Molecular and Cellular Endocrinology 445 (2017) 7–13

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Pivotal role of median eminence tanycytes for hypothalamic function and neurogenesis

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ARTICLE INFO

Article history:
Received 30 June 2016
Accepted 11 August 2016
Available online 13 August 2016

Keywords:
Median eminence
Tanycyte
Neurogenesis

ABSTRACT

Along with the sub-ventricular zone of the forebrain lateral ventricles and the sub-granular zone of the dentate gyrus in the hippocampus, the hypothalamus has recently emerged as a third gliogenic and neurogenic niche in the central nervous system. The hypothalamus is the main regulator of body homeostasis because it centralizes peripheral information to regulate crucial physiological functions through the pituitary gland and the autonomic nervous system. Its ability to sense signals originating outside the brain relies on its exposure to blood-born molecules through the median eminence, which is localized outside the blood brain barrier. Within the hypothalamus, a population of specialized radial glial cells, the tanycytes, control exposure to blood-born signals by acting both as sensors and regulators of the hypothalamic input and output. In addition, lineage-tracing experiments have recently revealed that tanycytes represent a population of hypothalamic stem cells, defining them as a pivotal cell type within the hypothalamus. Hypothalamic neurogenesis has moreover been shown to have an important role in feeding control and energy metabolism, which challenges previous knowledge and offers new therapeutic options.

1. Introduction

The neuronal and gliogenic cell types of the mammalian central nervous system (CNS) are essentially generated during embryonic development, but new cells also emerge post-natally both in normal and pathological situations. These encompass cell turnover for specific neuronal populations, such as olfactory bulb neurons, and, to some degree, regeneration in response to injury. Adult-born cells are also thought to underlay aspects of brain plasticity. At least some of these new cells differentiate from neural stem cells (NSCs) found in restricted microenvironments, defined as niches, where their maintenance, proliferative and differentiation potential are tightly controlled (Dimou and Gotz, 2014). The two main niches in the mammalian brain are located in the sub-ventricular zone (SVZ) of the forebrain lateral ventricles and in the sub-granular zone (SGZ) of the dentate gyrus of the hippocampus. In these two regions extensive studies have described the components and architecture of the niche. NSCs of the SVZ and SGZ are astroglial. They are mostly quiescent, while immediate progenitors, or transit-amplifying cells, are committed toward differentiation and possess a higher proliferative potential. Within the niche, interactions with neighbouring cells are important, but signals from the periphery are also sensed by NSCs as they are in direct contact with capillaries and, for SVZ NSCs, also with the cerebro-spinal fluid (CSF). In rodents and non-human primates, NSCs give rise to neurons, astrocytes and oligodendrocytes. In the SVZ of rodents and many other mammals the NSCs give rise to neuroblasts that form a rostral migratory stream (RMS) to give rise to olfactory bulb neurons. In humans, however, the adult SVZ generates mostly striatal interneurons. These therefore have a different identity compared to other mammals and they are hypothesized to underlay specific aspects of human neural plasticity (Ernst et al., 2014). In the hippocampus, many more neurons are generated than survive, but those that do integrate into existing circuits locally. Evidence suggests that neurogenesis in the dentate gyrus is important for certain types of learning and memory. The rates of neurogenesis in the dentate gyrus of human and rodents are comparable, but cell turnover appears more extensive in humans (Spalding et al., 2013).

Aside from these two regions, the hypothalamus has recently emerged as a third site of postnatal neurogenesis and gliogenesis. The hypothalamus is the central regulator of body homeostasis and

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http://dx.doi.org/10.1016/j.mce.2016.08.020

of several important processes such as feeding, growth, reproduction, stress and more generally metabolism (Saper and Lowell, 2014). It is organized in multiple nuclei, or groups of neurons, arranged around a small ventral region of the third ventricle. Each nucleus regulates different physiological functions, such as circadian rhythms by the supra-chiasmatic nucleus, or feeding behaviour by the arcuate nucleus. At the base of this ventricle, and therefore within the hypothalamus, the median eminence (ME) is an important site of information transfer because the blood-brain-barrier (BBB) is interrupted, defining the ME as a circumventricular organ (CVO) (Miyata, 2015). This implies a local transfer of molecules to and from the bed of fenestrated capillaries of the hypophyseal portal system located on the ventral-most aspect of ME. The hypothalamus can therefore sense and centralize information from the periphery, and also from other brain regions via neuronal connections, to regulate pituitary hormone secretions and to control other functions such as appetite, sleep and aging.

In contrast with the SVZ and the SGZ, we know very little about the hypothalamic NSC niche. As we will discuss here, lineage-tracing experiments have demonstrated that a population of specialized radial glial cells called tanycytes (Rodriguez et al., 2005) have gliogenic and neurogenic properties. Tanycyte cell bodies are located around the base of the third ventricle. These cells are morphologically defined by the presence of a single long basal process and are mostly devoid of cilia. Tanycytes are a heterogeneous cell population, with the different sub-types designated according to their dorso-ventral location, and whose processes reach toward the hypothalamic parenchyma, or, ventrally, toward the fenestrated capillaries of ME (Fig. 1). These tanycytes are therefore unique among other NSC populations because they have unrestricted access to blood-borne signals and are also in contact with the CSF. As we will review here, these features endow them with both unique and crucial properties as hypothalamic sensors and sentinels that distinguish them from other NSCs. Here we will first describe the ontogeny of hypothalamic tanycytes and review their specific properties at the ME before describing their NSC potential, and the significance of hypothalamic neurogenesis.

2. Embryonic origin of hypothalamic tanycytes

The hypothalamus develops from the embryonic ventral forebrain (Ferran et al., 2015). During the specification of the neural plate, at 8 days post-coitum (dpc) in mice, the prospective hypothalamus is situated at the midline, in the rostral most position. It is in contact with the future pituitary, which is present as the hypophyseal placode at this stage, in the adjacent ectoderm. As the neural plate bends to close (McShane et al., 2015), increased proliferation of the dorsal telencephalic progenitors versus ventral ones induces an apparent shift of the prospective hypothalamus, which becomes localized posteriorly and ventrally to the telencephalic vesicles in 9.5dpc mouse embryos. At the midline of the hypothalamic neuroepithelium, right above the developing pituitary or Rathke's Pouch, the infundibulum becomes apparent from 9.5dpc. Morphologically this appears as a local extension of the neuroepithelium toward the developing pituitary that gives rise to the ME, to the pituitary stalk, which connects ME to the gland, and to the posterior lobe of the pituitary (Fig. 2). Tanycytes also originate in the infundibulum, from which glial cell types will mostly differentiate in the embryo (Goto et al., 2015; Pearson and Placzek, 2013), however infundibular progenitors have the potential to generate neurons *in vitro* (Pearson et al., 2011).

The secreted molecule Sonic Hedgehog (SHH) is crucial early on for specification, and later for regionalisation of the hypothalamus (Manning et al., 2006; Szabo et al., 2009; Zhao et al., 2012; Trowe et al., 2013). Emergence of the infundibulum has been shown to rely on an antagonism between members of the bone morphogenetic protein (BMP) family and SHH, which is excluded from the infundibulum (Zhao et al., 2012; Trowe et al., 2013). Members of the fibroblast growth factor family (FGFs) are present in the infundibulum, and required for infundibular cell expansion in chick (Pearson et al., 2011). The NOTCH pathway is also necessary for infundibulum formation as deletion of the NOTCH effectors *Hes1*

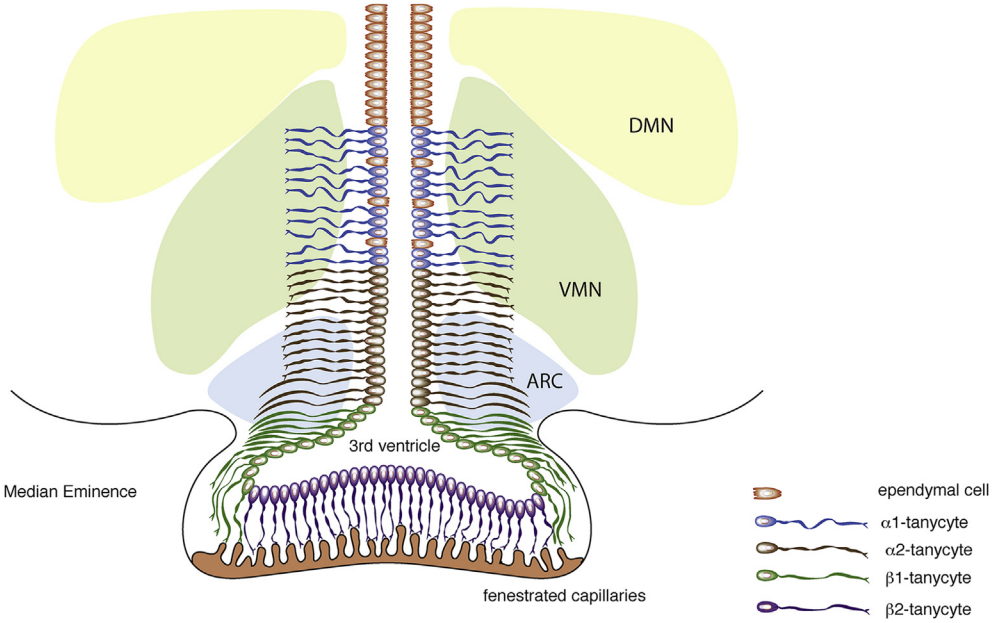

Fig. 1. Distribution of different tanycyte subtypes along the third ventricular surface. The dorso-ventral organization of tanycytes and ependymal cells in relation to the median eminence (ME) is illustrated here. β2-tanycytes are the most ventral tanycytes, they are in contact with the fenestrated capillaries of ME and the third ventricle CSF that they isolate from free diffusion of blood-borne signals (Mullier et al., 2010). Just dorsal to these, β1-tanycytes perform the same barrier function for the arcuate nucleus (Rodriguez et al., 2005). α1 and α2 tanycytes are present dorsally to β cells. ARC = arcuate nucleus, VMN = ventro-medial nucleus, DMN = dorso-medial nucleus.

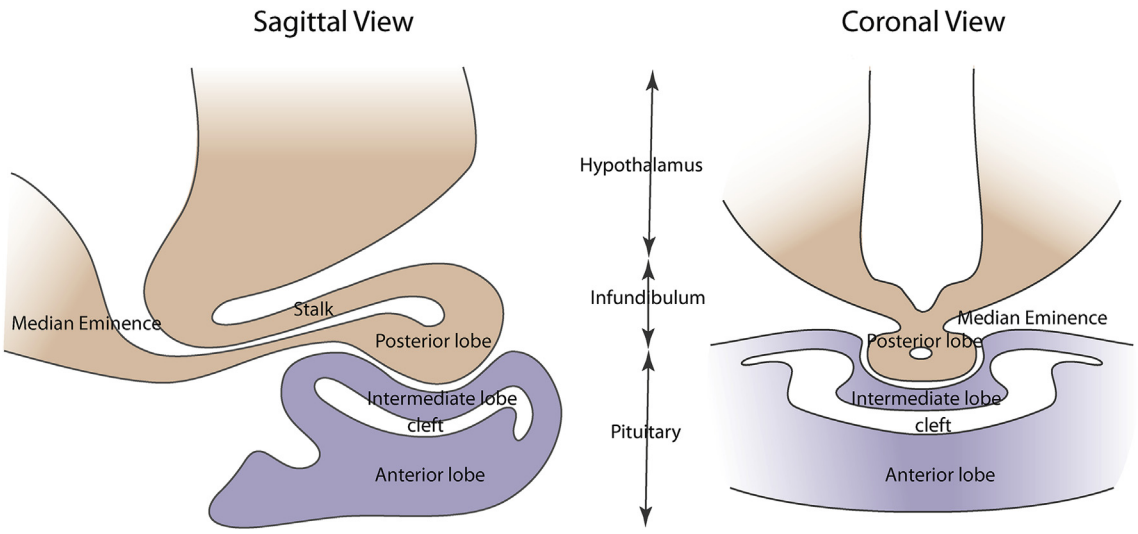

Fig. 2. Appearance of the infundibulum at 16.5dpc in the mouse. On a sagittal view the infundibulum is clearly observed as an extension from the ventral floor of the third ventricle. The distal most region in close apposition with the future intermediate lobe of the pituitary, will become the posterior lobe of the gland, containing specialized glial cells, termed pituicytes, and axons terminals from oxytocin and vasopressin neurons. The infundibulum will also give rise to the pituitary stalk, the physical link between the median eminence (ME) and the pituitary. Proximally, it will form ME itself, comprising tanycytes, axons terminals from hypothalamic neurons and a bed of fenestrated capillaries. Vascularization of mesodermal and neural crest origin gradually develops in the embryonic pituitary and median eminence (Etchevers et al., 2001).

and *Hes5* result in premature cell cycle exit in this region, preventing evagination (Goto et al., 2015). In contrast, the failures in infundibular formation observed in embryos deleted for the transcription factor LHX2 (Zhao et al., 2010) and also TBX3 (Trowe et al., 2013) are thought to result from hyperproliferation, demonstrating the requirement for a delicate balance between cell proliferation and migration for proper infundibular morphogenesis (Pearson et al., 2011). Proper infundibular morphogenesis is important because both induction and maintenance of Rathke's pouch rely on infundibular signals (Takuma et al., 1998).

Tanycytes emerge late during gestation and terminal differentiation is completed post-natally, within a month in rats (Rodriguez et al., 2005). The transcription factors LHX2 and RAX are important regulators of ventral hypothalamic development and tanycyte specification and differentiation (Zhao et al., 2010; Salvatierra et al., 2014; Lu et al., 2013; Shimogori et al., 2010). They are both expressed in the developing hypothalamus and maintained post-natally in tanycytes (Shimogori et al., 2010; Salvatierra et al., 2014). Embryonic deletion of *Lhx2* prevents proper tanycyte specification in the embryo where an expansion of ependymal cell fate marker expression is observed (Salvatierra et al., 2014). Post-natal terminal differentiation of α- and β-tanycytes is impaired in these animals; morphology is affected with acquisition of multiple cilia, characteristic of ependymal cells, but the phenotypic conversion is incomplete because retention of some tanycytic features is observed. Early post-natal deletion of *Lhx2* in tanycytes does not result in expansion of ependymal cell marker expression, but it still prevents proper tanycyte differentiation. Lack of RAX expression, a direct target of LHX2, is thought to explain this phenotype (Salvatierra et al., 2014). Altogether these data suggest that LHX2 is required for tanycyte specification in the embryo, and for their differentiation post-natally. Moreover, while there is a relative flexibility between tanycytic and ependymal cell fates in the embryo, once the cells have been specified post-natally this plasticity appears to be lost. In addition, manipulation of the WNT signalling pathway in the ventro-medial hypothalamus suggests that it is involved in post-natal regulation of tanycyte numbers (Wang et al., 2012). In conclusion, hypothalamic adult SCs originate from foetal infundibular progenitors, in parallel with what has been demonstrated in the SVZ where slowly dividing embryonic neural progenitors give rise to adult NSCs (Furutachi et al., 2015), and suggested in the pituitary where Rathke's Pouch progenitors were shown to generate adult SCs (Rizzoti et al., 2013).

3. Tanycytes act as hypothalamic sentinels, sensors, and neuroendocrine output modulators

3.1. Tanycytes regulate diffusion of blood-borne molecules

The blood-brain barrier (BBB) allows a restricted and regulated access of blood borne molecules to the brain. It is characterized by the presence of tight junctions between endothelial cells, preventing free diffusion of molecules across this layer. The seven CVOs of the brain, including the ME, are defined as areas where the BBB is interrupted: capillaries in these regions are fenestrated (Miyata, 2015). These CVOs are also characterized by the presence of tanycytes that are in contact with both endothelial cells and the ventricle. Examination of cell junctions and tissue permeability have suggested that, in the absence of BBB, tanycytes restrict the diffusion of blood-borne signals to protect CSF integrity, acting therefore as ventricular barriers (Langlet et al., 2013a).

In the ME, this barrier function is restricted to ventral β2 tanycytes (Mullier et al., 2010), while β1 tanycytes are proposed to limit parenchymal diffusion of blood-borne molecules to the arcuate nucleus (Rodriguez et al., 2005). Permeability of the ME is modulated according to changing physiological situations, such as fasting. Metabolic signals need to reach feeding control circuits in the arcuate nucleus rapidly and fenestration of the capillaries is consequently increased. Tanycytes that have been demonstrated to act as glucose sensors are involved in these changes (Bolborea and Dale, 2013). In response to fasting, and a consequent a drop in blood glucose, they can induce an increased vascular permeability through enhanced secretion of VEGFA (Langlet et al., 2013b). Leptin is a crucial peptide regulating food intake that is mostly secreted by adipocytes. It activates leptin receptors in the brain to regulate food intake, and resistance to leptin is associated with obesity (Roh et al., 2016). Mechanisms underlining resistance are unclear but a defective transport across the BBB has been proposed (El-Haschimi

et al., 2000). Tanycytes have been proposed to represent intermediates for its diffusion in the medio-basal hypothalamus (MBH), suggesting that they regulate the hypothalamic response to leptin (Balland et al., 2014). Tanycytes may not be the only cell type to regulate this response as a very recent study demonstrated that ME oligodendrocyte precursor cells are required for maintenance of leptin receptor positive dendrites, and therefore hypothalamic leptin sensing (Djogo et al., 2016).

Alterations in hypothalamic glucose sensing have been reported in Alzheimer disease (AD) patients and transgenic mouse model (Niwa et al., 2002). In addition, alterations in leptin levels and hypothalamic dysfunction are increasingly implicated in the weight loss characterizing AD (Ishii and Iadecola, 2015). It would therefore be of interest to investigate the functionality of tanycytes and a possible link with AD.

3.2. Tanycytes control neuroendocrine output at the ME

Fasting has pleiotropic physiological consequences, initially a drop in blood glucose as mentioned earlier, that tanycytes and some hypothalamic neurons sense. It also induces a transient reduction in activity of the hypothalamo-pituitary-thyroid (HPT) axis, a crucial regulator of metabolism (Joseph-Bravo et al., 2015), and this contributes to reduced energy expenditure when calorific intake is low. On top of the HPT axis, hypothalamic Thyrotropin Releasing Hormone (TRH) is collected by ME capillaries and transported to the pituitary where it stimulates the secretion of Thyroid Stimulating Hormone (TSH) and prolactin. TSH induces secretion of the thyroid pro-hormone T_4 that must be converted to T_3 by the deiodinases Dio1 and 2 to be active. In turn, TH exerts a negative feedback on TRH synthesis and secretion. In the brain, Dio2 is predominantly expressed by ME tanycytes. These are therefore important regulators of hypothalamic TH levels (Bolborea and Dale, 2013). TRH levels are also finely regulated, in particular by an ectopeptidase, the pyroglutamyl peptidase II (PPII) that hydrolyses the neuropeptide. In the hypothalamus, PPII is present in tanycytes, particularly of the β2 type, where its expression and activity are regulated positively by TH (Sanchez et al., 2009). β2-tanycytes are also associated with TRH neuron termini at the ME. Inhibition of PPII *in vivo* results in more TRH being secreted at the ME, strongly suggesting that β2-tanycytes regulate TRH levels and that they participate in the negative feedback action of TH on TRH secretion (Sanchez et al., 2009). Finally, tanycytic PPII levels increase transiently during fasting, implying that tanycytes are involved in the reduction of TRH levels induced by caloric restriction (Lazcano et al., 2015). Moreover, regulation of the HPT axis by tanycytes is proposed to be involved in weight fluctuations observed in some seasonal mammals (Ebling, 2015).

Gonadotrophin Releasing Hormone (GnRH) controls reproductive function. It is released at the ME and induces secretion of pituitary luteinising and folliculo-stimulating hormones; these in turn stimulate production of steroids within the gonads (Herbison, 2016). In addition, while decreased GnRH levels had been associated with aging (Yin et al., 2009), a causative link has been demonstrated where reduction in GnRH levels initiate systemic aging (Zhang et al., 2013). GnRH secretion is tightly regulated and tanycytes, along with ME astrocytes and endothelial cells, play an important role (Prevot et al., 2010). Their cytoplasmic processes engulf GnRH axon termini at the ME, and this ensheathment is modulated according to the phase of the oestrous cycle (Prevot et al., 1999). Ensheathment is associated with a restricted access of axon termini to the perivascular space, while tanycyte endfeet retraction allows access to blood vessels and leads to increased GnRH release (Prevot et al., 2003). The secreted molecules TGFα, β and Semaphorin7A, a chemorepulsive axon guidance molecule, regulate the morphological changes observed in tanycytes during the oestrous cycle (Prevot et al., 2010; Parkash et al., 2015). Sema7A is expressed by tanycytes and has a dual role at the ME: it induces GnRH axon termini retraction and tanycyte endfeet engulfment, resulting in decreased GnRH secretion (Parkash et al., 2015). All together these data show that tanycytes have an important role in the control of GnRH secretion and therefore reproduction. Moreover, the causative effect of reduced GnRH levels during aging (Zhang et al., 2013) may suggest a role for tanycyte during this process (see below).

4. Tanycytes comprise a population of hypothalamic stem cells

Cell division had been detected in the post-natal hypothalamus, particularly in the ventral region surrounding the third ventricle, and in rodents this can be stimulated by infusion of different growth factors, such as BDNF (Pencea et al., 2001), EFG and FGF (Xu et al., 2005), IGF (Perez-Martin et al., 2010) and CNTF (Kokoeva et al., 2005). The presence of hypothalamic progenitors was suggested by experiments *in vitro* (Markakis et al., 2004), while active neurogenesis was proposed to occur in the hypothalamus (Xu et al., 2005; Perez-Martin et al., 2010; Kokoeva et al., 2005; Kokoeva et al., 2007; Batailler et al., 2014). The physiological relevance of this was first suggested by Kokoeva et al., in 2005, on the basis of the link that was seen between newly generated neurons and long-term weight loss observed in CNTF treated animals (Kokoeva et al., 2005). Thanks to the availability of different relevant Cre strains, cell lineage tracing experiments have now firmly established the existence of active hypothalamic neurogenesis and gliogenesis, as well as the SC potential of tanycytes (Lee et al., 2012; Li et al., 2012; Robins et al., 2013; Haan et al., 2013; Robins et al., 2013a; Chaker et al., 2016). However there is still debate about the type(s) of tanycyte that really represents hypothalamic NSCs (Fig. 3). In addition, more remains to be known about the physiological significance of hypothalamic neurogenesis. For example, in seasonally breeding mammals, the rate of hypothalamic cell proliferation has been shown to vary according to day length, with increased levels in the short photoperiod in sheep (Batailler et al., 2015), and similar seasonal changes relating to food intake correlate with changes in tanycyte function and neurogenesis in Syrian hamsters (Ebling, 2015; Samms et al., 2015). However, while the correlations are good, functional data is lacking.

4.1. Characterization of hypothalamic NSCs

Several observations including morphological features pointed toward α2-tanycytes as potential NSCs (Rodriguez et al., 2005), and this was recently confirmed (Robins et al., 2013a). More precisely, $GLAST^{CreERT2}$ lineage tracing experiments first showed that α-tanycytes are the only subtype to express GLAST. These α-tanycytes give rise to β1-tanycytes, suggesting that the former may represent NSCs while the latter are committed progenitors. In addition, precise dissection of the third ventricle sub-ventricular zone further revealed that α2 are the only tanycytes with neurosphere forming ability, implying that they are NSCs (Robins et al., 2013a). Consistent with the biology of other NSC populations, α-tanycyte proliferation is stimulated by FGF2 (Robins et al., 2013a) and IGF (Perez-Martin et al., 2010). However, in the adult, $GLAST^{CreERT2}$ lineage tracing analyses have revealed that α-tanycytes mostly give rise to parenchymal astrocytes while very few neurons are generated (Robins et al., 2013a).

The secreted factor FGF10 is expressed selectively in some β-tanycytes, revealing previously unsuspected cell heterogeneity in this population (Haan et al., 2013; Hajihosseini et al., 2008). Lineage

tracing experiments using FGF10^{CreERT2} show that β-tanycytes differentiate more during the early post-weaning period and, in contrast with α-tanycytes (Robins et al., 2013a), and that their progeny is predominantly neuronal. Newly generated neurons integrate in the arcuate and ventromedial nuclei (Haan et al., 2013).

An additional site of neurogenesis was detected using Nestin-CreERT2 (Lee et al., 2012). Early post-natally, β2 cells are the most proliferative among tanycytes. Lineage tracing using Nestin-CreERT2 reveals that these cells are also the most neurogenic in young animals (Lee et al., 2012). Both in young animals and in adults, newly generated neurons remain within the ME (Lee et al., 2012; Lee et al., 2014). In addition, lineage tracing in the adult using an independently generated strain of Nestin-CreERT2 recently showed that neurogenesis persist as the animal is aging, and that new neurons are produced in all regions of the hypothalamus (Chaker et al., 2016).

In conclusion, while it is difficult to compare lineage-tracing experiments using different drivers, especially when inducible recombinases are used and varying degrees of mosaicism obtained, tanycyte sub-types appear to differ significantly both in their potential and contribution to hypothalamic cell-turnover. Importantly, a parenchymal NSC population has also been proposed to exist in the hypothalamus (Robins et al., 2013b; Li et al., 2012). Regardless of their ventricular or parenchymal origin, the newly generated neurons appear to be predominantly associated with feeding control.

4.2. Physiological relevance of hypothalamic neurogenesis

There is significant cell turn-over in the arcuate nucleus post-natally (McNay et al., 2012) and, in both young and adult animals, new hypothalamic neurons are responsive to signals related to feeding control (Kokoeva et al., 2005; Lee et al., 2012; Li et al., 2012; Haan et al., 2013). In addition, hypothalamic neurogenesis is modulated in response to diet, where high fat diet (HFD) has been reproducibly shown to inhibit neurogenesis within the MBH and increase progenitor apoptosis (Li et al., 2012; Lee et al., 2014; McNay et al., 2012). In sharp contrast, neurogenesis in the ME is increased in response to HFD, specifically in females (Lee et al., 2012, 2014). The physiological significance of this effect is suggested by a reduction in weight gain when ME neurogenesis is prevented (Lee et al., 2012). In addition, caloric restriction is associated with reduced proliferation and a tendency toward reduced neurogenesis within the ME (Lee et al., 2014).

Leptin deficiency, which is associated with obesity, also results in loss of hypothalamic SCs and impaired MBH neurogenesis in mice (McNay et al., 2012). The association between HFD, impaired hypothalamic neurogenesis and weight gain is further strengthened by the observation that hypothalamic inflammation also affects hypothalamic SCs (Li et al., 2012). Obesity is associated with hypothalamic inflammation (Cai and Liu, 2011). As this inflammation precedes obesity onset, it is increasingly suspected to be the cause, rather than the consequence, of diet-induced metabolic disease (Valdearcos et al., 2015). Hypothalamic microglia mediate inflammation induced by HFD (Li et al., 2012) and this affects hypothalamic SCs, which display increased apoptosis, reduced proliferation and inhibition of neural differentiation (Li et al., 2012). Therefore, in response to HFD and as a target of hypothalamic inflammation, reduced MBH neurogenesis is clearly associated with weight gain.

Microglia mediated hypothalamic inflammation also appears to have a crucial role in initiating systemic aging (Zhang et al., 2013). In this context, the relevant targets of the inflammatory cascade are the GnRH neurons, causing them to secrete less GnRH, and this results in systemic aging (Zhang et al., 2013). Decreased neurogenesis is observed in both the hypothalamus and hippocampus. GnRH administration can slow the ageing process and rescues neurogenesis in old mice; while a causative effect is not demonstrated, both at least correlate (Zhang et al., 2013). Interestingly aging is associated with a tendency to gain weight, in both humans and rodents. It would be of interest to examine a potential connection between decreased hypothalamic neurogenesis and weight gain in this context.

Hypothalamic neurogenesis is clearly associated with feeding control and energy metabolism. The tanycytes are increasingly appearing as a pivotal hypothalamic cell type regulating peripheral input, neuroendocrine output and to generate new hypothalamic cells. It is now crucial to understand how signals are integrated and

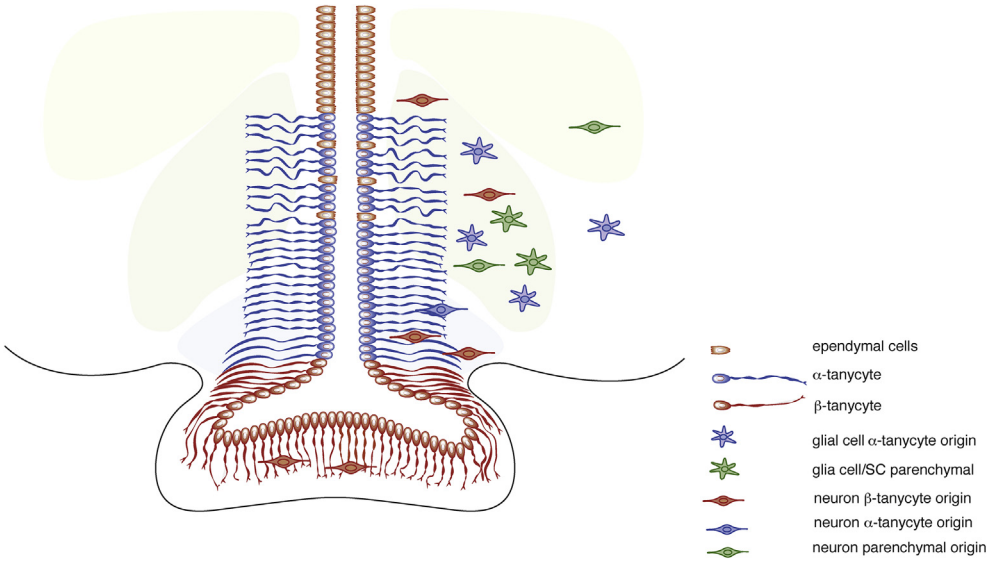

Fig. 3. Hypothalamic SCs and their progeny. β-tanycytes can generate neurons that populate ME (Lee et al., 2012), and the mediobasal hypothalamus (MBH) (Haan et al., 2013). α-tanycytes mostly generate parenchymal astrocytes and some rare neurons (Robins et al., 2013a). α-tanycytes have also been proposed to give rise to β-tanycytes defining the former as SCs, and the latter as progenitors (Robins et al., 2013a). Finally a parenchymal population of progenitors has been proposed to be present in the MBH (Li et al., 2012; Robins et al., 2013b).

the degree to which heterogeneity exists within this remarkable cell population.

5. Conclusion

Plasticity is an important aspect of hypothalamic function because constant adaptation to changing conditions is required to maintain homeostasis and to release appropriate signals, such as satiety after feeding. The recent demonstration that neurogenesis occurs in this region, and is altered in response to diet modification, suggests that modulation of the number of hypothalamic neurons may represent another way to adapt in response to changing physiological situations. This also implies that therapeutically modulating hypothalamic neurogenesis and/or neuronal populations may be beneficial, particularly in the context of metabolic syndromes. The development of induced Pluripotent SCs (iPSCs) ten years ago (Takahashi and Yamanaka, 2006) has been followed by remarkable progress toward regenerative medicine, disease modelling and drug screening. We can now generate many differentiated cell types from embryonic and/or iPSC, comprising hypothalamic neurons (Wataya et al., 2008; Wang et al., 2015; Merkle et al., 2015). In addition, hypothalamic cell transplantation can partially restore leptin responsiveness in leptin receptor-deficient mice (Czupryn et al., 2011), demonstrating that cell manipulation in the hypothalamus has therapeutic benefits. Finally, it now appears essential to examine whether hypothalamic neurogenesis is involved in other physiological processes, such as puberty, pregnancy and lactation, where the organism needs to adapt to and trigger, especially in the case of puberty, a new physiological status. It would also be important to ask how neurogenesis relates functionally to seasonal changes in physiology and behaviour, associated with feeding or reproduction, and to aging.

Acknowledgements

We would like to thank members of the Lovell-Badge's lab for help and support, and the Research Illustration team at the Francis Crick Institute for assistance with the figures. This work was supported by the Francis Crick Institute, grant number 10107.

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