Cellular components of CNS

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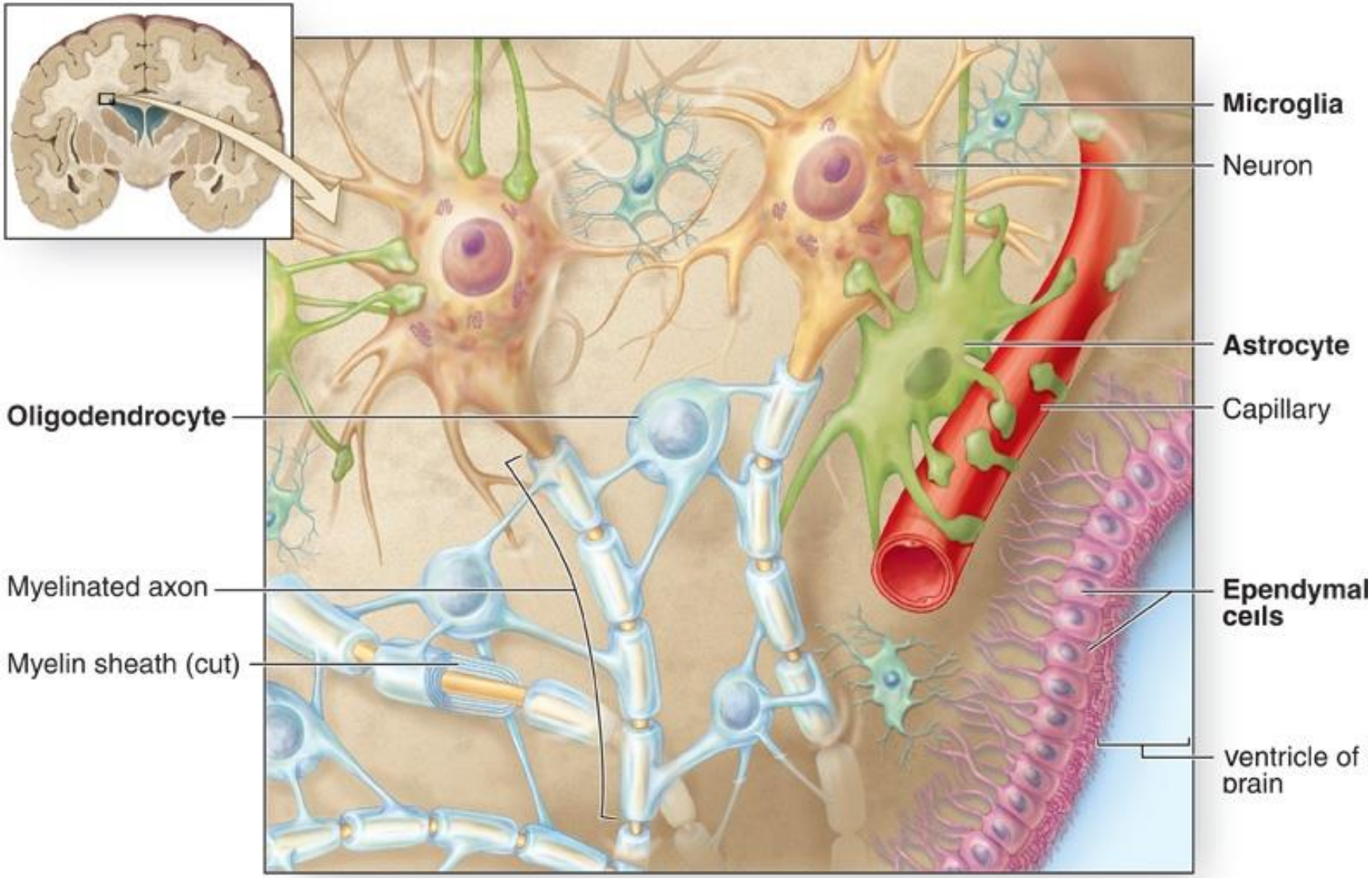


Cellular components of CNS

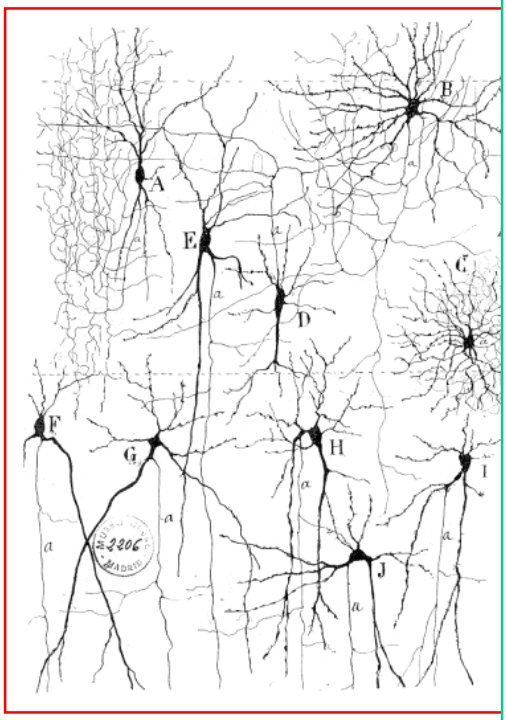
- Neurons
- Glial cells:

Astrocytes (including radial glia), oligodendrocytes, microglia, ependymal cells

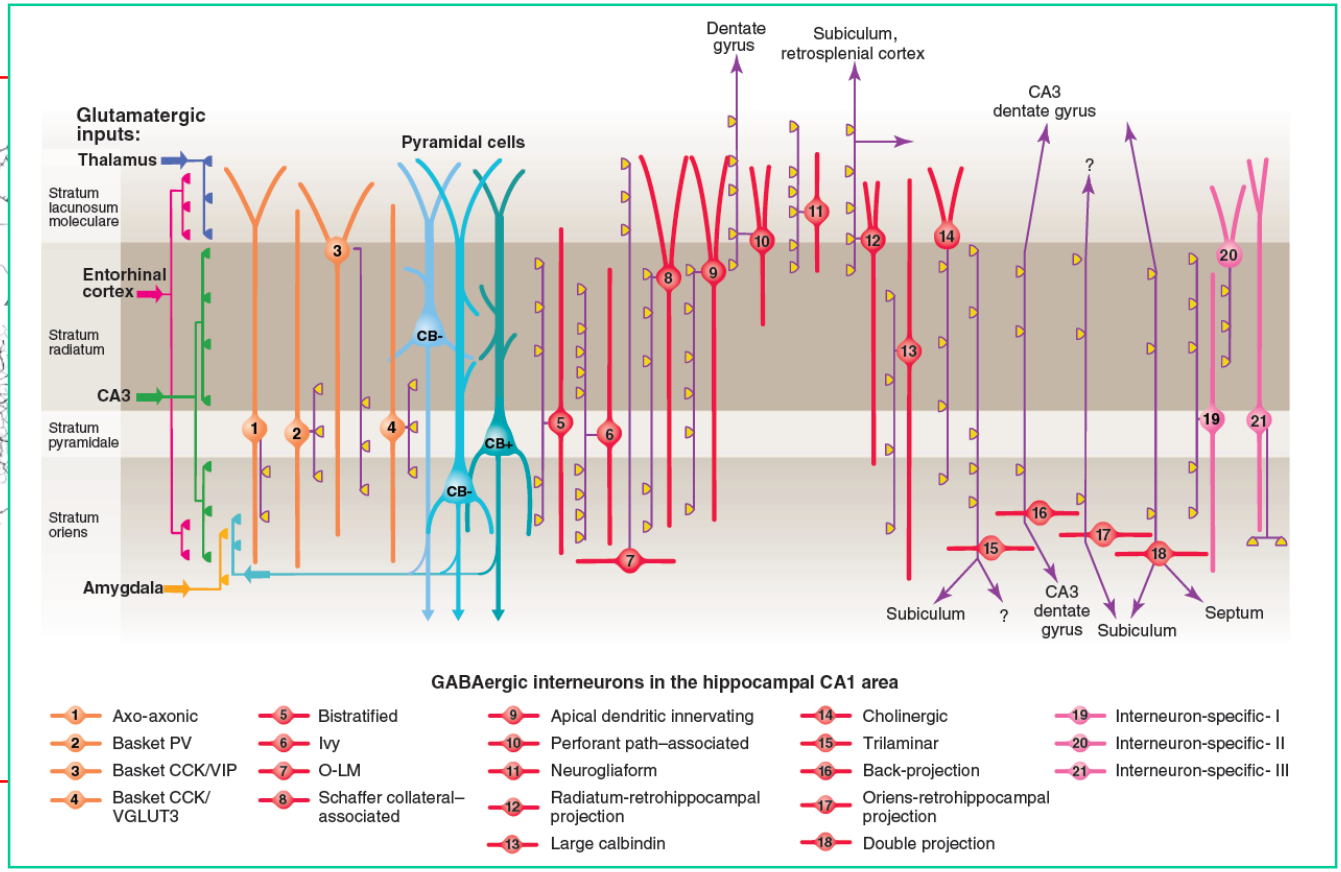
- Endothelial cells of CNS capillaries
- Epithelial cells of choroid plexus

The neuron is the basic functional unit of the nervous system

Neurons come in many different shapes and functions……



(Cajal, 1905)

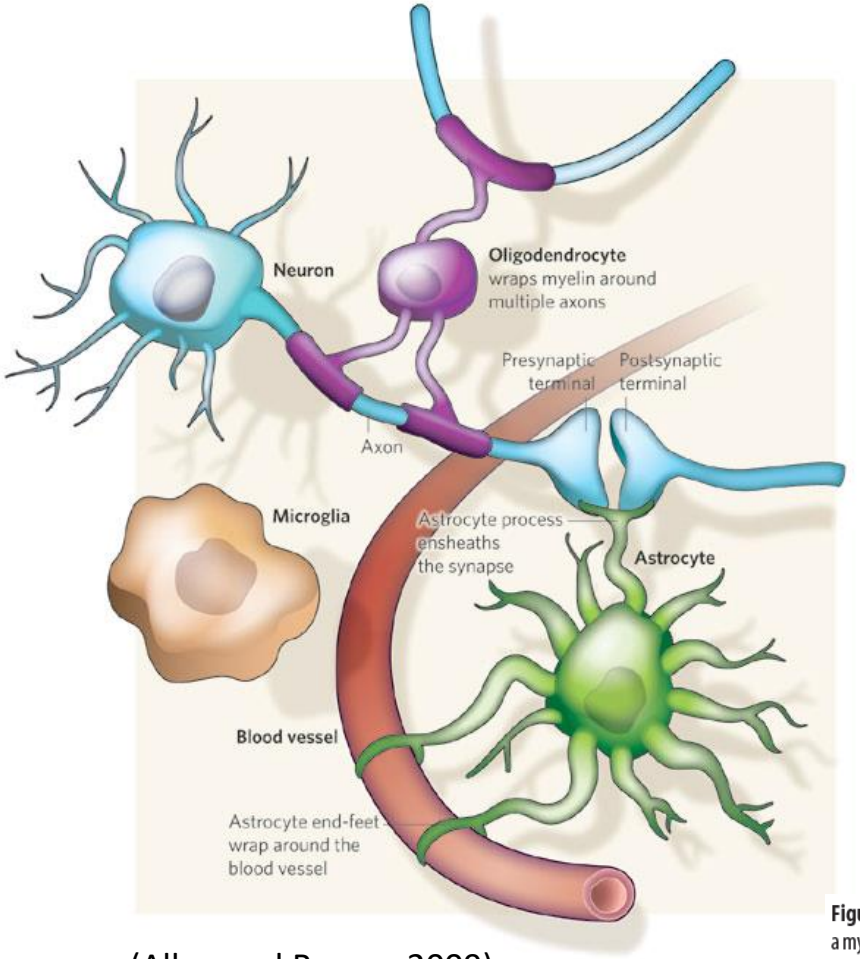


Thomas Klausberger[1,2]* and Peter Somogyi[1]*

SCIENCE VOL 321 4 JULY 2008

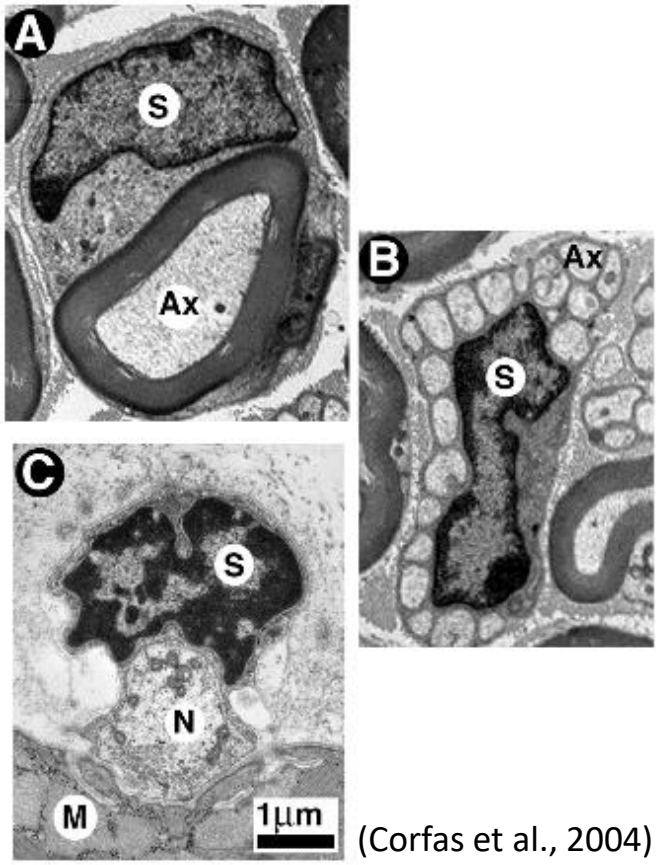
Yet, glia (can) outnumber neurons 10:1 in the human brain

Some examples of CNS glia:



(Allen and Barres, 2009)

Some examples of PNS glia:



(Corfas et al., 2004)

Figure 1. Myelinated, unmyelinated, and perisynaptic Schwann cells as seen with the electron microscope. *A*, Cross section of a myelinated axon of an adult mouse sciatic nerve. The myelin sheath (MS) surrounding the axon (Ax) and the Schwann cell nucleus (S) are clearly visible. *B*, Cross section of a bundle of unmyelinated axons of an adult mouse sciatic nerve. The Schwann cell forms the Remak bundle, a bouquet-like bundle of thin axons, each separated from its neighbor by thin cytoplasmic extensions of the Schwann cell. *C*, Cross section of a frog neuromuscular junction reveals three juxtaposed cellular elements: the perisynaptic Schwann cell, nerve terminal (N), and muscle fiber (M). The perisynaptic Schwann cell body (S indicates nucleus) and its processes cap the nerve terminal, but the processes do not wrap around the nerve terminal region facing acetylcholine receptors on muscle.

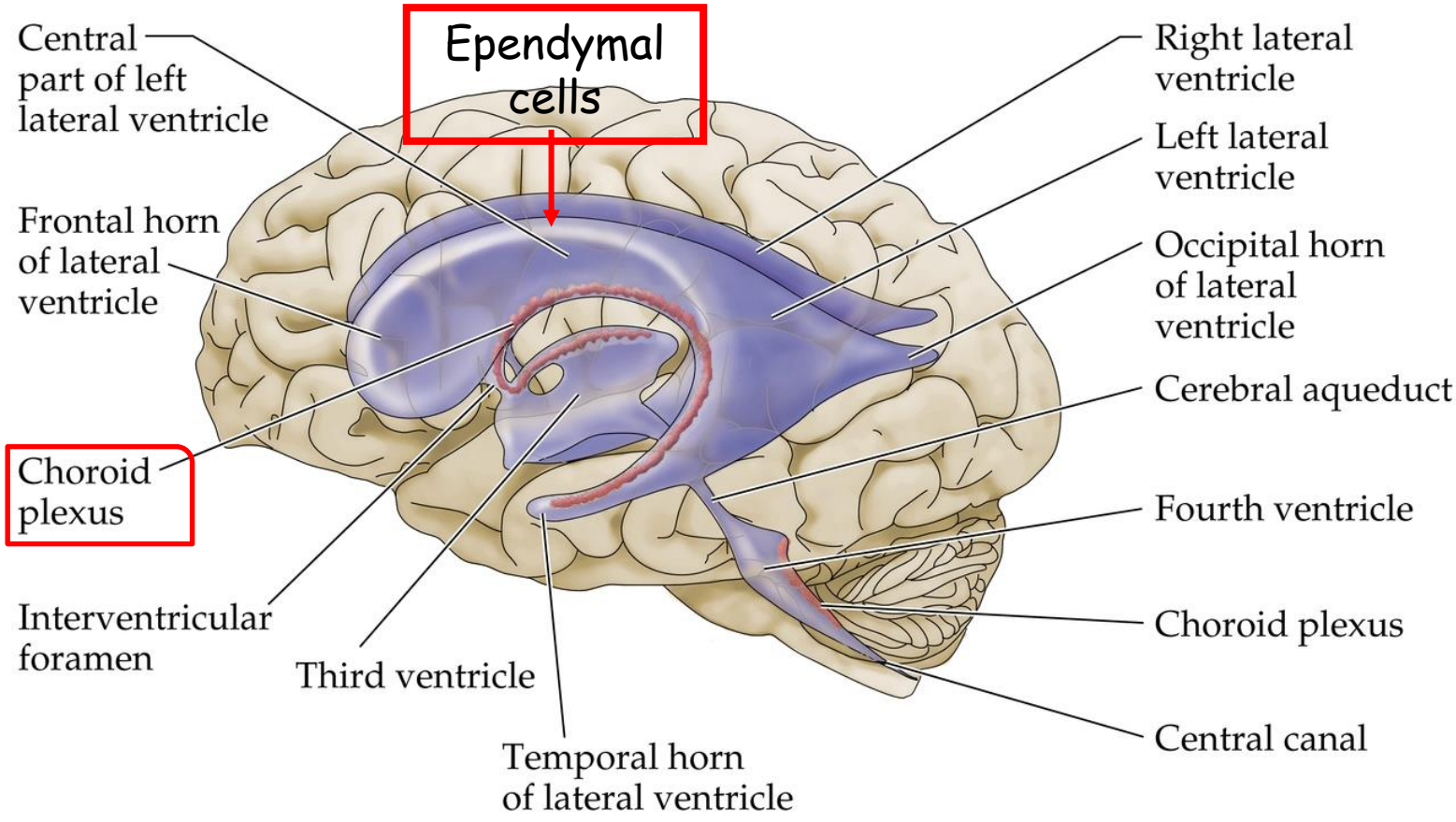
Let’s start with cells that are mostly neglected in the the study of the CNS:

Ependymal cells /Tanycytes - ventricular system

Choroid plexus cells - cerebrospinal fluid

Endothelial cells - Blood Brain Barrier (BBB)

The ventricular system



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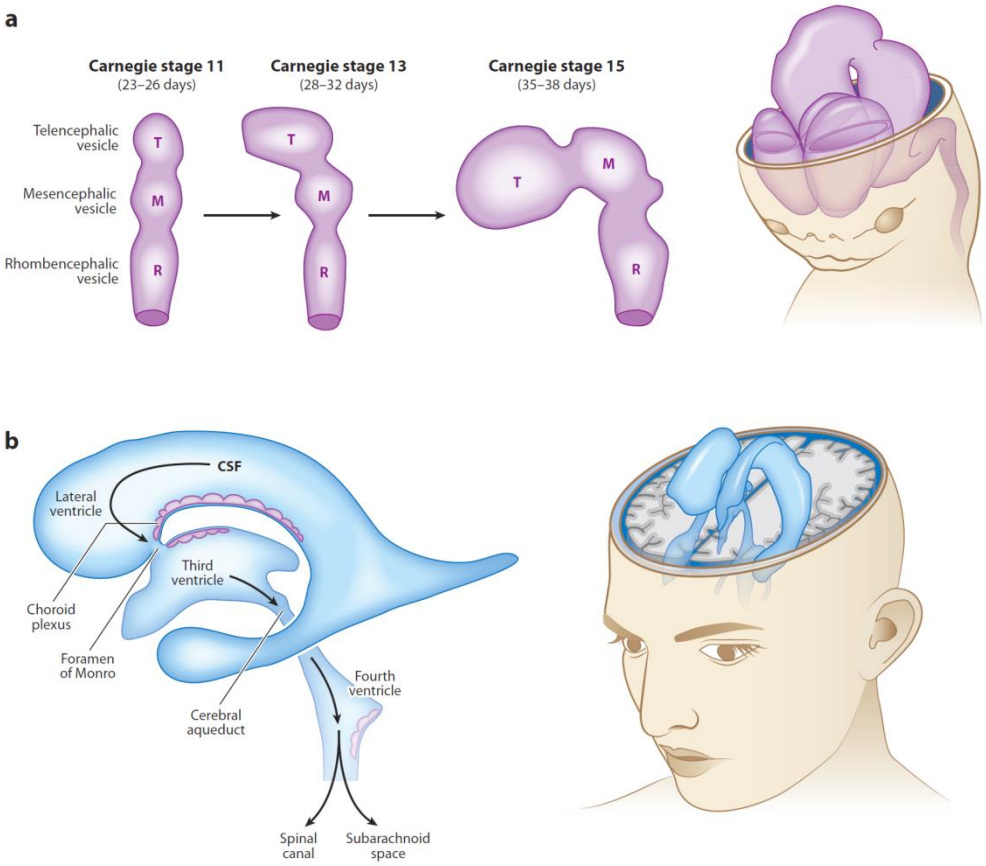
Development of the cerebral ventricles



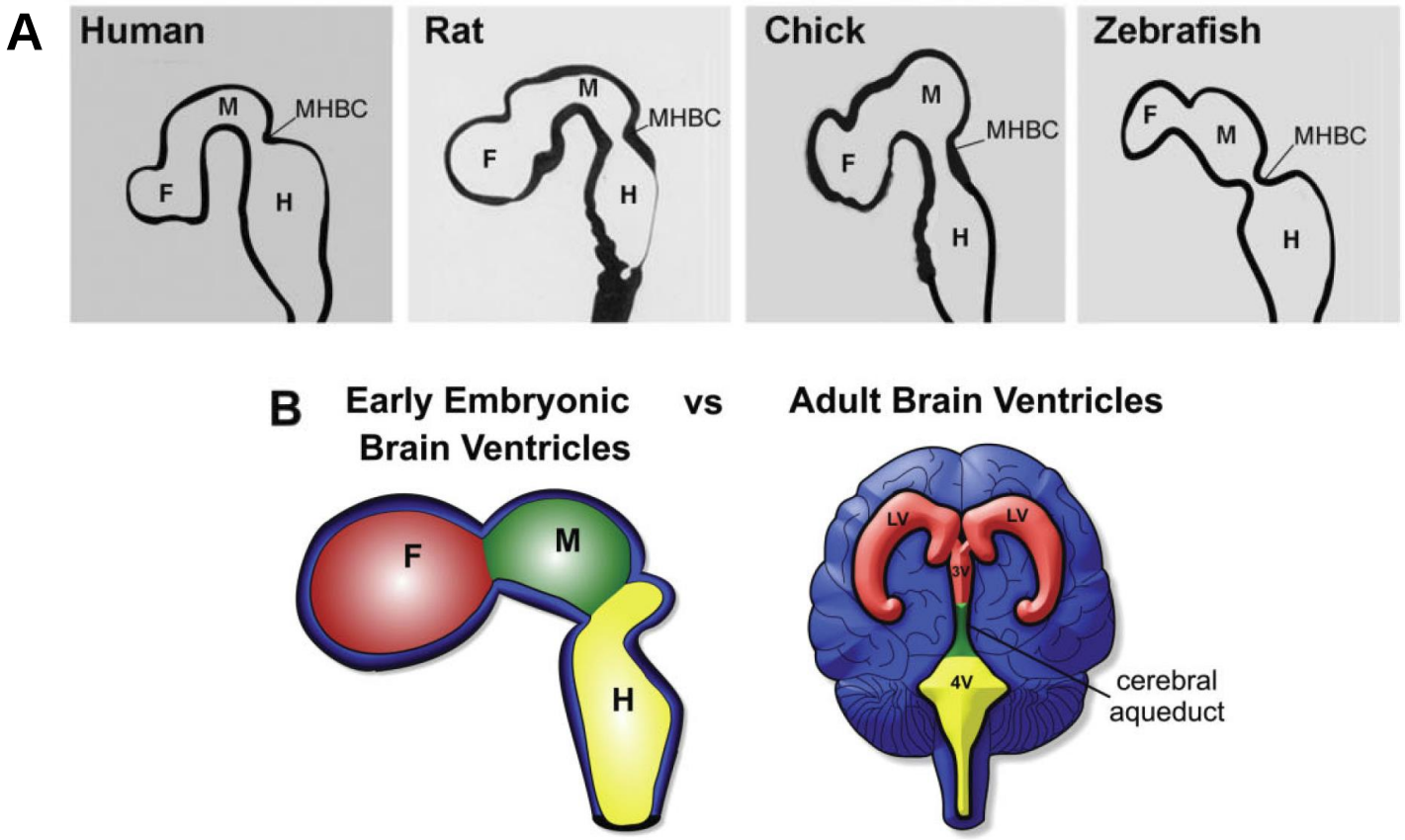
Lehtinen & Walsh. Annu. Rev. Cell Dev. Biol. 2011. 27:653–79

Schematics of the cerebroventricular system during early human brain development and in the mature adult brain

(a) Upon anterior neural tube closure, the three primary brain vesicles [telencephalic (T), mesencephalic (M), and rhombencephalic (R) vesicles] serve as the rudimentary cerebroventricular system for the developing central nervous system (CNS).

(b) In the mature CNS, CSF generated primarily by the choroid plexus tissues located in each ventricle in the brain fills the ventricles, subarachnoid space, and spinal canal. CSF flows from the lateral ventricles via the foramen of Monro/intraventricular foramen into the mesencephalic/third ventricle, and then via the aqueduct of Sylvius/cerebral aqueduct into the hindbrain/fourth ventricle. The CSF then continues through the foramina of Magendie/median apertures and Luschka/lateral apertures into the spinal canal and subarachnoid space, and is finally resorbed into the venous system via arachnoid villi. An adult human circulates approximately 150 ml of CSF within the cerebroventricular system. The CSF is estimated to turn over approximately three to four times per day, so a healthy CNS produces close to 500 ml of CSF daily.

Evolutionary conservation of embryonic brain ventricle structure



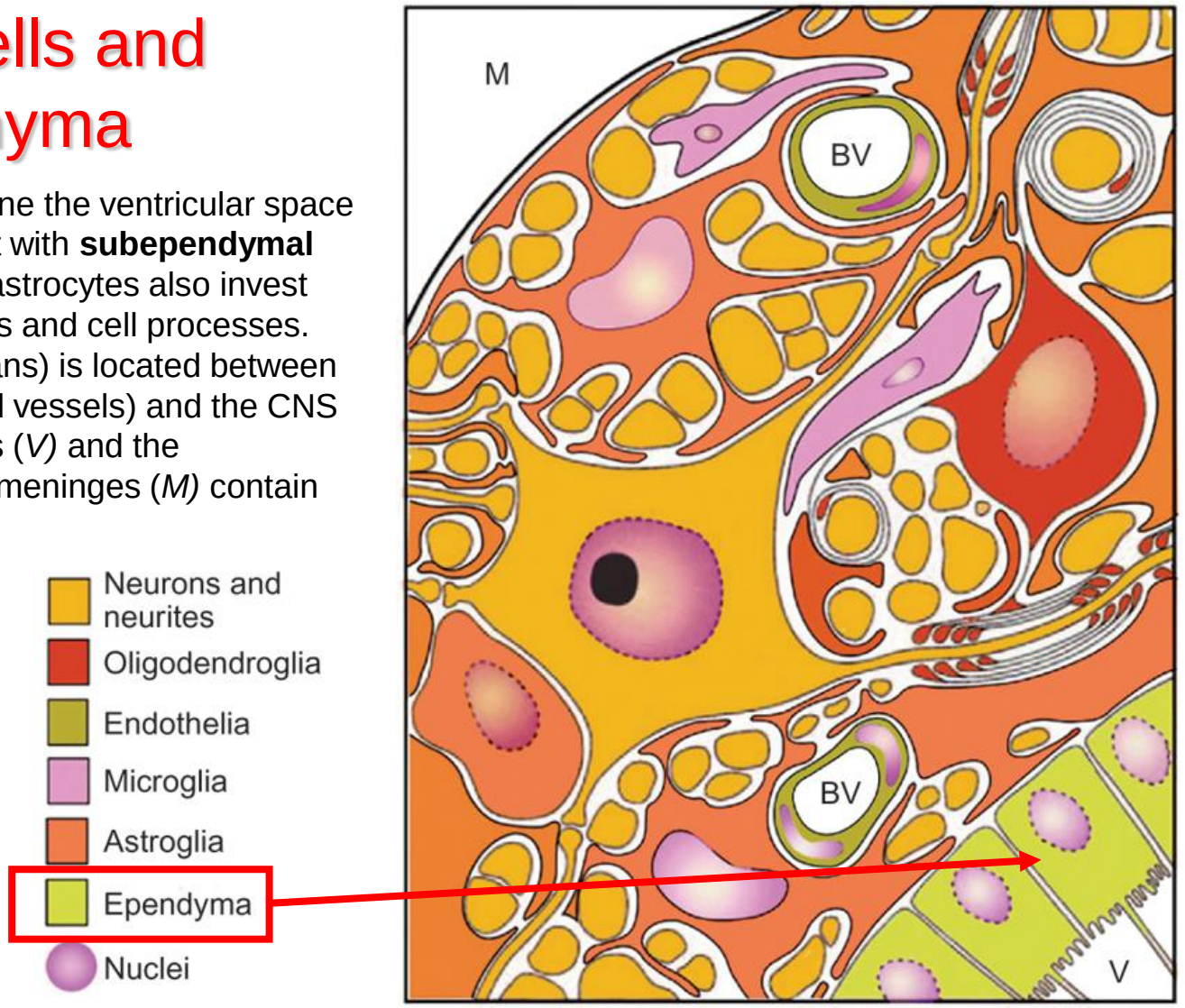
A: Conservation of embryonic brain ventricle structure. Tracings of embryonic brain ventricles at similar corresponding stages in development, all lateral views.

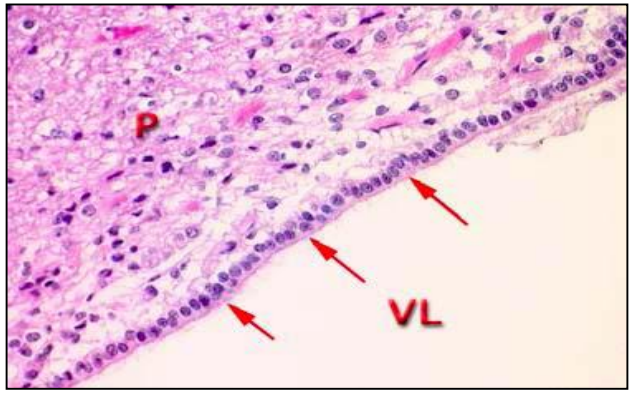
B: Comparison of early embryonic and adult brain ventricles. Colors correspond to the same ventricle regions in the embryo and adult. Not to scale. F, forebrain (telencephalon plus diencephalon); M, midbrain (mesencephalon); H, hindbrain (rhombencephalon); MHBC, midbrain hindbrain boundary constriction

Lowery & Sive, BioEssays 31:446–458, 2009

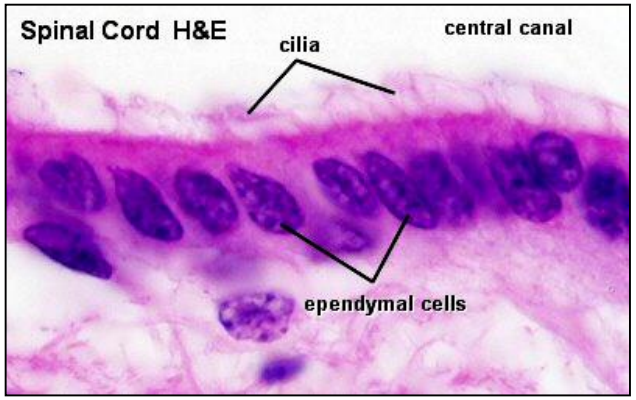
Relations between ependymal cells and brain parenchyma

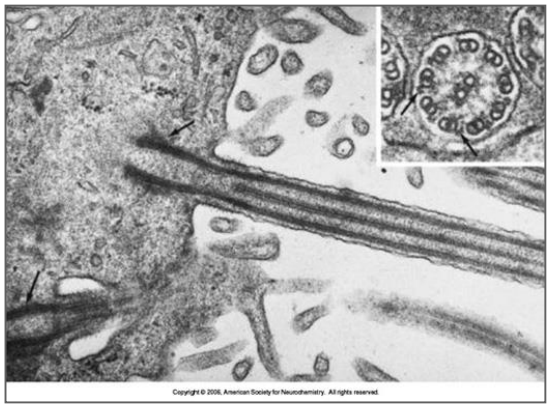
Ciliated **ependymal cells** line the ventricular space (*V)* and are in close contact with **subependymal astrocytes**. Note how the astrocytes also invest blood vessels (*BV)*, neurons and cell processes. The pia-astroglia (glia limitans) is located between the exterior (dura and blood vessels) and the CNS parenchyma. The ventricles (*V)* and the subarachnoid space of the meninges (*M)* contain cerebrospinal fluid.

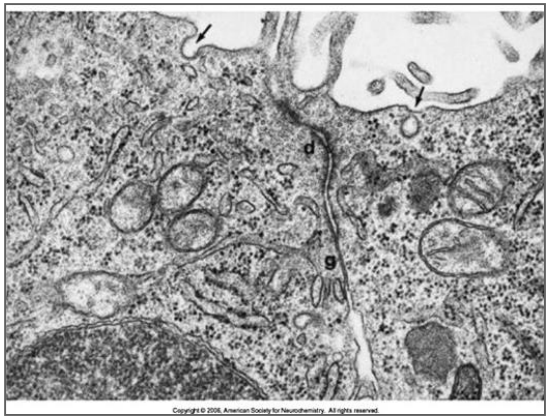




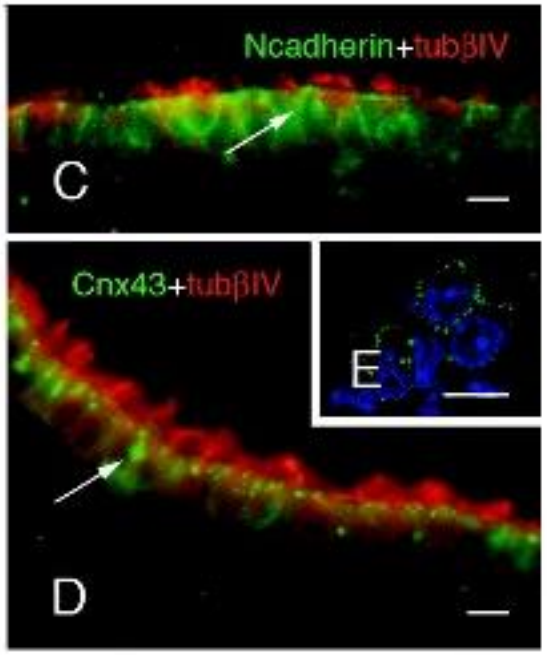
The ventricles of the brain and the central canal of the spinal cord are lined with ependymal cells. These cells are often **ciliated** and form a simple cuboidal or low columnar epithelium. The **lack of tight junctions** between ependymal cells allows a free exchange between cerebrospinal fluid and nervous tissue.







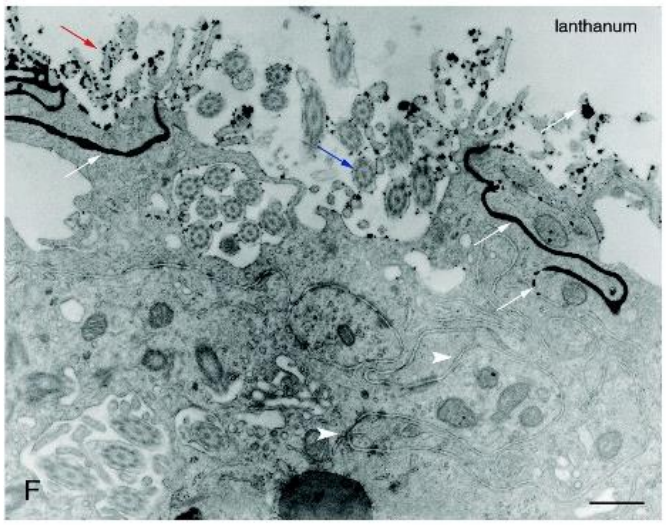
Top panel: The surface of an ependymal cell. Surface contains basal bodies (*arrows*) connected to the microtubules of cilia, seen here in longitudinal section. Several microvilli are also present.
Inset: Ependymal cilia in transverse section possess a central doublet of microtubules surrounded by nine pairs, one of each pair having a characteristic hook-like appendage (*arrows*).
Bottom panel: A typical **desmosome (*d*)** and **gap junction (*g*)** between two ependymal cells. Microvilli and coated pits (*arrows*) are seen along the cell surface.

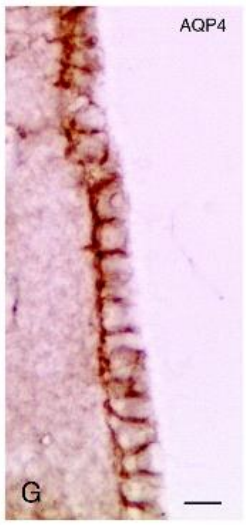


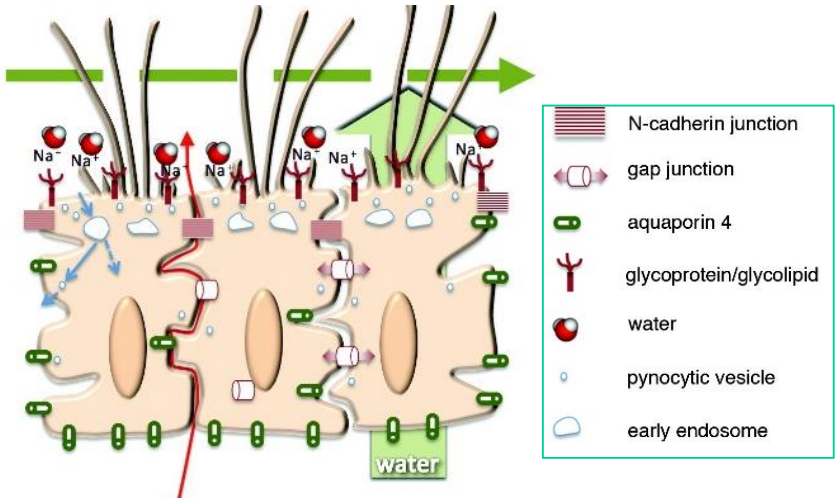
Molecular features of the multiciliated ependyma in the ventricle of the mouse.

Ependymal cells (**C**) express N-cadherin-containing junctions (in green, arrows) in their lateral plasma membrane domains. Tubulin βIV (tubβIV, in red) labels cilia in **C** and **D**. **(D and E).** Multiciliated ependymal cells are joined with connexin43-containing (Cnx43) gap junctions (in green, arrow). Gap junctions in ependymal cells are involved in electrical and metabolic couplings integrating the functioning of the cell layer. Gap junctions play a role in the synchronization of cilia beating and in CSF circulation.

(F) Multiciliated ependymal cells lack tight junctions, as shown with lanthanum nitrate applied to the ventricle and observed under transmission electron microscopy. The tracer (with black electrodensity, white arrows) is passing through the lateral winding extracellular spaces (white arrowheads), proving the absence of functional tight junctions. Motile cilia (blue arrow) and microvilli (yellow arrow) are appreciated in the luminal pole of ependymocytes. **(G)** Aquaporin 4 (AQP4) is present in the laterobasal domain of multiciliated ependyma.







Modified from Jiménez et al.,*Tissue Barriers* **2014,** 2, DOI: 10.4161/tisb.28426

Live Imaging of the Ependymal Cilia in the Lateral Ventricles of the Mouse Brain

http://www.jove.com/video/52853/live-imaging-ependymal-cilia-lateral-ventricles-mouse

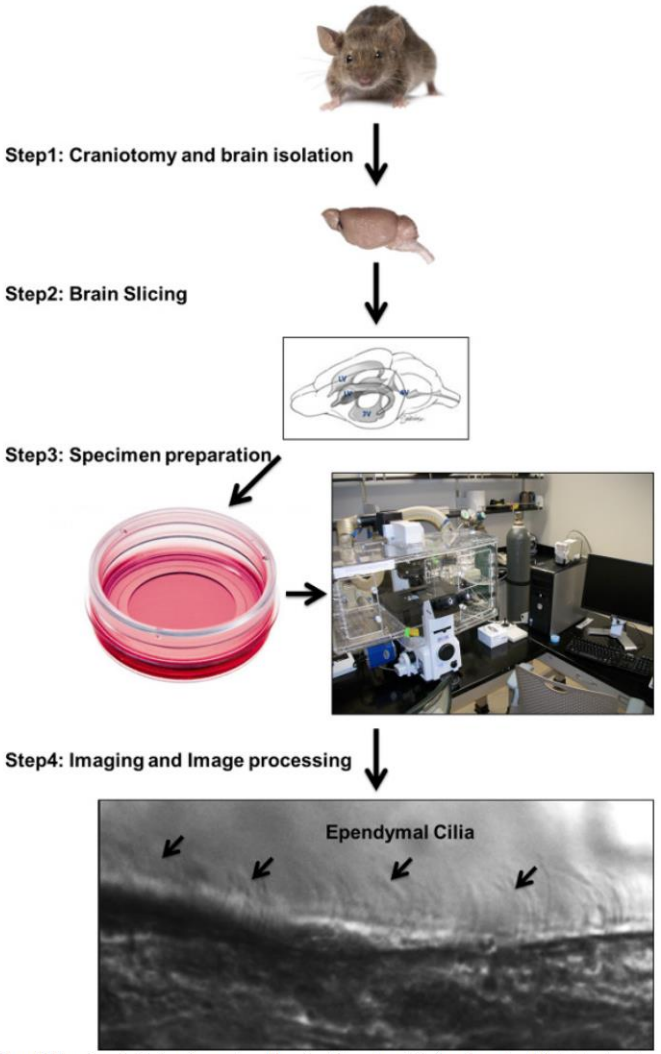


Figure 1: Ependymal cilia imaging protocol flowchart. Ependymal cilia imaging protocol illustrates steps to complete an experiment starting from mouse brainextraction, sectioning and tissue preparation to image acquisition and analysis. An approximate one hour timeline is presented with step-by-step procedure.

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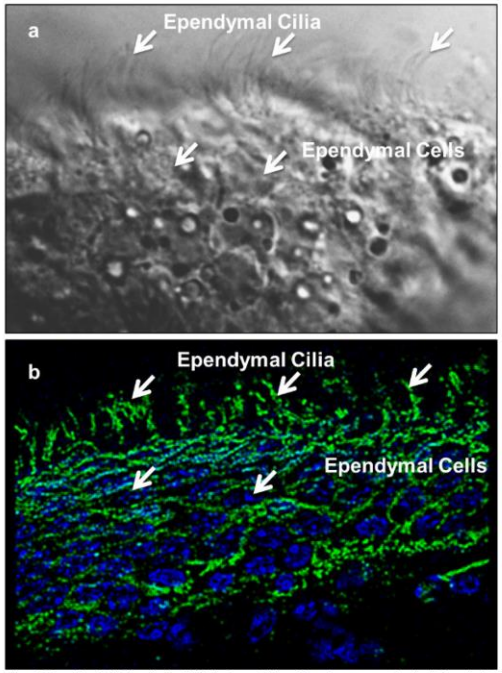


Figure 2: Ependymal cilia localization in the brain ventricles. Shown here are ependymal cells from the lateral ventricle of a mouse brain. (**a**) DIC images of individual ependymal cells (bottom arrows) and cilia (top arrows) are shown. (**b**) An overlay image of a brain section is stained with antibody against a ciliary marker, acetylated a-tubulin, shown in green (top arrows), and counterstained with a nuclear/DNA marker, DAPI, shown in blue (bottom arrows). Please note that panels a and b represent different brain sections.

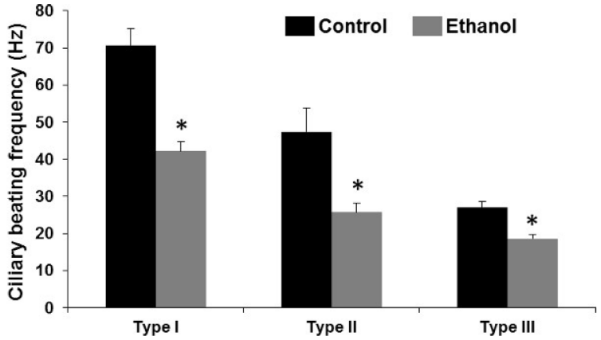


Figure 3: Alcohol and differences in cilia beating frequencies among types of ependymal cells of the mouse brain lateral ventricle. The *ex vivo* brain slice was incubated without (Control) or with (Ethanol) 0.25 % alcohol for 5 min. Compared to control, alcohol treatment significantly decreased cilia beating frequency, as indicated by an asterisk. At least 5-10 independent preparations were used for each ependymal cell type and treatment group.

TANYCYTES

Ependymal cells can specialize into tanycytes, which are rarely ciliated and have long basal processes. Tanycytes form the ventricular lining over the few CNS regions in which the blood-brain barrier is incomplete. They do form **tight junctions** and control the exchange of substances between these regions and surrounding nervous tissue or cerebrospinal fluid.

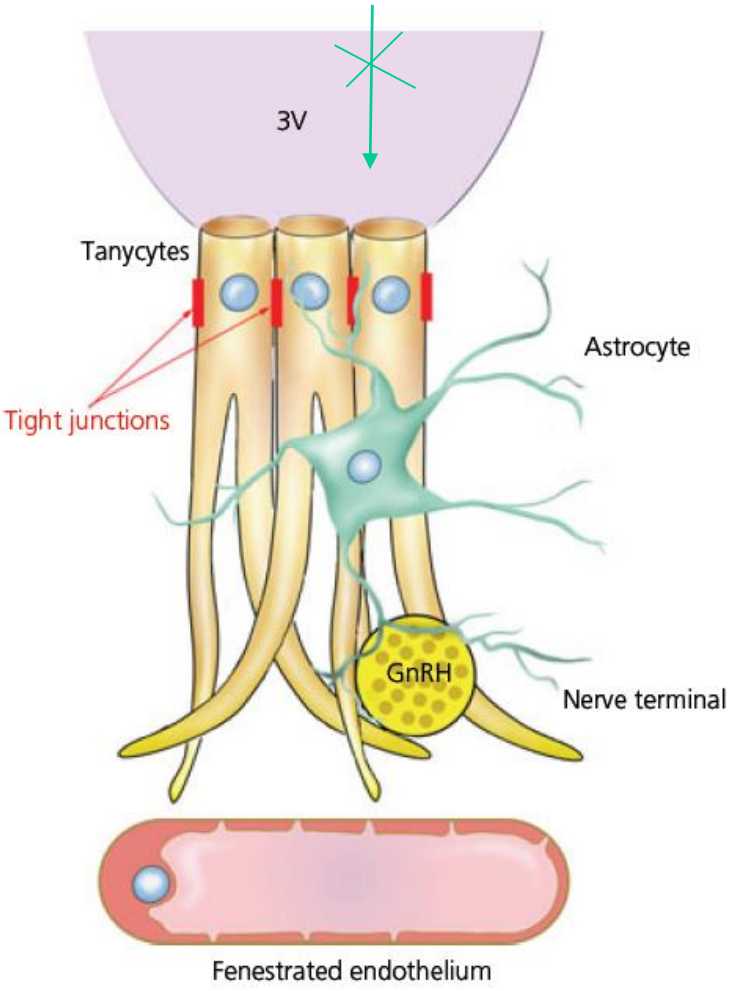


Fig. 1. Schematic representation of the cell types (tanycytes, astrocytes and endothelial cells) and neuronal elements (neuroendocrine terminals) that reside within the median eminence of the hypothalamus. The median eminence of the hypothalamus is the brain structure forming the floor of the third ventricle (3V). The median eminence, which is one of the circumventricular organs of the brain, is capable of conveying information from the brain to the periphery via the release of neurohormones into the circulation and, conversely, sensing information reaching the brain via the bloodstream.

Prevot *et al.* 2010
Journal of Neuroendocrinology **22**, 639–649

Different tanycyte populations in the hypotalamus / median eminence

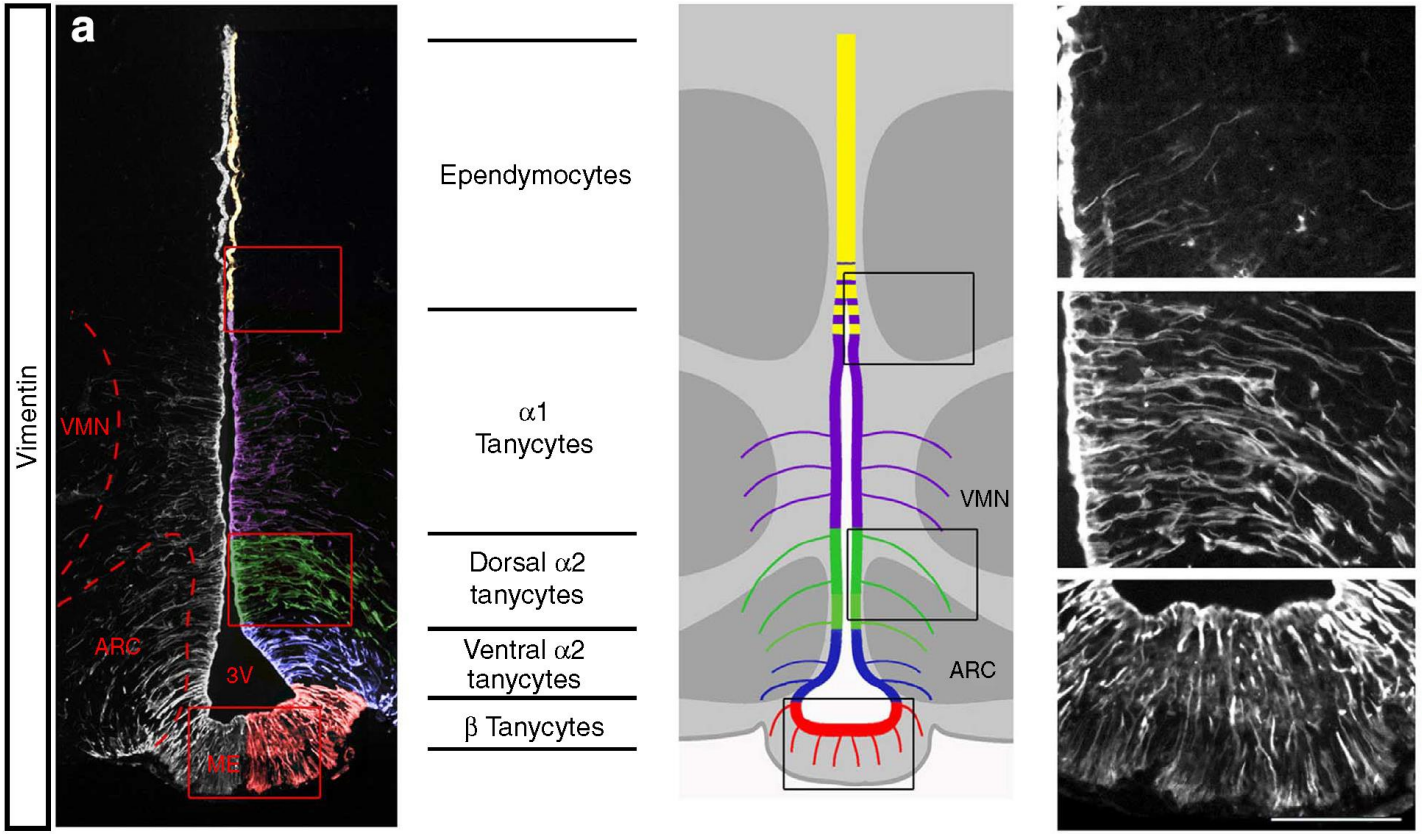


Figure 1 | *GLAST::CreER*^{T2} marks α-tanycytes subpopulations in the adult hypothalamus. (**a**) Left hand panel: coronal section (c.s.) through third ventricle (3V), immunolabelled with Vimentin. The Vimentin^{+ive} process distinguishes tanycytes (false-coloured in right-hand side of image) from ependymocytes. Central panel cartoon shows position and process projection of tanycyte subtypes: purple, α1; green, dα2; blue, vα2; red, β. Note β-tanycytes divide into medial β2 and lateral β1 subsets[13,14]. Right-hand (rh) panel shows high-power magnifications of boxed regions. Ventrally, all ventricular cells appear to have a Vimentin^{+ive} process; medially, many ventricular cells have a Vimentin^{+ive} process; dorsally, the ependymocyte/α1 boundary is indistinct, with intermingling of tanycytes and ependymocytes. (**b–d**): Confocal images, showing c.s. through central hypothalamus, counter-

Robins et al., 2013

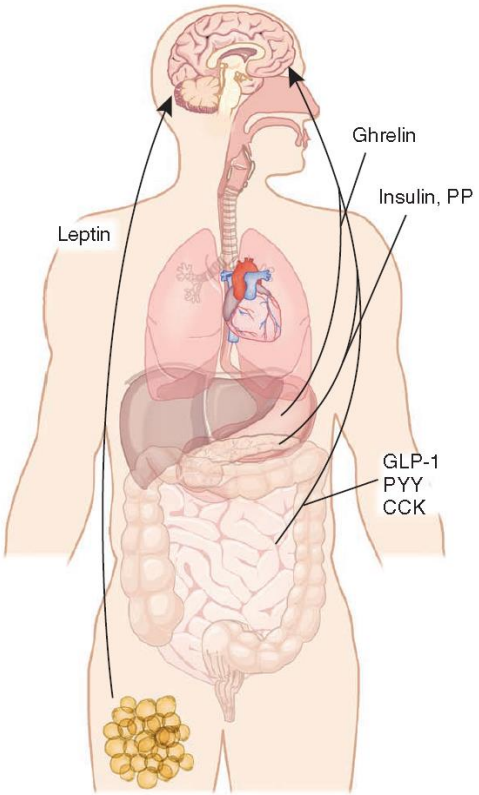
NATURE COMMUNICATIONS | 4:2049 | DOI: 10.1038

Tanycytes: A Gateway to the Metabolic Hypothalamus

F. Langlet*†‡

Journal of Neuroendocrinology, 2014, **26**, 753–760

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.



Central regulation of food intake and energy expenditure. Multiple peripheral factors have been shown to modify food intake and energy expenditure through direct effects on the CNS

The organization of the blood-hypothalamus (Arcuate Nucleus, Median Eminence) **interface**

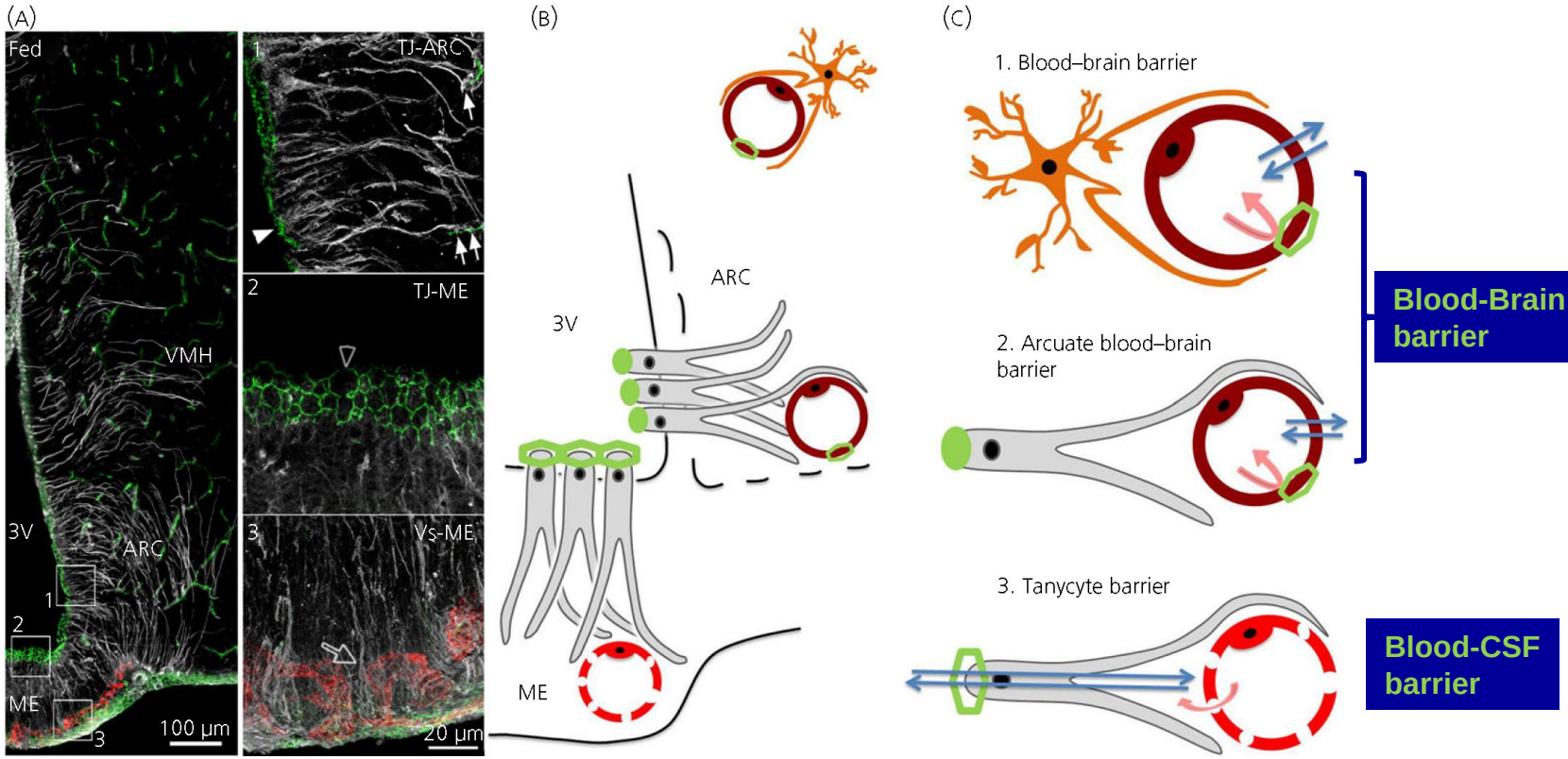
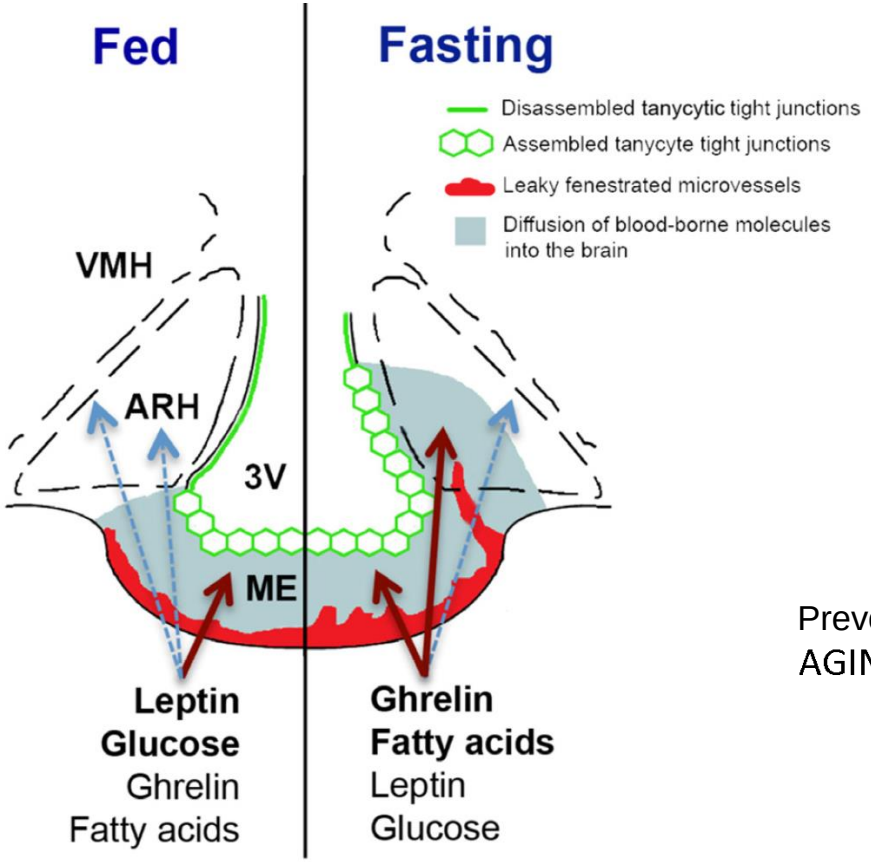


Fig. 1. Organisation of the blood–arcuate nucleus (ARC) interface in the mediobasal hypothalamus. (A) Vimentin (white), zonula occludens-1 (ZO-1; green) and MECA-32 (red) immunoreactivity in coronal sections of the hypothalamic tuberal region in fed animals. Tanycytes exhibit a diffuse pattern of tight 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.

Langlet et al., 2014

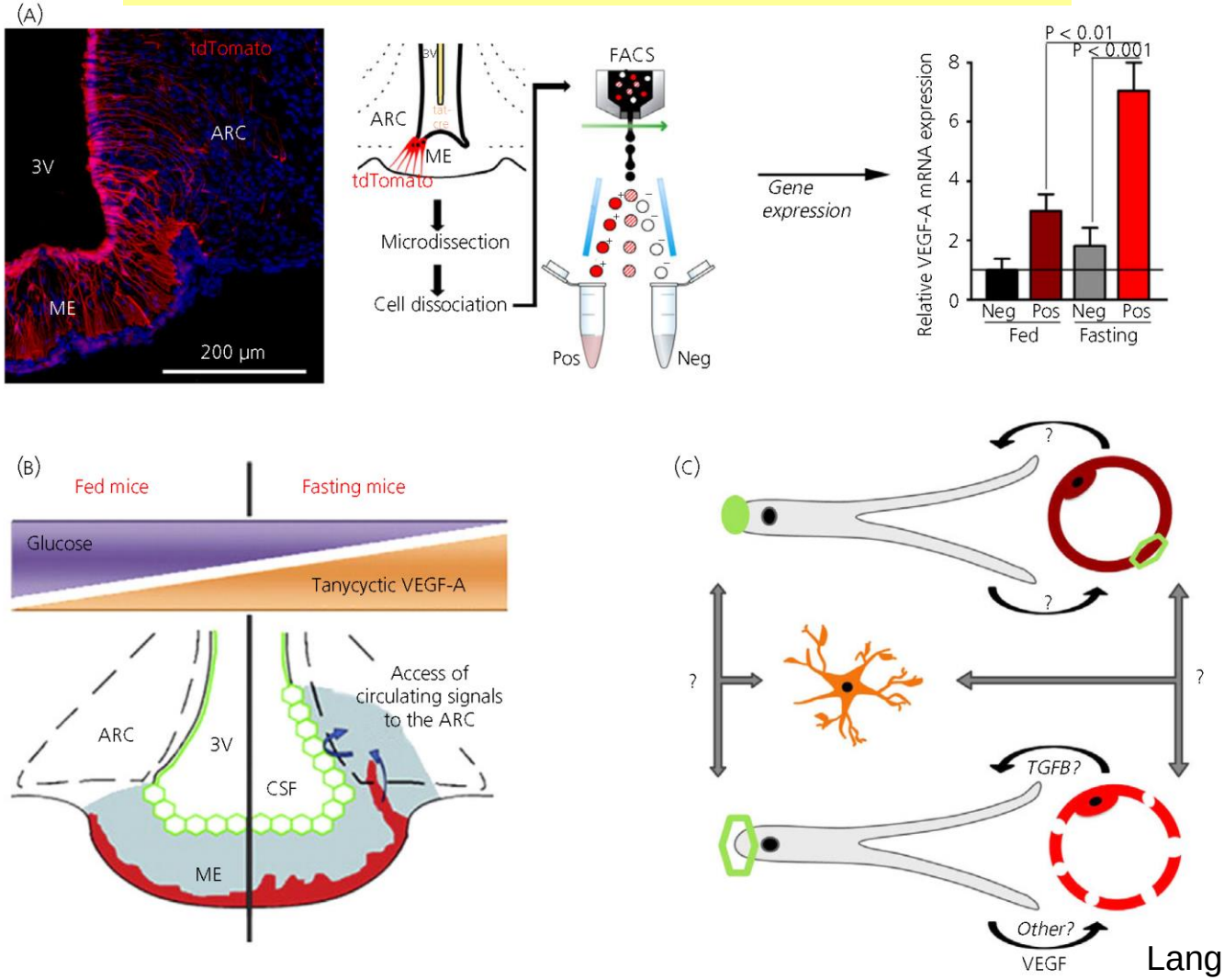
Tanycytes



Prevot et al., 2013
AGING, May 2013, Vol. 5 No.5

Figure 1. Schematic diagram illustrating structural differences between the median eminence and ARH of mice fed *ad libitum* and fasting mice, and their effects on the diffusion of blood-borne signals into the brain. The arcuate nucleus of the hypothalamus (ARH) lies lateral to the third ventricle (3V) and immediately dorsolateral to the median eminence (ME). In mice fed normally (left half of the figure), the fenestrated blood vessels of the ME permit the local diffusion of macromolecules from the circulation, while vessels in the ARH proper exhibit blood-brain barrier properties that block this diffusion (not shown). Hence, circulating metabolic signals whose levels are high in the fed state (e.g., leptin and glucose) require BBB transport to access ARH neurons. Under these conditions, tight junctions (green) between tanycytes line the ventricular wall of the ME, preventing the diffusion of circulating factors into the 3V and CSF. During fasting or energy restriction (right half of the figure), the levels of hormones such as ghrelin rise, along with products of lipolysis (e.g., fatty acids), while leptin and glucose levels fall. Concomitantly, some ME vessels extending into the ARH become fenestrated, while the tight junction barrier along the 3V extends dorsally. These changes allow the freer diffusion of circulating signals that indicate energy restriction to ARH cells, including AgRP/NPY neurons that lie in the ventromedial ARH, while preventing the access of these substances to the rest of the brain through the CSF. The focal plasticity of this dual-faceted blood-hypothalamus barrier thus enhances the orexigenic/anabolic response to energy deficits.

Blood-Arcuate Nucleus interface plasticity



Langlet et al., 2014

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.