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Pivotal role of median eminence tanycytes for hypothalamic function and neurogenesis

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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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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*

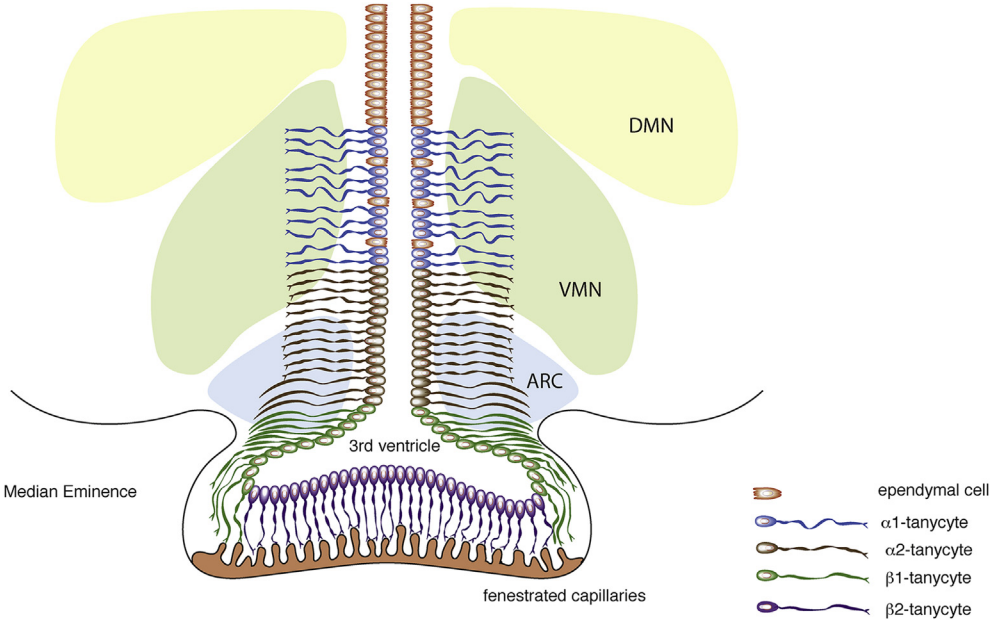

Fig. 1. Distribution of different tanycyte subtypes along the third ventricular surface. The dorso-ventral organization of tanycytes and ependymal cells in relation to the median eminence (ME) is illustrated here. β2-tanycytes are the most ventral tanycytes, they are in contact with the fenestrated capillaries 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.