a role in the reduction of energy expenditure to sustain hypothemic and hypometabolism, conditions that are not well tolerated by animals, potentially resulting in death if prolonged (67, 68).

Concerning fasting-induced torpor, several mechanisms have also been postulated. A current hypothesis suggests that the concomitance of circulating levels of feeding hormones such as leptin and the depletion of central energy stores are key in the process (69). Indeed, high levels of leptin are able to block torpor in the Siberian hamster despite low GRP50 expression, and obese ob/ob mice are more likely to show torpor episodes despite increased adipose tissue (69, 70). Similarly, ghrelin deepens torpor episodes via NPY neurons in mice, although ghrelin levels are unchanged in photoperiodic Siberian hamsters (71). As tanycytes are considered hypothalamic gatekeepers for hormonal access to the brain (9), their role in fast-induced torpor should be studied further.

**TANYCYTES REGULATE GLUCOSE HOMEOSTASIS**

Glucose homeostasis is regulated primarily through peripheral cross talk between the pancreas and its effectors such as the liver, the adipose tissue, the muscles, and the kidneys. The brain is also able to regulate general glycaemia through the hypothalamic-pituitary axis and the autonomic nervous system by fine-tuning pancreatic insulin/glucagon secretion, hepatic glucose production, and skeletal muscle glucose uptake. The hypothesis that tanycytes are involved in the regulation of glucose homeostasis is based on their glucose-sensing function. However, their physiological functions in peripheral metabolic organs remain sparsely studied.

The first study to report a role for tanycytes in glucose homeostasis relied on the central injection of alloxan, a pharmacological inhibitor of glucokinase activity in rats (17). The drug injection in the third ventricle led to the destruction of α and β1 tanycytes associated with an impairment in glucose counterregulation (17). This phenotype is associated with an alteration in Npy expression, known to be involved in counterregulatory responses (72, 73), and reversed with the restoration of the tanycyte layer (17). In addition, alloxan-injected rats also display higher fasting glycemia (17). This last phenotype was also reported more recently by Geller et al. (54) in mice where tanycyte lipid sensing was altered by Fgfl21 ablation. These mice also displayed higher blood glucose levels after intraperitoneal injection of pyruvate (PTT) or glucose (GTT) tolerance tests, suggesting an impact on liver metabolism through a higher capacity to produce glucose and/or difficulty in regulating glycemia (54). Finally, tanycytes may also modulate insulin sensitivity; indeed, the ablation of ME and ARH tanycytes using tamoxifen injections in Rax-CreERT2 mice induces an alteration in insulin sensitivity (22).

One potential mechanism to regulate glucose homeostasis would be through FGF receptors, key receptors in central metabolism control. Indeed, tanycytes express FGFR1 and FGFR2 III c isoforms, especially in β tanycytes (74), and plasma- and cerebrospinal fluid-derived FGFs have a direct action on these cells (75). Interestingly, FGFs levels increase in the cerebrospinal fluid after a meal or after a peripheral injection of glucose (76, 77). It has been reported that central administration of FGF1 can lower circulating glucose and even induce diabetes remission in diabetic mice and rats independently of body weight loss (78). Interestingly, central FGF1 administration induces a robust pERK activation and c-Fos expression in tanycytes (78, 79), suggesting a functional link between tanycytes and diabetes remission induced by FGF1. Furthermore, antibody-mediated inhibition of FGFR1 also induces reversible weight loss due to a decrease in food intake and fat deposition, and thus improved glucose control in rodents, Siberian hamsters, and monkeys (80–82). These metabolic effects would also apply to tanycyte functions (80–82), showing the ambivalent effect of the FGF-tanycyte pathway.

**THE POTENTIAL ROLE OF TANYCYTES IN METABOLIC DISEASES AND THERAPEUTIC PERSPECTIVES**

Obesity and diabetes result from a combination of genetic and environmental factors that interact and/or correlate with each other leading to a chronic homeostasis imbalance. Tanyctes are increasingly described as putative players in the pathophysiology of these diseases and, consequently, as putative targets for new treatments. Tanycytes, identified by single-cell RNAseq among ARH-ME cell populations, notably display significant enrichment in genes related to the waist-hip ratio (WHR), an indicator of fat distribution and associated health issues such as heart disease and type 2 diabetes (83).

Among the different aberrant brain functions affecting obesity progression, the brain’s impaired ability to sense and respond to variations in energy homeostasis, commonly named hormonoresistance, remains the most convincing argument in the pathophysiology of obesity. This resistance to metabolic hormones progressively appears during the development of obesity through an alteration of hormonal
transport into the brain, followed by a central impairment in the hormonal signaling pathway (84). As tanycytes are able to both transport and sense metabolic signals, their impairment in obesity development has drawn attention. Notably, Balland et al. (27) showed that the deficiency in ERK-dependent leptin transport through tanycytes is involved in the pathophysiology of central leptin resistance. Interestingly, leptin fails to activate STAT3 signaling in tanycytes and remains stuck in the ME after an 8-wk high-fat diet (27), suggesting that tanycytes are the first neural cells to become leptin resistant. The restoration of ERK signaling in tanycytes through EGF treatment in obese mice restores leptin release in the mediobasal hypothalamus and promotes a rapid loss of body weight when switched to a standard chow diet (27).

As metabolic signals impact the development of hypothalamic feeding circuits, the alteration of hormonal levels induced by malnutrition during the perinatal period also plays a role in the onset of metabolic disorders later in life (85, 86). In this context, an alteration in hormonal transport by tanycytes could be associated with an impairment in the development of feeding circuits and, thus, the predisposition to metabolic diseases. Indeed, it has been shown that postnatal overnutrition in mice causes an early central resistance to ghrelin, a key hormone in hypothalamic circuit development (87), due to an impairment of its transport into the mediobasal hypothalamus (29). Further studies are, however, required to determine if this alteration in tanycyte function during the perinatal period plays a role in the pathophysiology of metabolic disorders.

Hypothalamic neural circuits are continuously remodeled to adapt appropriately to the metabolic state of the individual and ensure the maintenance of energy homeostasis. A defect in this adaptation alters the brain's ability to match eating behavior to energy expenditure, leading to metabolic disorders. One way to control brain circuit plasticity in adulthood is through neurogenesis (88). The role of tanycytes as hypothalamic neural stem cells able to generate both neuronal and glial cells that incorporate into hypothalamic circuits and respond to metabolic signals (89, 90) has been studied by several groups, also considering potential alterations in metabolic disorders. In the mediobasal hypothalamus, a high-fat diet inhibits neurogenesis, increases apoptosis of newborn neurons, and, thus, decreases hypothalamic neuronal turnover rates (91, 92), leading to weight gain. This diet-induced alteration seems to be due to leptin resistance (92) and/or hypothalamic inflammation (91). In contrast, a high-fat diet increases neurogenesis in the ME, especially in females (93–95). Interestingly, the inhibition of this neurogenesis using computed tomography-guided focal irradiation reduces body weight and fat mass by increasing oxygen consumption, energy expenditure, and locomotor activity (94). These results support the idea that ME neurogenesis during a high-fat diet exacerbates weight gain. In addition, the authors also showed that caloric restriction is associated with reduced proliferation in the ME (95). These contradictory data may result from diverse neural cell populations, highlighting the necessity for the use of new strategies to assess the role of selected hypothalamic progenitor cell populations, in particular tanycyte-derived neurogenesis.

Another way to remodel neural circuits relies on synaptic remodeling (96). Although the involvement of tanycytes in this process remains to be proved, this function is suggested by recent observations of close associations between tanycyte endfeet/swelling and synapses in the hypthalamic parenchyma (14) as well as the electrical activation of hypothalamic neurons (26).

The seasonal models are considered by many as perfect models (ethically and pecuniary) to study “obesogenic and anorexic” factors within a single animal, as physiological changes due to photoperiodic changes induce significant changes in body weight and food intake (97). Although pathological situations are far from these natural phenomena, they can partially recapitulate the molecular and cellular mechanisms involved. From this perspective, seasonal animals could bring us new information about tanycyte-dependent neuronal plasticity for the control of body weight and the pathophysiology of obesity. Indeed, a new theory has emerged in recent years involving neurogenesis and synaptic remodeling throughout the normal cycle of seasons and their effect on physiological functions, such as body weight variations. The histogenesis hypothesis proposed by Hazlerigg and Lincoln (98) supports the idea that reversible changes can be induced by seasons in the hypothalamus, and especially the apoptosis/neurodegeneration of feeding neurons (AgRP/NPY—POMC) during the nonbreeding season and consequently inducing the winter “lean” state. Tanycytes as a neurogenesis niche of the region slowly generate new neurons to replace the dead ones for the reproductive/“obese” state. This natural cycle of connections and disconnections of neurons within feeding centers permits the natural changes in body weight, food intake, and energy balance observed in seasonal animals (38, 98). Although this hypothesis is elegant, more experimental proofs will need to be built to demonstrate it, such as tanycyte manipulations in these models.

As tanycytes are glucose-sensing cells, they are also considered critical players in the pathogenesis of type 2 diabetes. Indeed, tanycytes express several molecules known to be essential for glucose metabolism such as GLUT2 (16) and glucokinase enzyme (24). Furthermore, tanycytes are able to initiate a calcic wave through taste receptors in response to glucose analogs (35, 99). The first association between diabetes and tanycytes dates back to the 1980s when Bestetti and Rossi (100) showed that peripheral injections of streptozotocin, a toxic agent for glucose-sensing β cells leading to diabetes, induce profound alterations in tanycyte morphology. Using light and electron microscopics, the authors described degenerative changes in the ventromedial ARH and the ME. Tanycytes are described as hypotrophic, with a reduced basal cytoplasmic process and a smooth apical surface (100). A comparable event was observed following alloxan (i.e., another killer of the insulin-producing β cells) injection in the third ventricle. The degradation of the tanycyte layer resulted in an alteration in the glucose counterregulatory response and hyperphagia (17). Finally, as described previously, activation of ERK signaling in tanycytes has been associated with diabetes remission induced by central administration FGF1 (20, 81). Further mechanistical studies are, however, required to link tanycytes and diabetes.
Besides obesity and diabetes, tanycytes have been recently described as putative players in the pathophysiology of inflammation-associated anorexia (39). Systemic infusion of inflammatory mediator IL-1β activates NF-κB signaling in tanycytes, resulting in an increase in cyclooxygenase-2 (Cox-2) and the release of the anorexigenic PGE2 (39). In contrast, the inhibition of NF-κB signaling through Nemo deletion in tanycytes reduces IL-1β-induced anorexia (39), showing that tanycytes would mediate the anorexic effect of systemic inflammation in the hypothalamus.

Tanycytes are nowadays recognized as potential targets in therapeutics for obesity and metabolic-related diseases, and future works plan to optimize their targeting (101). This interest first relies on the fact that the reactivation of tanocyte functions in pathological conditions, in particular the reactivation of ERK signaling (27, 79), improves the physiological state of the individual. Moreover, although tanycytes’ strength lies in their special anatomical position, this advantage also presents an Achilles’ heel. Indeed, their position at the interface between the blood and the brain makes them easier targets for pharmacological molecules without crossing the blood-brain barrier. Much work must be done in advancing specific tanocyte-drug discovery programs. However, to develop efficient drugs for metabolic diseases, some critical points should not be overlooked. First, tanycytes form a heterogeneous cell population composed of different subgroups with different locations and functions (15): optimizing our targeting strategies will significantly improve our knowledge about the role of specific tanocyte subgroups and, consequently, improve treatment efficiency. Second, as tanycytes interact with and modulate numerous partners that have various and opposite functions, tanycytes should not be considered as an entity per se but as a component of the network: to decipher tanocyte position within this network is, therefore, crucial. Finally, tanocyte functions are highly plastic, in particular, according to the physiological state of the individual or time of day. The window of opportunity is, therefore, crucial in tanocyte biology, making the condition and the timing of drug administration essential to improving its efficiency.

**PERSPECTIVES AND SIGNIFICANCE**

Tanycytes are clearly involved in the regulation of energy balance and glucose homeostasis through the interactions with key hypothalamic neuronal populations, in particular NPY and POMC neurons. Although the molecular mechanisms underlying these interactions are yet to be understood, their physiological consequences are multiple and may generate a negative or positive balance, prompting us to consider tanycytes as modulators rather than regulators of energy balance. In addition, tanycytes certainly play a role in the pathophysiology of metabolic diseases, making them promising therapeutic targets.

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**AUTHOR CONTRIBUTIONS**

F.L. drafted manuscript; M.B. and F.L. edited and revised manuscript; M.B. and F.L. approved final version of manuscript.

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