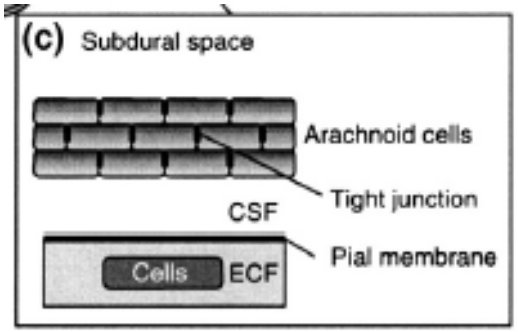
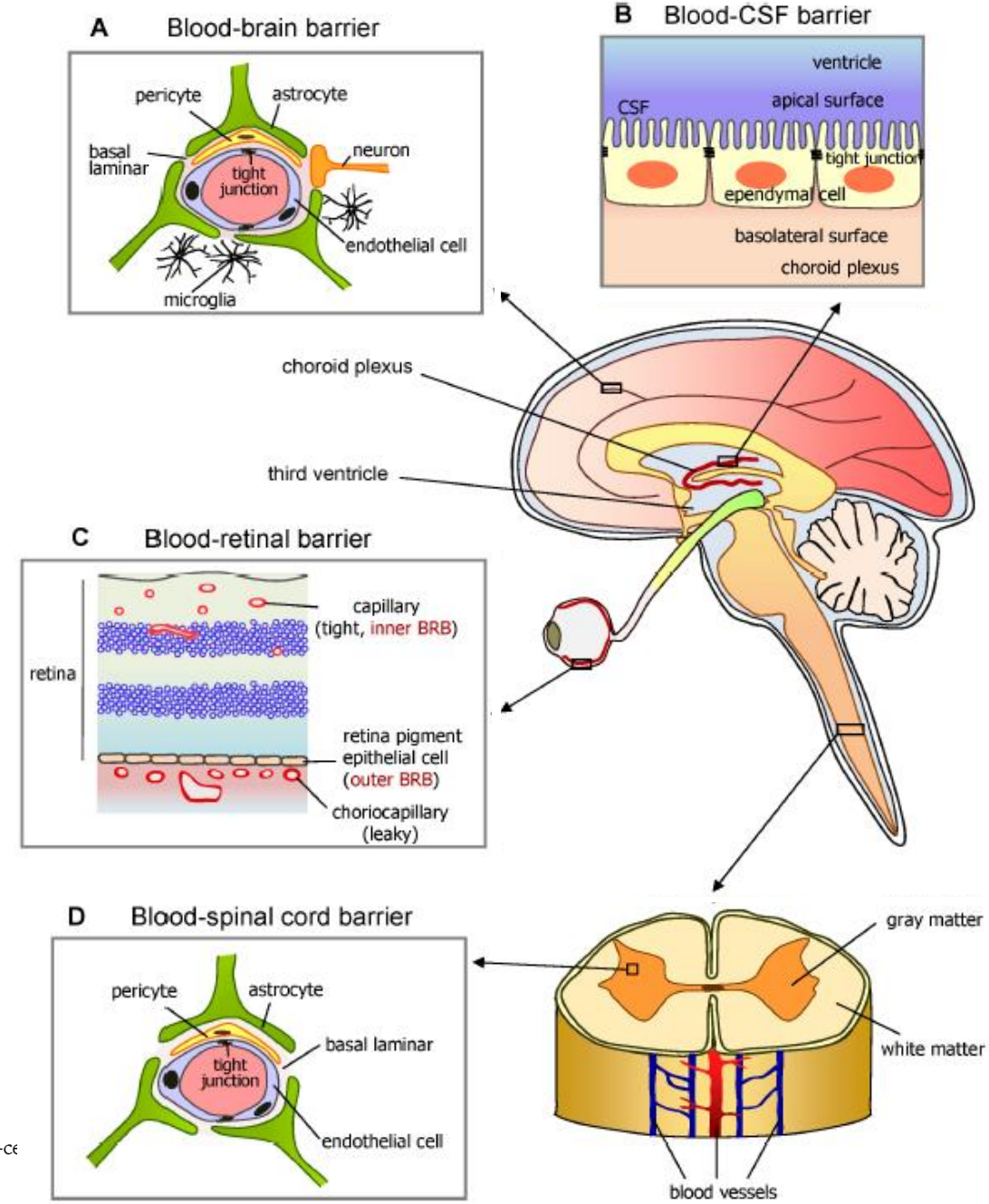
Az idegrendszer határfelszínei és a neurovaszkuláris egység

Határfelszínek az idegrendszerben

- vér-agy gát [blood-brain barrier (BBB)]
- vér-liquor gát [blood-cerebrospinal fluid barrier (BCSFB)]
- arachnoid gát
- vér-retina gát
- vér-gerincvelő gát



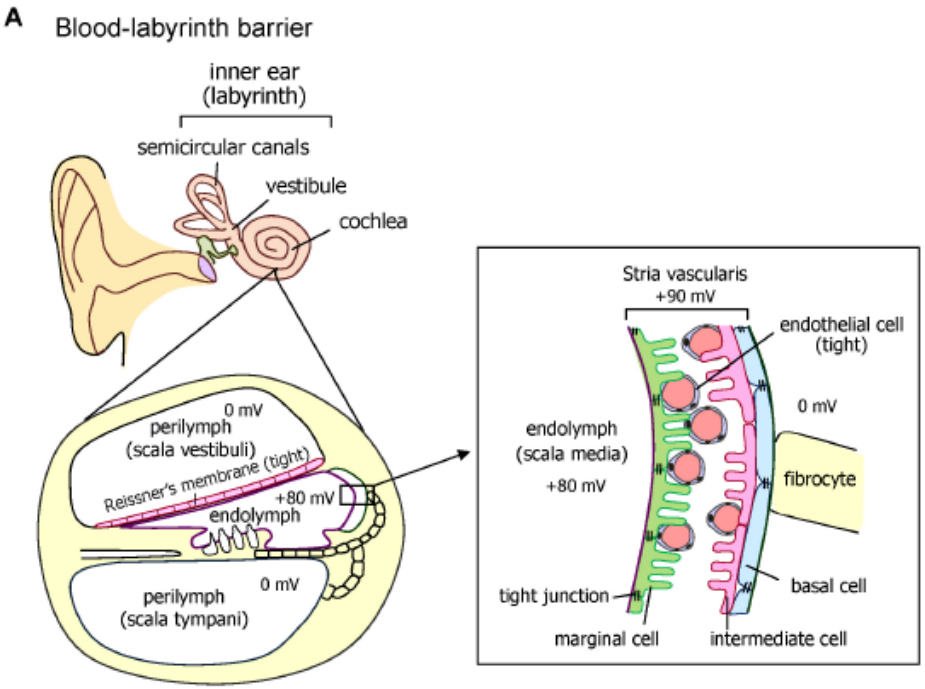


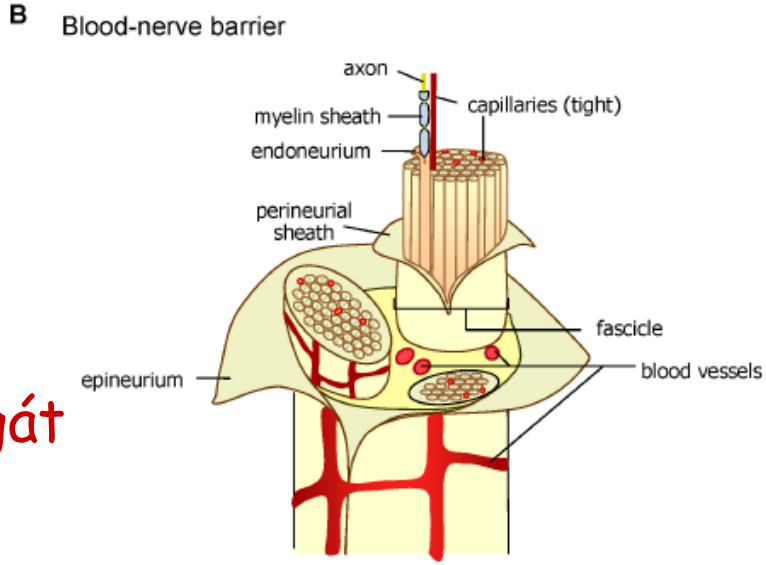
Blood-neural barrier: its diversity and coordinated cell-to-ce communication

*Yoon Kyung Choi & Kyu-Won Kim**

Határfelszínek az idegrendszerben

- vér-agy gát [blood-brain barrier (BBB)]
- vér-liquor gát [blood-cerebrospinal fluid barrier (BCSFB)]
- arachnoid gát
- vér-retina gát
- vér-gerincvelő gát
- vér-belső fül gát
- vér-ideg gát





fizikai – transzport – metabolikus gát

Blood-neural barrier: its diversity and coordinated cell-to-cell communication

*Yoon Kyung Choi & Kyu-Won Kim**

A központi idegrendszer védőrétegei: agyhártyák

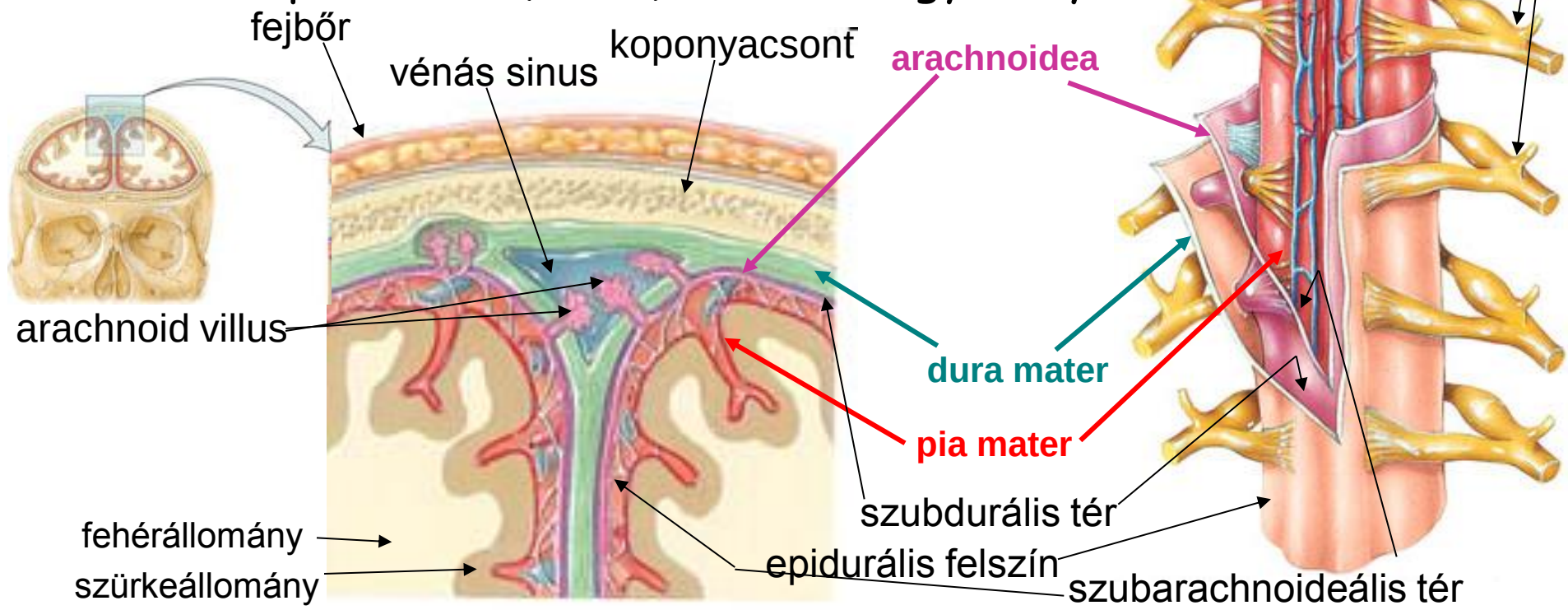
- csontos koponya / gerinc + agyburkok
  - dura mater (külső): kemény agyhártya

szubdurális tér ⇨

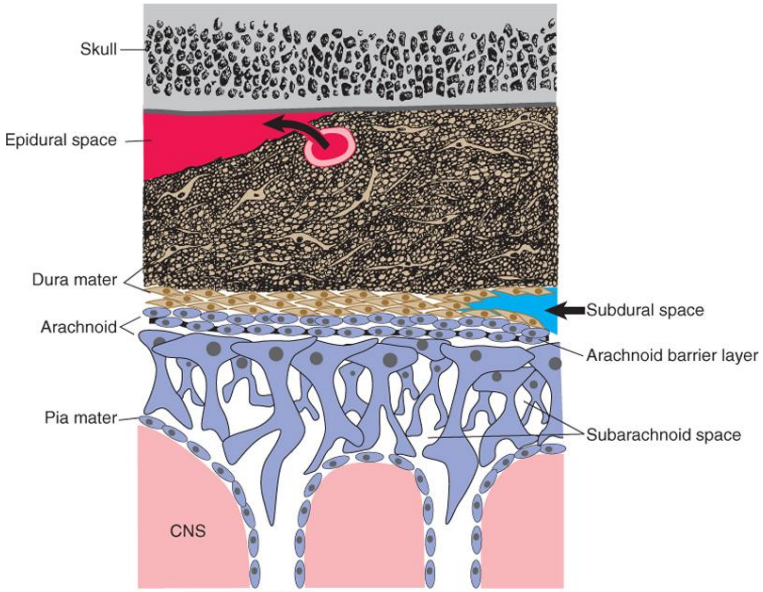
  - arachnoidea (középső): pókhálóhártya

szubarachnoideális tér ⇨ *agyfolyadék (likvor)*

  - pia mater (belső): érhordó agyhártya



A központi idegrendszer védőrétegei: agyhártyák



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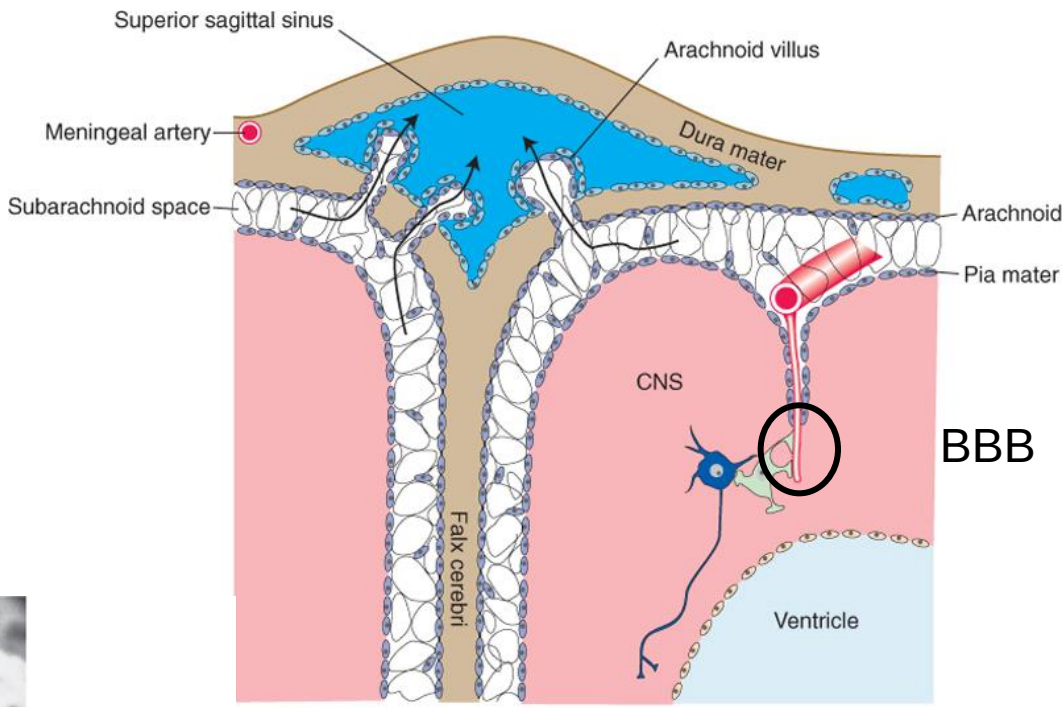

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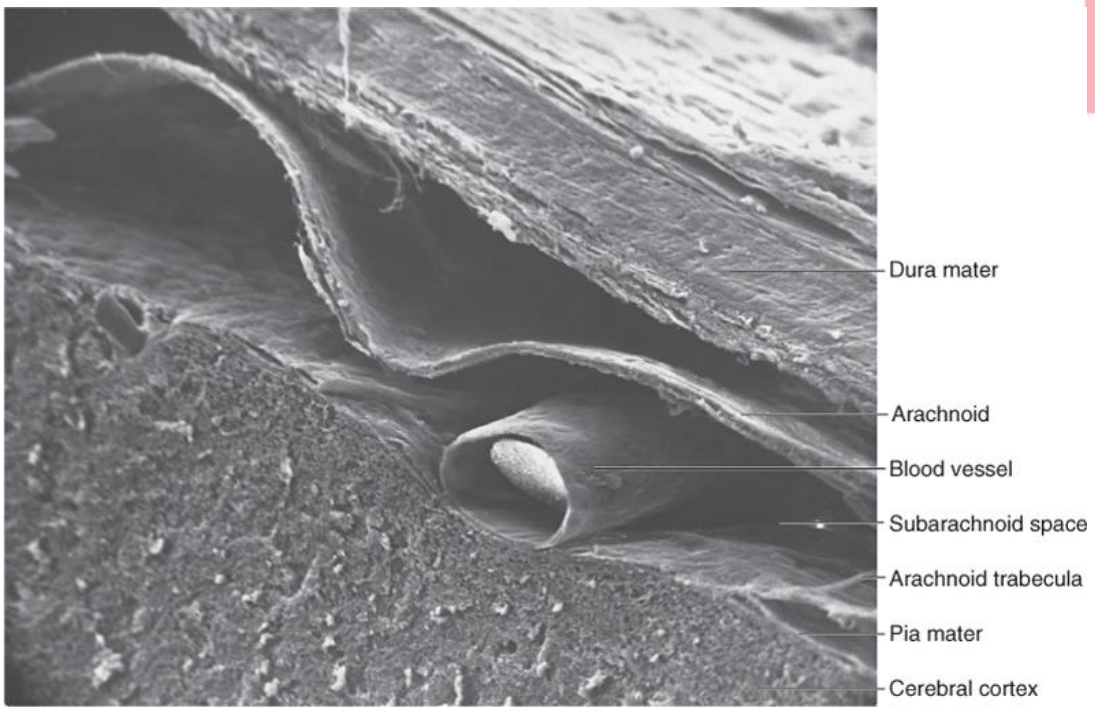

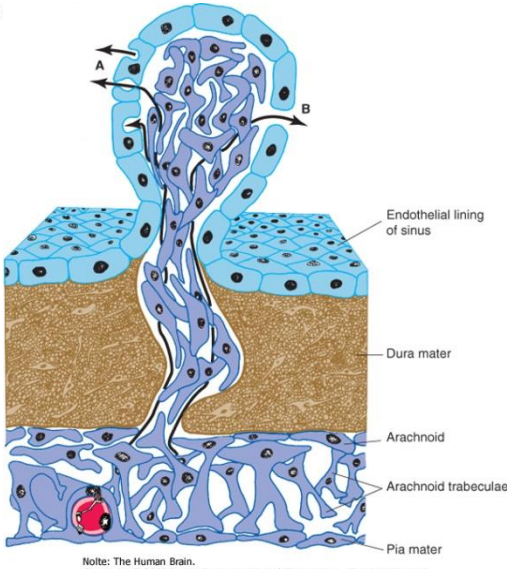

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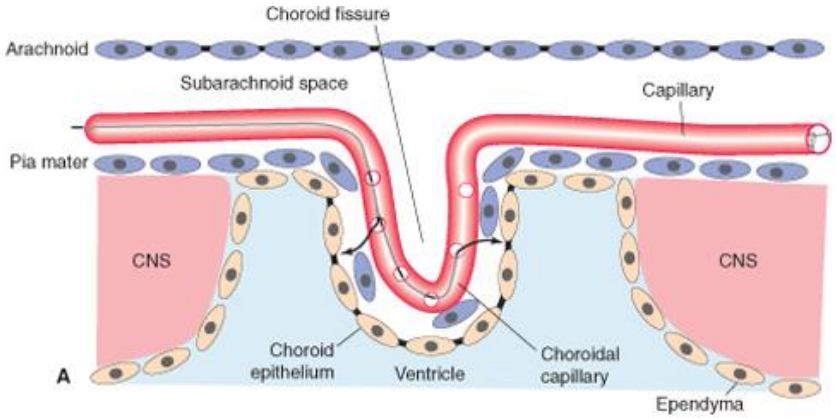
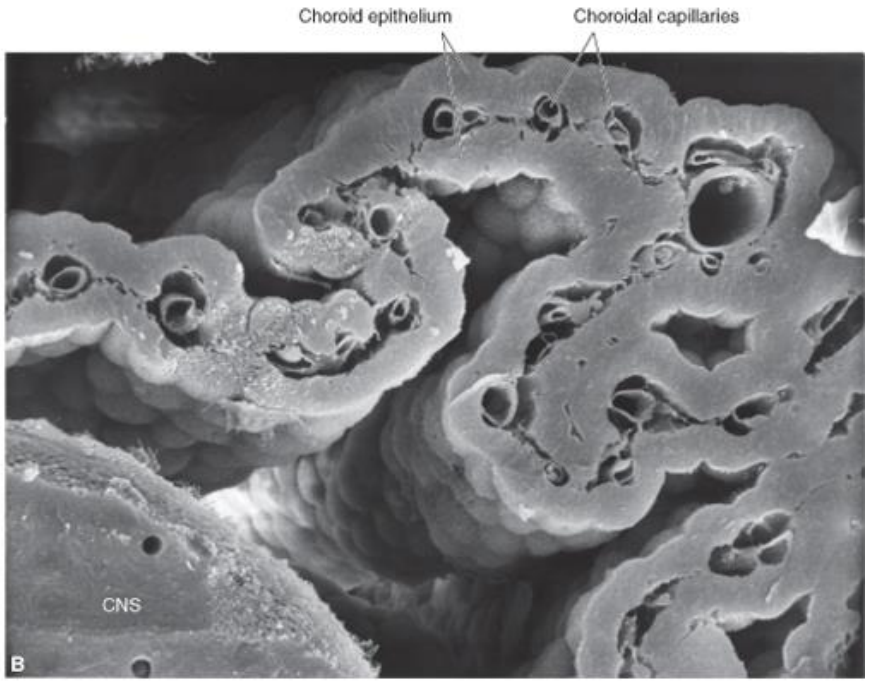
A choroid plexus





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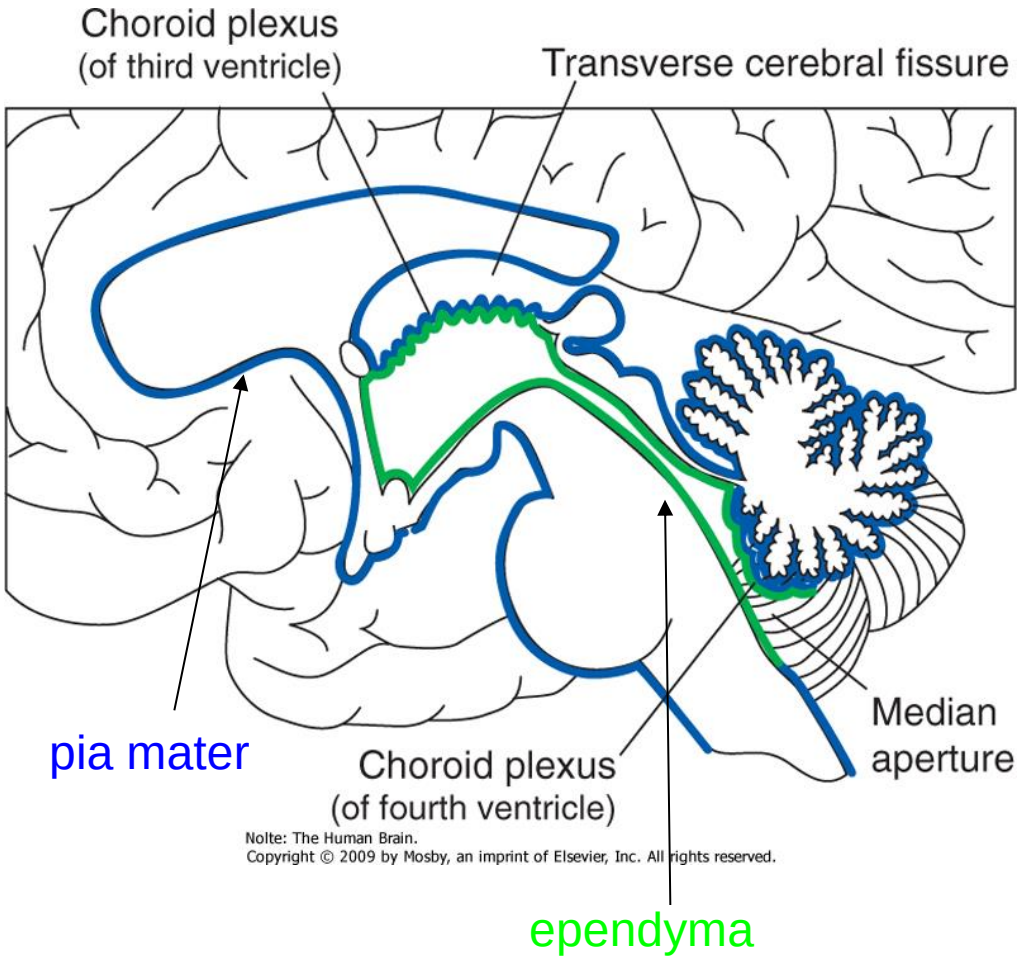

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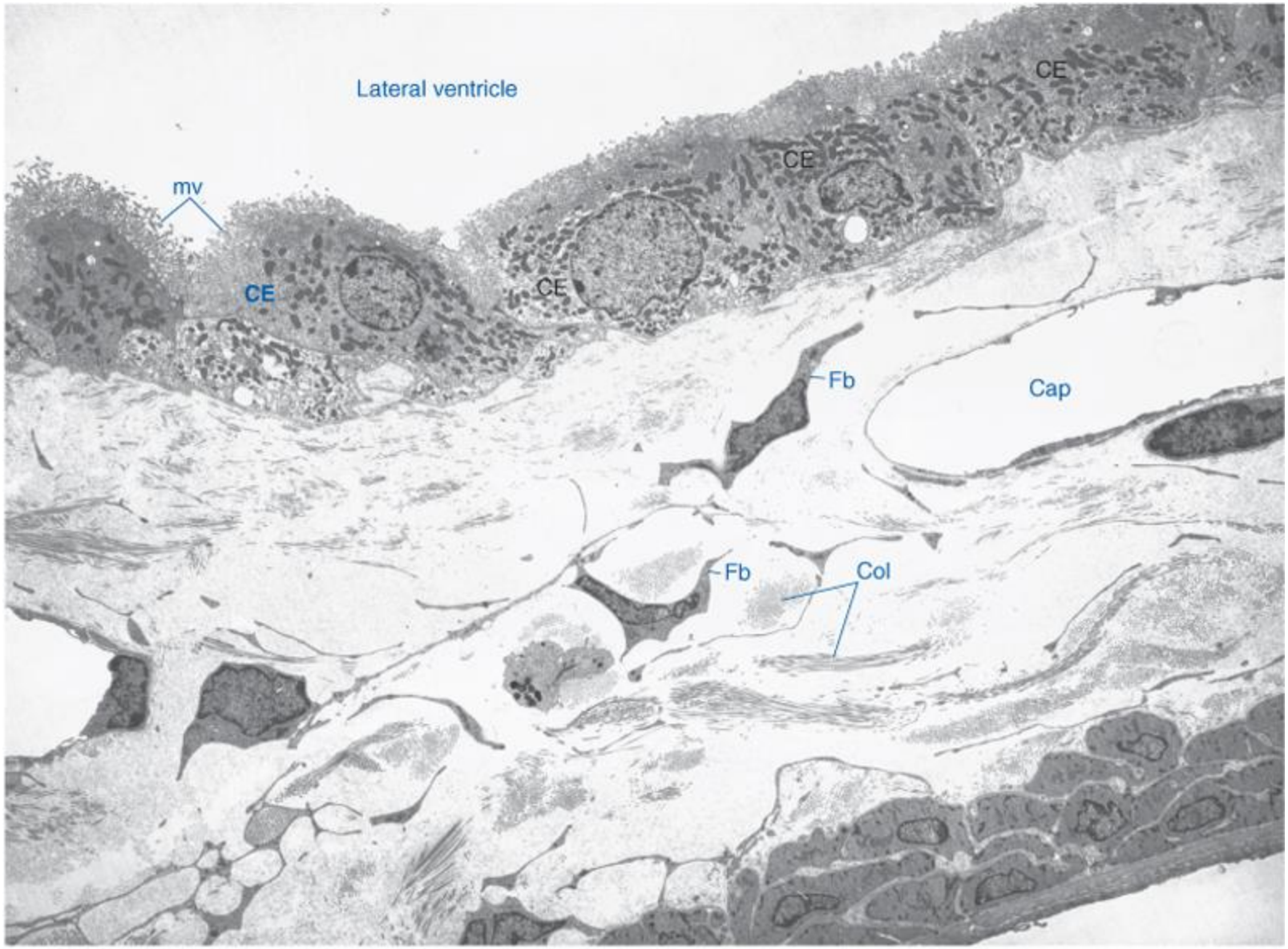
A choroid plexus



A

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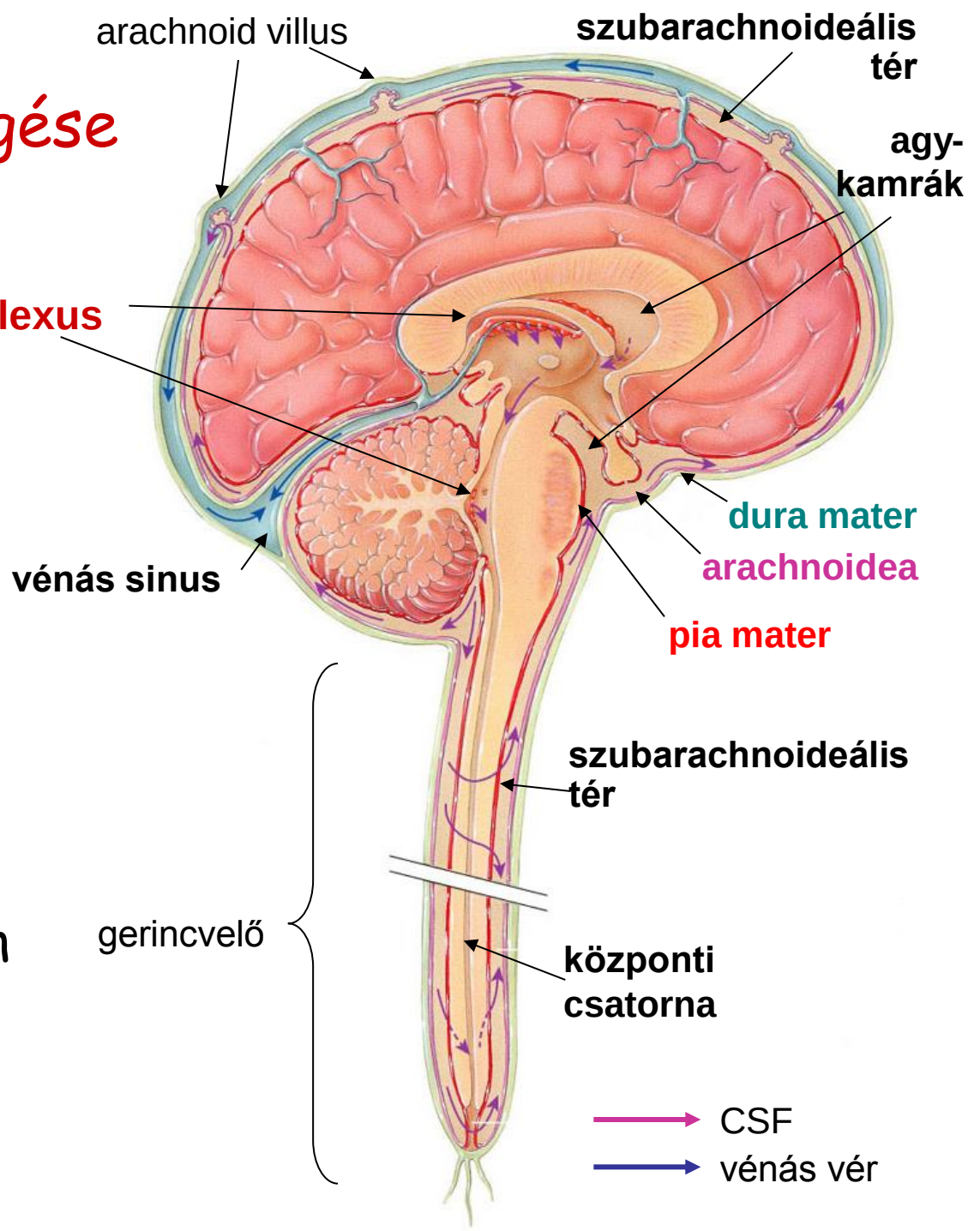
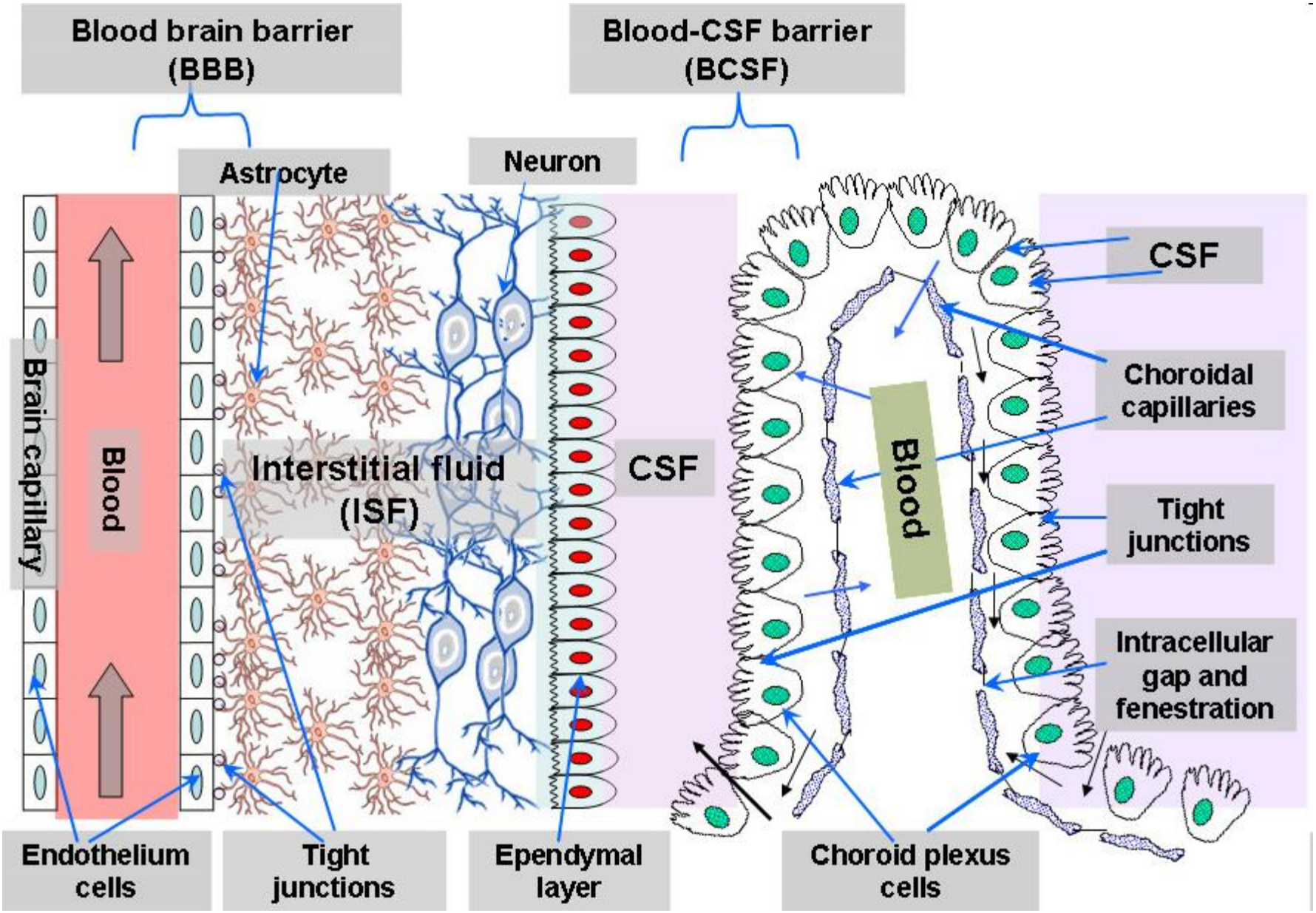
A cerebrospinális folyadék (CSF) keringése

- termelődés (főleg) az agykamrák choroid plexusaiban
- visszaszívódás agyi vénás szinuszokból (arachnoid villus) a hidrosztatikai nyomáskülönbség alapján



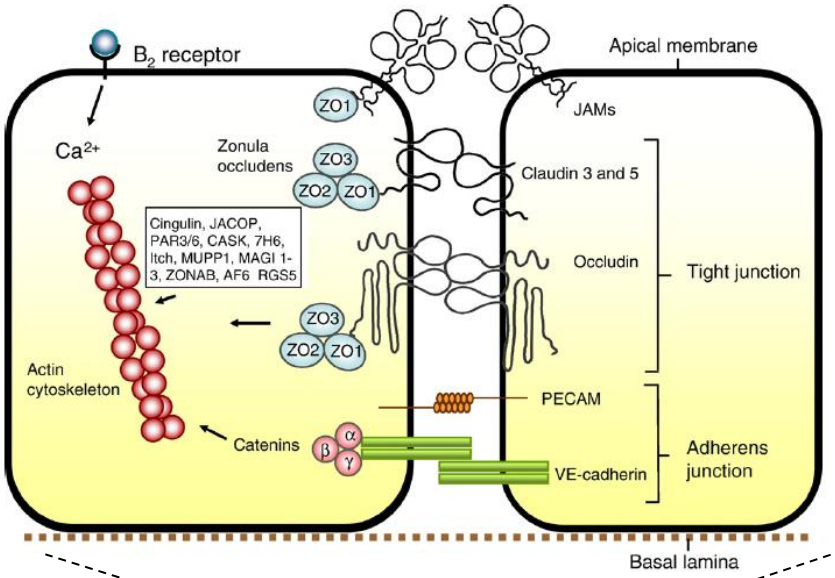
Az agyi érhálózatok és folyadékterek

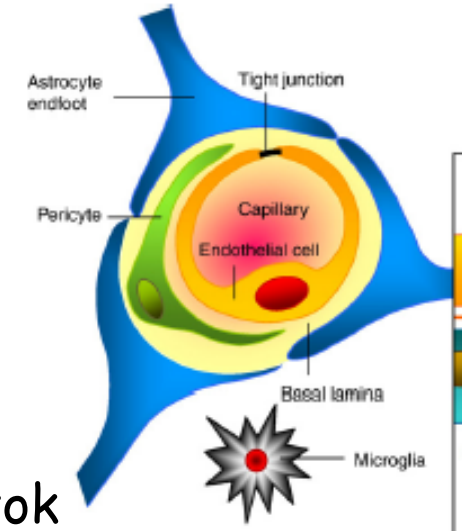


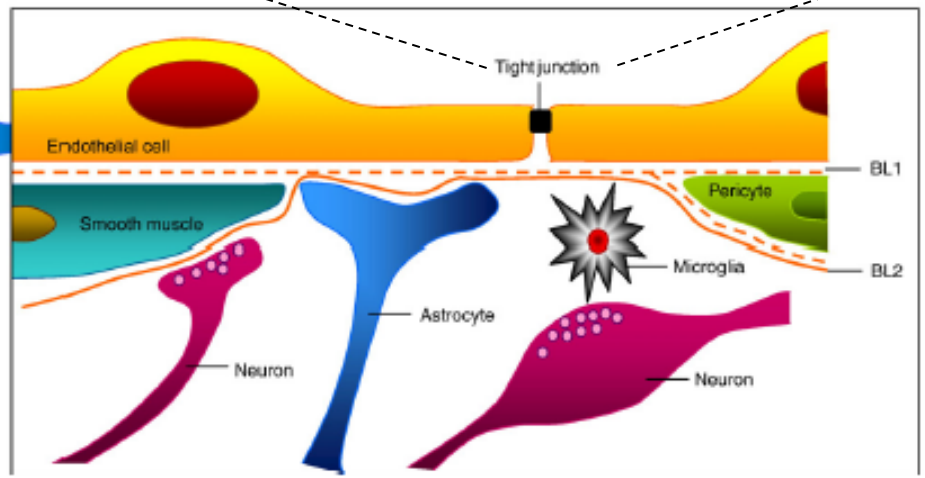
A vér-agy gát [BBB]

- legnagyobb határfelszín: 12-18 m^2 / humán agy; 600-700 km hosszú érhálózat; sejtek max. 25 μm távolságra – diffúzió is elég
- *zonula occludentes* : nagyon szoros tight junction az endotél sejtek között
  - paracelluláris transzport gyak. gátolt -> nagy elektromos ellenállás (~1800 Ohm/cm^2); ionokra, glükózra nem permeábilis
  - egyes vazoaktív anyagok növelhetik a paracelluláris permeabilitást
  - polarizált transzporter-eloszlás
- vér és agyi ISF folyadékterek „szigetelése" + szabályozott transzportfolyamatok

JAM: junctional adhesion molecule







Structure and function of the blood–brain barrier

N. Joan Abbott *, Adjanie A.K. Patabendige, Diana E.M. Dolman, Siti R. Yusof, David J. Begley

A neurovaszkuláris egység

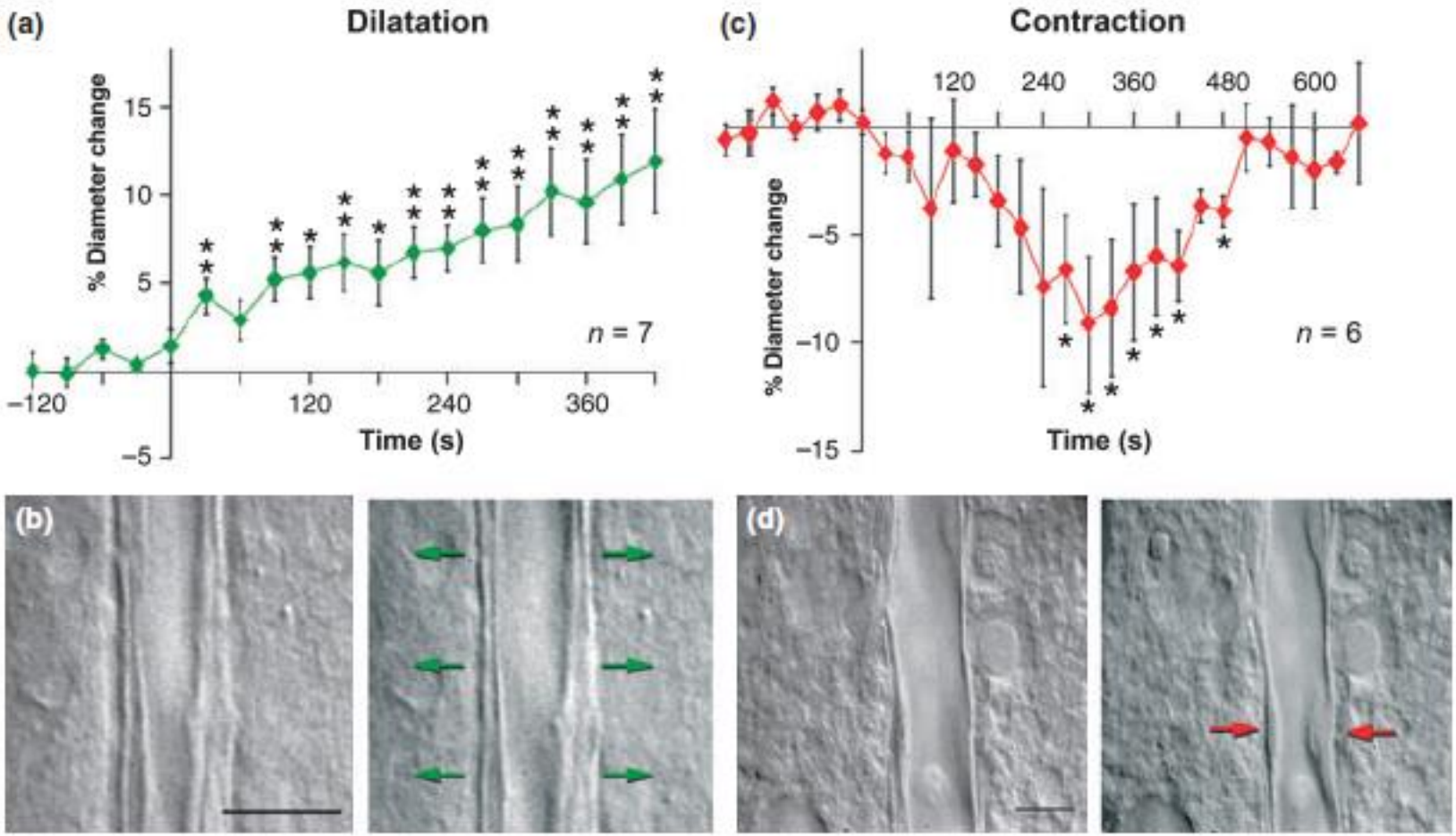
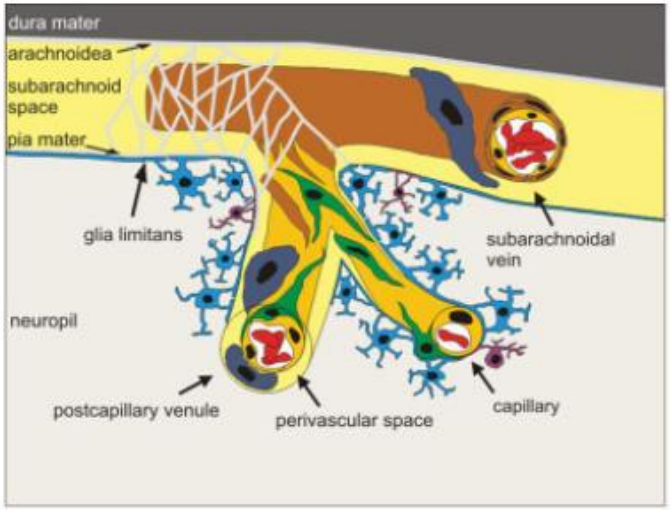


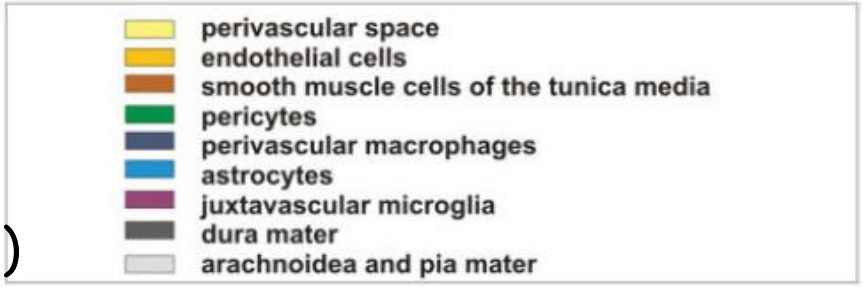
Figure 2 Dilation or constriction of cortical blood vessels evoked by single interneuron stimulation. Mean values of dilating (a) and contracting (c) responses induced by evoked firing of different cortical GABA interneurons. $^{*}P < 0.05$ and $^{**}P < 0.01$ from pre-stimulation value. (b and d) images of blood vessels before (left) and after (right) electrical stimulation (120 s) of interneurons. From Cauli *et al*. 2004 with permission.

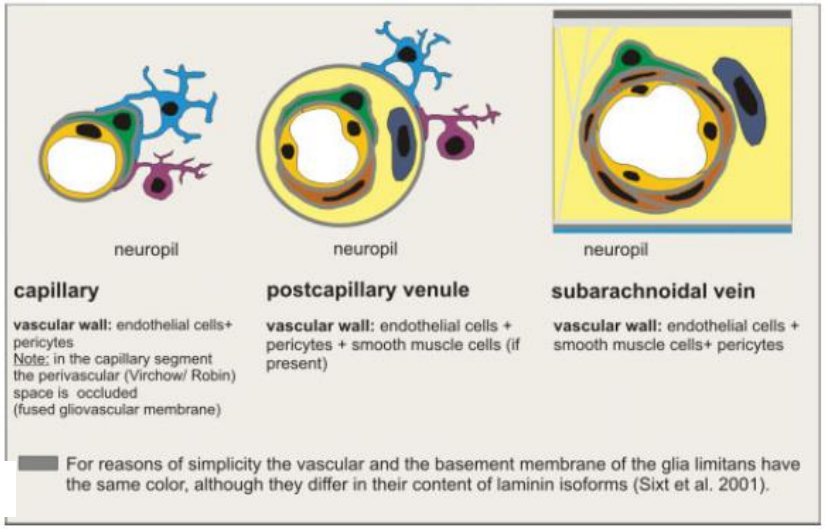
A neurovaszkuláris egység

- érfal
  - endotél sejtek (*tunica intima*) + alaphártya
  - simaizom (kapillárisokban nincs!!)
  - pericíták
- perivaszkuláris (Virchow-Robin) tér
  - leptomeningeális sejtek
  - makrofágok
  - egyéb AP sejtek
- juxtavaszkuláris parenchima (neuropil)
  - glia limitans: asztrocita talpak
  - mikroglia
  - \+ axonok

• az egyes szakaszok MB összetétele eltérő

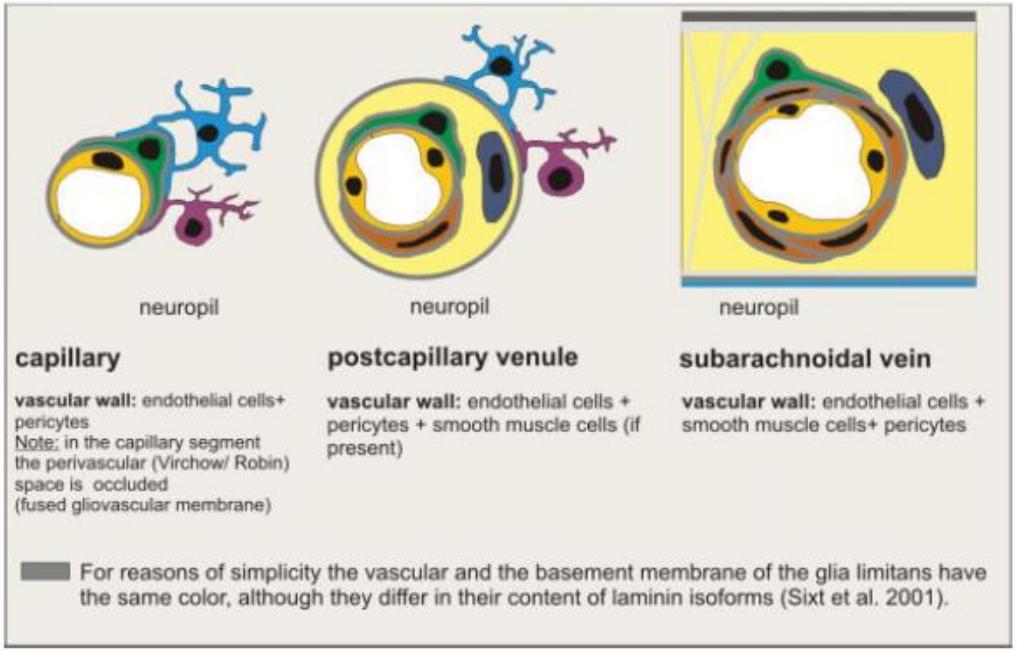


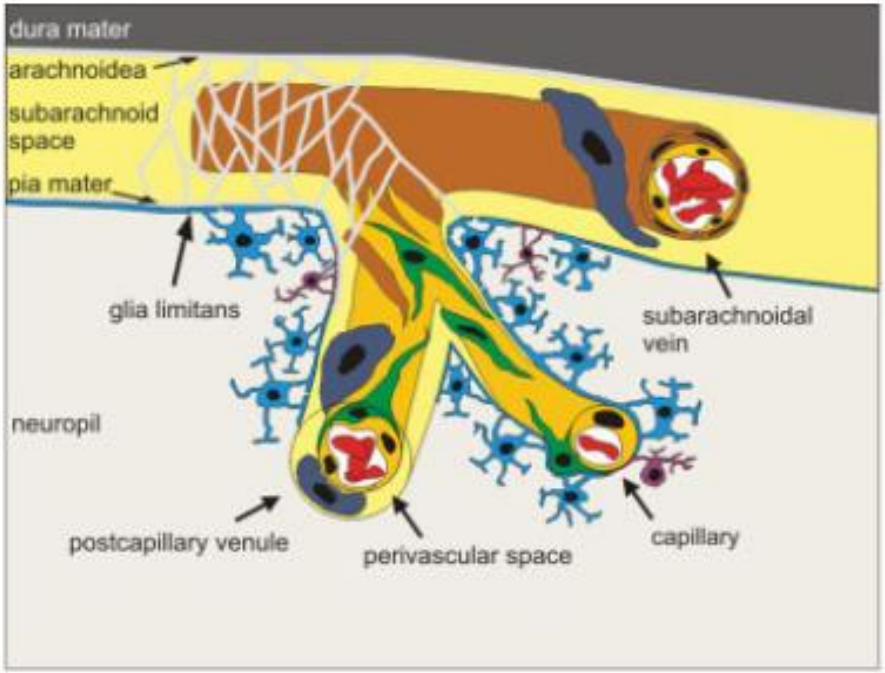




CNS Pericytes: Concepts, Misconceptions, and a Way Out
MARTIN KRUEGER AND INGO BECHMANN*
GLIA 58:1–10 (2010)

A neurovaszkuláris egység





CNS Pericytes: Concepts, Misconceptions, and a Way Out

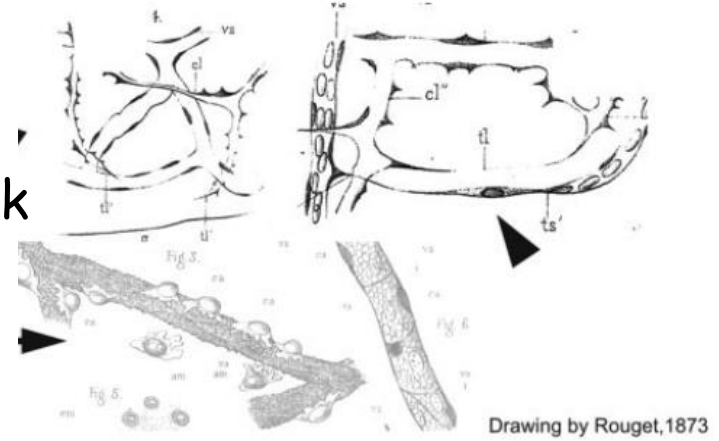
MARTIN KRUEGER AND INGO BECHMANN*

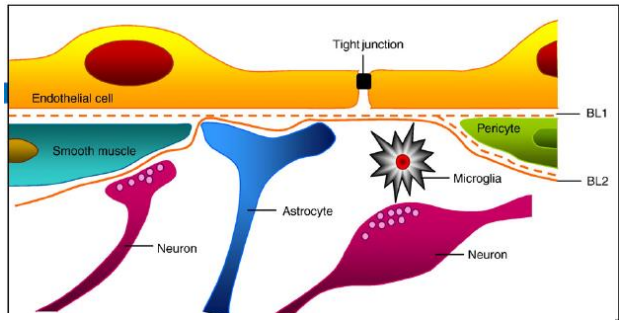
Fig. 1. Topography of the neurovascular unit. (**A**) The scheme gives an overview of the neurovascular interface showing a subarachnoid vein, a postcapillary venule, and a capillary. The vascular wall is formed by endothelial cells, pericytes, and in larger vessels additionally smooth muscle cells of the tunica media. By definition, pericytes are part of the vascular wall (first compartment) and are therefore morphologically separated from cells of the perivascular (Virchow/Robin) space or the juxtavascular parenchyma. This distinction is only possible at the ultrastructural level or in semi-thin sections where the different compartments are visible. (**B**) These schemes represent cross sections through capillaries and larger vessels. The basement membranes (in red) provide clear-cut morphological borders to distinguish the different compartments. The inner basement membrane surrounds the endothelium while the outer one surrounds the vascular wall including pericytes or smooth muscle cells. In capillary vessels, the basement membrane of the glia limitans fuses with the outer vascular basement membrane, thus occluding the perivascular space.

A periciták

- 1873, Rouget: ér körüli, kontraktilis (?) elemek
  - endotél sejtek mellett, MB alatt
  - agyi homeosztázis
  - BBB integritás
  - angiogenezis, neovaszkularizáció
  - CBF (cerebral blood flow)

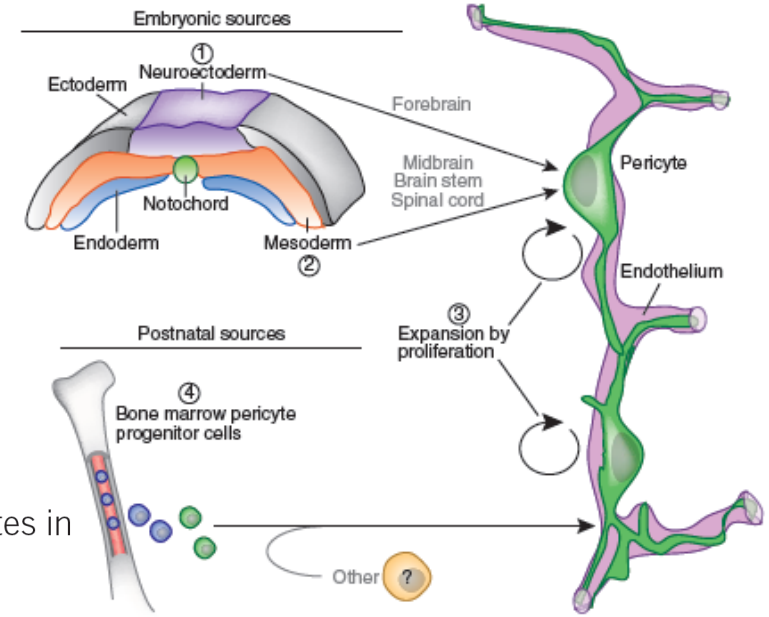
szabá-lyozása





- mezodermális + velősánc (embrionális) és csontvelői (főleg felnőtt) eredet

- egyes érszakaszokon más-más arányban fordulnak elő, nehéz azonosítás



Central nervous system pericytes in health and disease

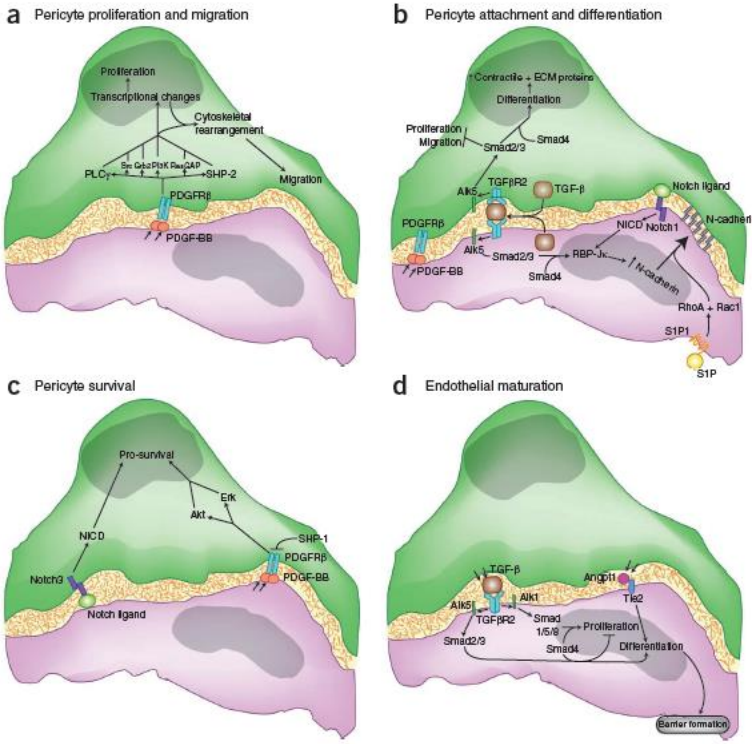
Ethan A Winkler[1,2], Robert D Bell[1,2] & Berislav V Zlokovic[1]

VOLUME 14 | NUMBER 11 | NOVEMBER 2011 NATURE NEUROSCIENCE

A periciták

- endotél sejtek PDGFβ-függő borítása -> BBB integritás ⇧

- hipoxiára (<2h) elsőként reagál morfológiai változással:
  - luminális MB vastagszik, glia limitans alatt vékonyodik; migráló sejtalak
  - uPA (urokináz plazminogén aktivátor) expresszió -> synaptic stripping – szinapszis redisztibúció
  - VEGF-érzékenység ⇧



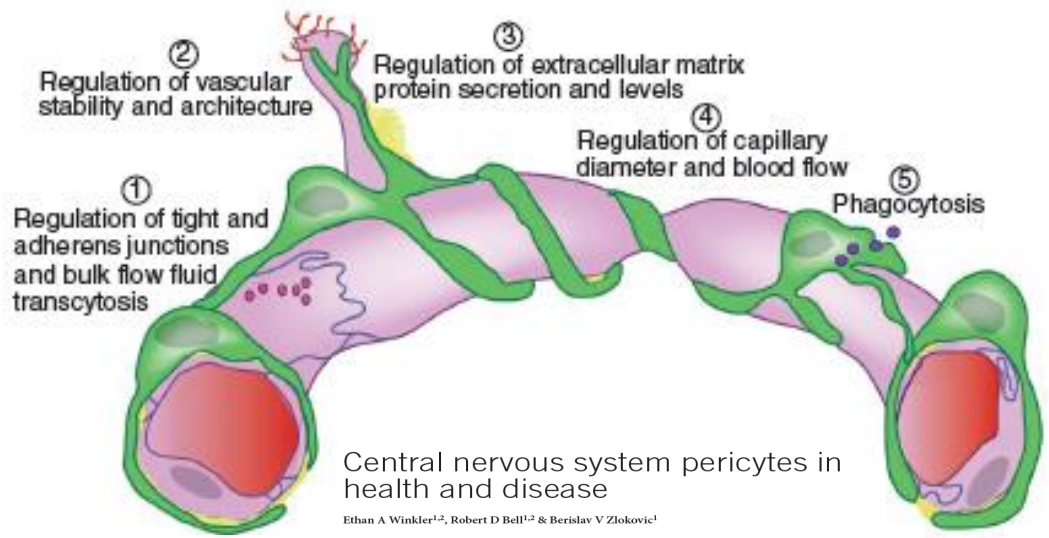
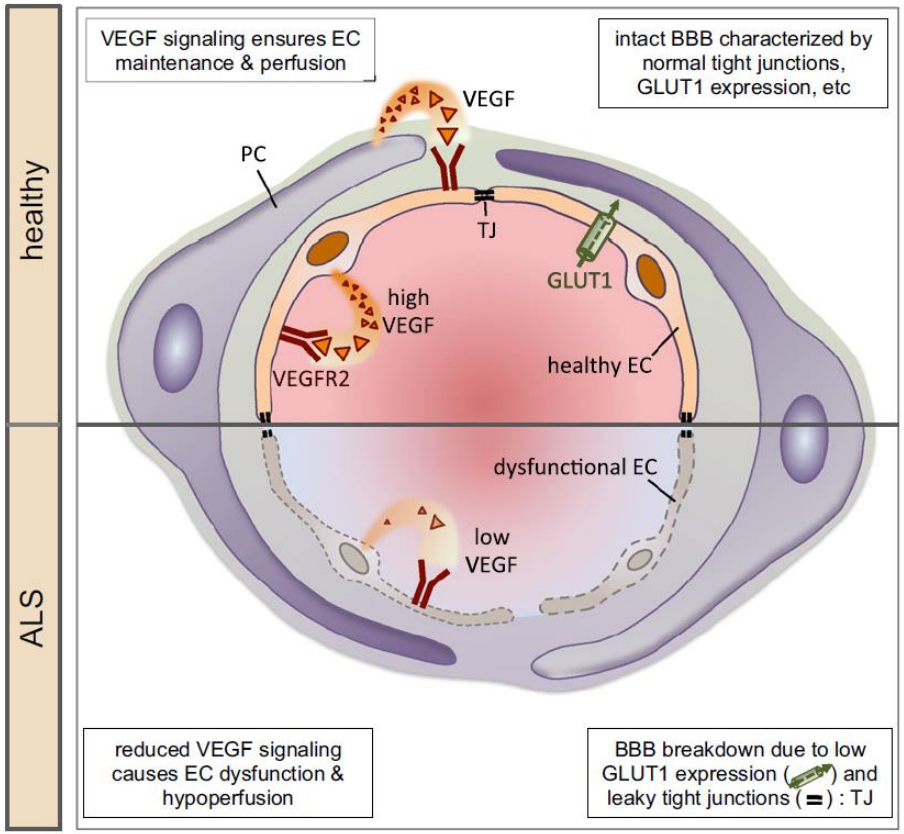


Figure 4 Pericytes are multi-functional members of the neurovascular unit. Pericytes (1) control BBB integrity by regulating the orientation and abundar of endothelial tight and adherens junction proteins, as well as the rate of bul flow fluid transcytosis (transendothelial transport of fluid-filled vesicles); (2) regulate the stability and architecture of newly formed cerebral microves (3) contribute to secretion and regulate the levels of extracellular matrix prot forming the basement membrane; (4) regulate capillary diameter and blood flow; and (5) provide clearance and phagocytotic functions in brain.

A periciták

- agy vérátáramlás (CBF) szabályozás:
  - neurodegeneratív betegségekben BBB gyakran sérül: VEGF termelés csökken, hipoperfúzió
  - kontraktilitás, ill. beidegzés mértéke változik
  - agyi kapillárisok: 65%-a a NAerg beidegzésnek itt végződik és nem a prekapillárisokon
    - ATP, NA: vazokonstrikció
    - GABAR blokkolás: vazokonstrikció
    - Glu serkentés: vazodilatáció



The Neurovascular Link in Health and Disease: Molecular Mechanisms and Therapeutic Implications

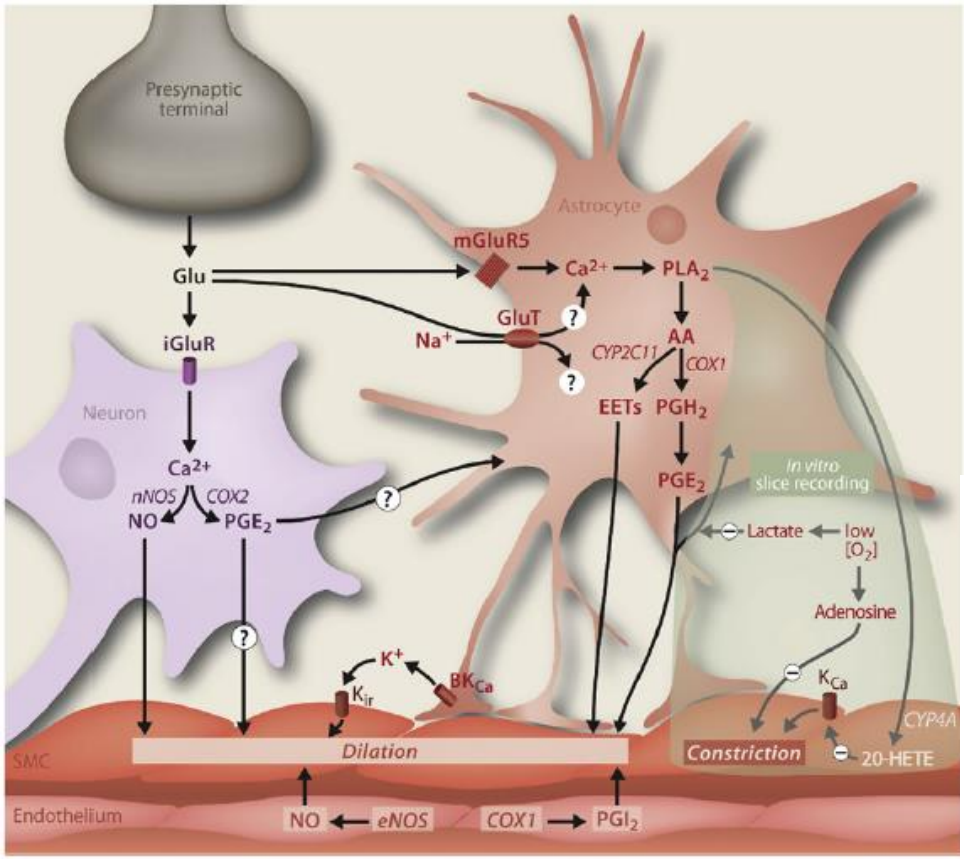
Neuron *71*, August 11, 2011

- funkcionális hiperémia

Asztroglia és a neurovaszkuláris egység

Role of Astrocytes in Neurovascular Coupling
Neuron 71, September 8, 2011

- „funkcionális intermedier": asztroglia-borítás



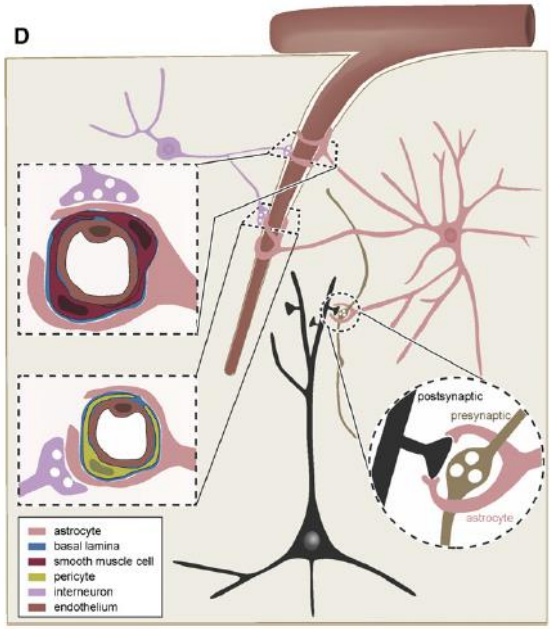
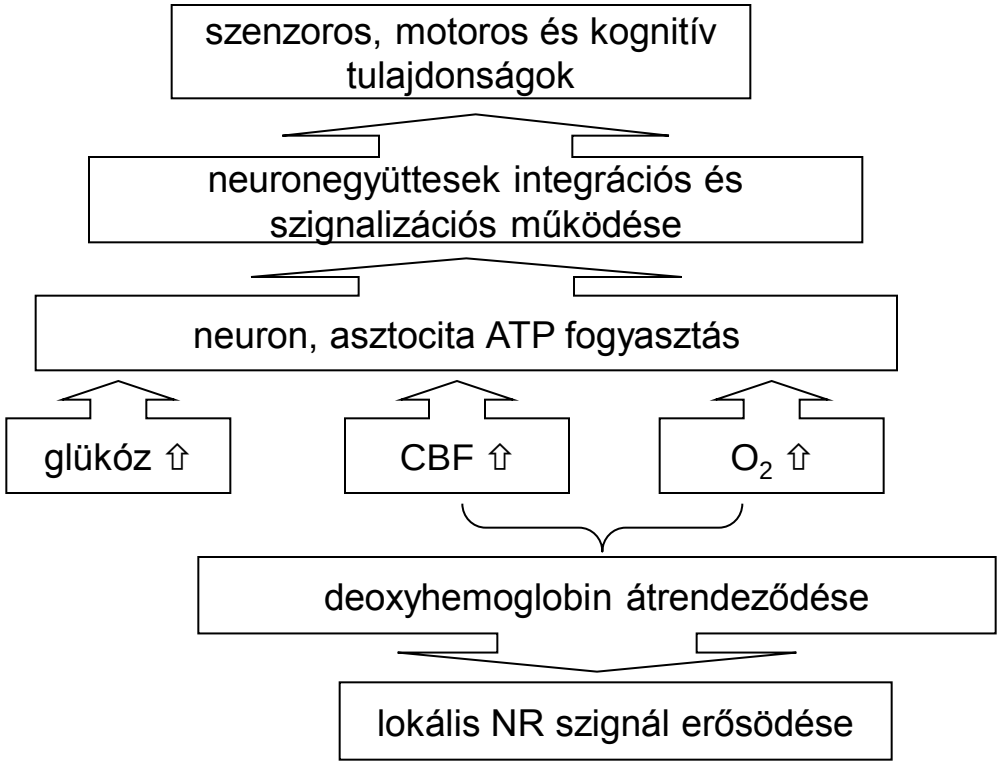


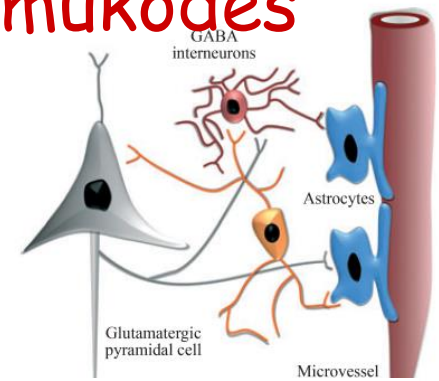
Figure 4. Postulated Signaling Pathways from Synapse to Blood Vessel

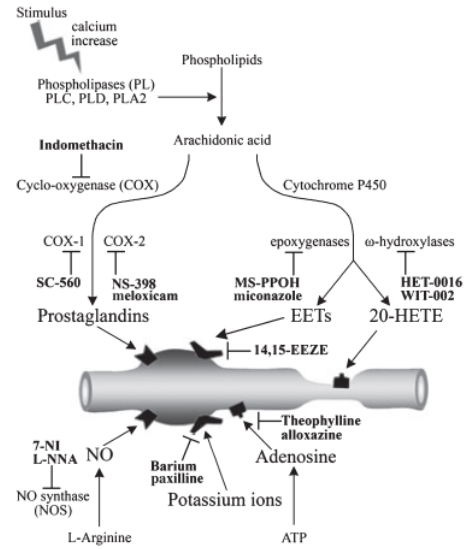
Molecular pathways that have been identified in in vivo and in vitro studies are displayed. Pathways that have only been identified in vitro, but await characterization in vivo, have been highlighted to the right. Question marks indicate unknown molecular mediators. In summary, presynaptic terminals release glutamate (Glu), which acts on postsynaptic neurons and astrocytes. In postsynaptic neurons, glutamate activates ionotropic receptors (iGluR), which trigger calcium elevations that activate neuronal NO synthase (nNOS) and cyclooxygenase 2 (COX2), which in turn leads to production of PGE_2. It is not known whether PGE_2 dilates blood vessels by acting on smooth muscle cells or on astrocytes. In astrocytes, glutamate activates metabotropic glutamate receptors-5 (mGluR5), which triggers calcium elevations that—by phospholipase A_2 (PLA_2)-mediated synthesis of arachidonic acid (AA)—lead to production of PGE_2 through COX1 and epoxyeicosatrienoic acids (EETs) through cytochrome P450 2C11 epoxygenase (CYP2C11). Moreover, calcium induces potassium release from astrocytic endfeet through large conductance calcium-dependent potassium channels (BK_{Ca}), which in turn triggers vasodilation through hyperpolarization of smooth muscle cells via inward-rectifier potassium channels (K_{ir}). Glutamate is also taken up into astrocytes through glutamate/Na^+-cotransport, but the pathways that eventually lead to vasodilation remain unknown. In addition to these neurovascular pathways, endothelial cells can also trigger vasodilation via endothelial NO synthase (eNOS) and PGI_2 production by COX1. Slice studies have suggested that astrocytic calcium can by unknown mechanisms also lead to vasoconstriction

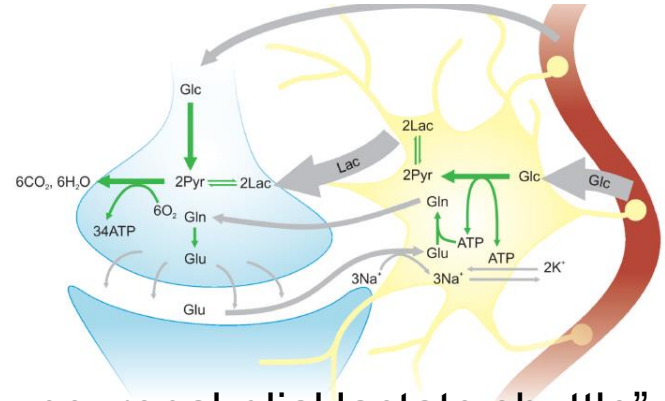
A neurovaszkuláris egység és az agyi működés

- funkcionális hiperémia / neurovaszkuláris csatolás: agyműködés ⇧ -> lokális CBF ⇧; főleg artériákon
- ált. feedforward hatás: neuronális aktivitás ⇧ -> Glu release ⇧ -> gliális uptake ⇧ -> laktát, ATP release ⇧
- fMRI / BOLD (blood oxygenation level dependent contrast) mérések









„neuronal-glial lactate shuttle”

EEG-fMRI mérések

Magn Reson Mater Phy (2010) 23:309–316

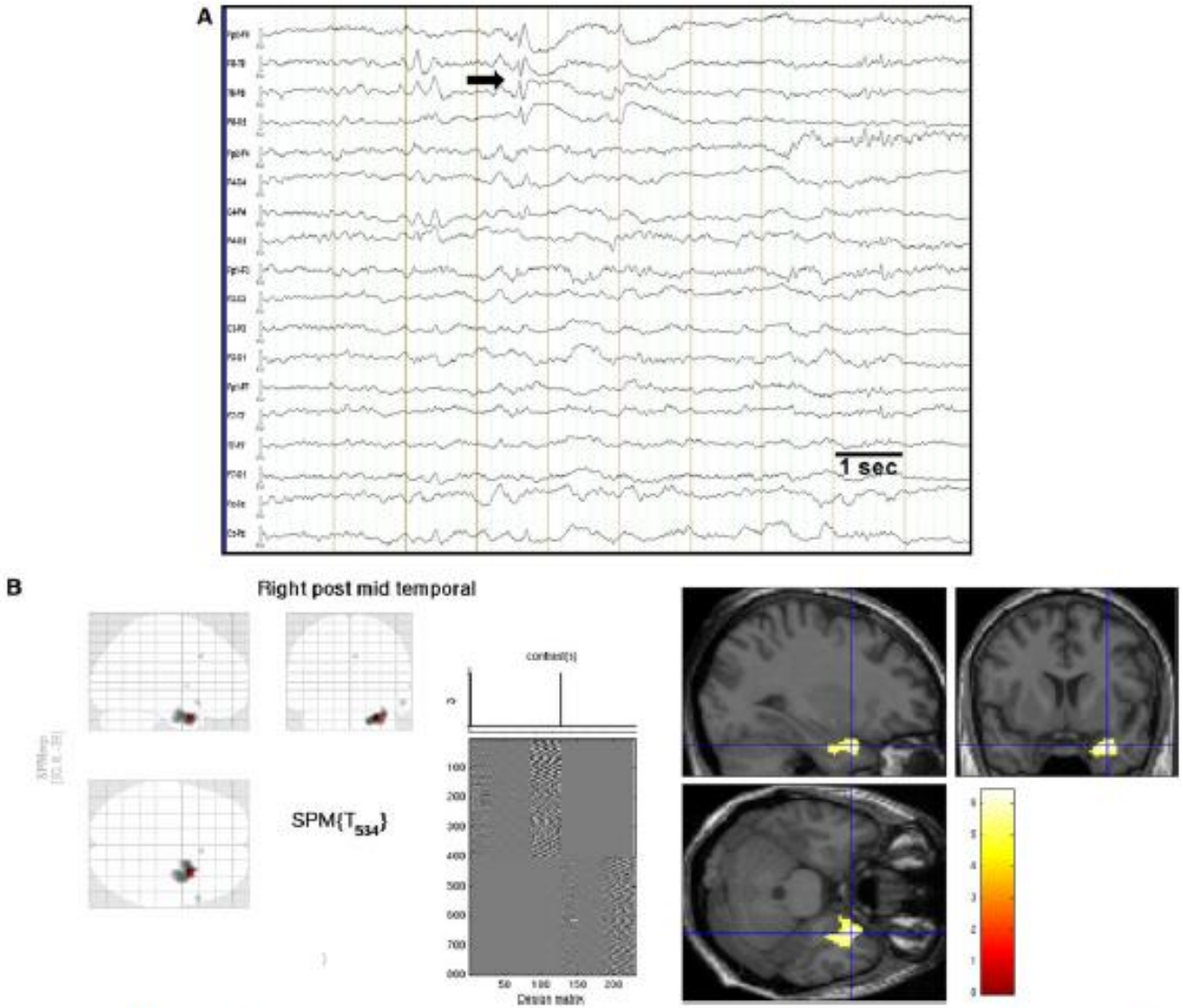


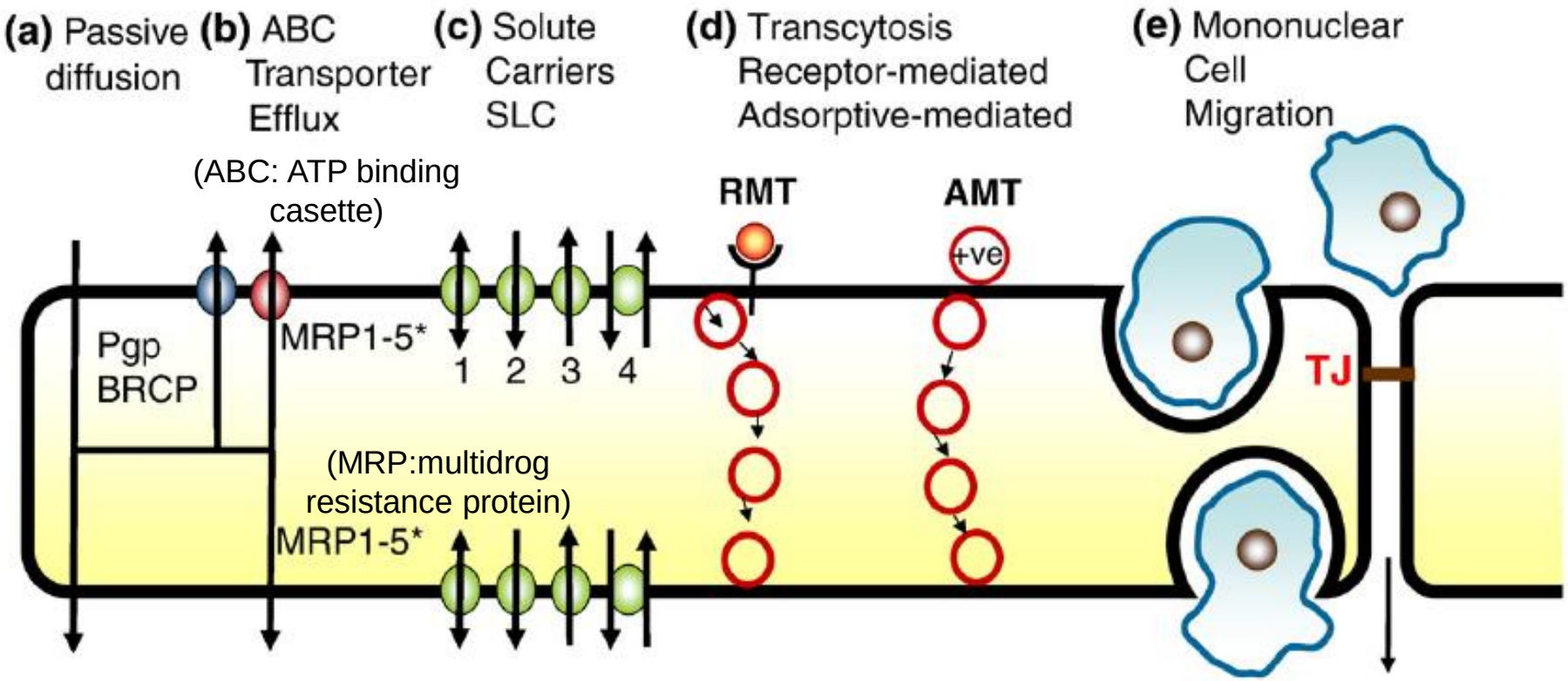
Fig. 1 EEG-fMRI study of interictal activity in a patient with right temporal lobe epilepsy. **a** shows a 10-s epoch of scalp EEG recorded during fMRI scanning after correction for image acquisition and pulse-related artifacts, displayed in a bipolar montage. The *arrow marks* an interictal spike with phase reversal over the right frontal electrode F8. *Left* SPM(T) ($P < 0.05$ corrected for Family-Wise-Error) for spike-related BOLD increases projected onto a glass brain. **b** *Middle* the design matrix (GLM) for the two separate EEG-fMRI sessions (20-min recording each) is shown. *Right* SPM(T) shown as color-coded overlay on sections (sagittal, coronal, and axial) of the patient's structural MRI going through the global statistical maximum. The map shows regions of significant spike-related BOLD signal increase in the right hippocampus and right superior temporal gyrus

Present and future of simultaneous EEG-fMRI

Karin Rosenkranz · Louis Lemieux

Transzport a vér-agy gáton át

transzporterek



transcellular; diapedesis

Lipid soluble non-polar molecules	Lipid soluble non-polar molecules and conjugates	Glucose	Transferrin	Cationised albumin
		Amino acids	Melanotransferrin	Histone
		Nucleosides	Lipoproteins	Avidin
		Monocarboxylates	Amyloid β	TAT
		Small peptides	Glycosylated proteins	$SynB_1$
		FFAs	IgG	(Cell penetrating peptides)
		Organic anions	Insulin	
		Organic cations	Leptin	
			TNFα	
			EGF	

O_2
CO_2

Structure and function of the blood–brain barrier

N. Joan Abbott *, Adjanie A.K. Patabendige, Diana E.M. Dolman, Siti R. Yusof, David J. Begley

Fig. 4. Routes of transport across the BBB. (a) Solutes may passively diffuse through the cell membrane and cross the endothelium. A higher lipid solubility and several other physico-chemical factors favour this process (see text). (b) Active efflux carriers (ABC transporters) may intercept some of these passively penetrating solutes and pump them out of the endothelial cell either as they diffuse through the cell membrane or from the cytoplasm. Pgp and BCRP are strategically placed in the luminal membrane of the BBB endothelium. MRPs 1–5* are inserted into either luminal or abluminal membranes; there appear to be some species differences in both the polarity and the isoforms of MRPs expressed at the BBB (Begley, 2004a,b). (c) Carrier-mediated influx via solute carriers (SLCs) may be passive or primarily or secondarily active and can transport many essential polar molecules such as glucose, amino acids and nucleosides into the CNS. The solute carriers may be bi-directional, the direction of net transport being determined by the substrate concentration gradient (1), unidirectional either into or out of the cell (2/3), or involve an exchange of one substrate for another or be driven by an ion gradient (4). In this last case the direction of transport is also reversible depending on electrochemical gradients. (d) RMT requires receptor binding of ligand and can transport a variety of macromolecules such as peptides and proteins across the cerebral endothelium (transcytosis). AMT appears to be induced in a non-specific manner by positively charged macromolecules and can also transport across the endothelium. Both RMT and AMT appear to be vesicular-based systems which carry their macromolecule content across the endothelial cells. (e) Leukocytes cross the BBB either by a process of diapedesis through the endothelial cells (penetrating close to the tight junctional regions), or via modified tight junctions. The junction-associated molecules (JAMs) and the cell surface protein CD99 may interact with the leukocytes to initiate diapedesis. Tight junction modulation can result from signals from cells associated with the brain endothelium or be induced pharmacologically; molecular re-arrangement of the proteins of the tight junctions results in complete or partial opening of the paracellular aqueous diffusional pathway (modified from Begley, 2007).

Patológiás elváltozások és a BBB sérülése

CNS pathologies involving BBB dysfunction.

CNS pathology	BBB dysfunction
Stroke	Astrocytes secrete transforming growth factor-β (TGFβ), which downregulates brain capillary endothelial expression of fibrinolytic enzyme tissue plasminogen activator (tPA) and anticoagulant thrombomodulin (TM). Proteolysis of vascular basement membrane/matrix. Induction of aquaporin 4 (AQP4) mRNA and protein at BBB disruption. Treatment with arginine vasopressin V1 receptor antagonist reduced the increase in BBB permeability induced in stroke model.
Trauma	Bradykinin, a mediator of inflammation, is produced and stimulates production and release of interleukin-6 (IL-6) from astrocytes, which leads to opening of the BBB.
Infectious or inflammatory processes	Examples include bacterial infections, meningitis, encephalitis and sepsis. The bacterial protein lipopolysaccharide (LPS) affects the permeability of BBB tight junctions. This is mediated by the production of free radicals, IL-6 and IL-1 β. Interferon-β prevents BBB disruption. Alterations in P-glycoprotein expression and activity in the BBB.
Multiple sclerosis	Breakdown of the BBB. Tight junction abnormalities. Downregulation of laminin in the basement membrane. Selective loss of claudin3 (shown with antibody vs Cl 1/3) in experimental autoimmune encephalomyelitis.
HIV	BBB tight junction disruption.
Alzheimer's disease	Decreased glucose transport, downregulation of glucose transporter GLUT1, altered agrin levels, upregulation of AQP4 expression. Accumulation of amyloid-β, a key neuropathological feature of Alzheimer's disease, by decreased levels of P-glycoprotein transporter expression. Altered cellular relations at the BBB, and changes in the basal lamina and amyloid-β clearance.
Parkinson's disease	Dysfunction of the BBB by reduced efficacy of P-glycoprotein.
Epilepsy	Transient BBB opening in epileptogenic foci, and upregulated expression of P-glycoprotein and other drug efflux transporters in astrocytes and endothelium.
Brain tumours	Breakdown of the BBB. Downregulation of tight junction protein claudin 3; redistribution of astrocyte AQP4 and Kir4.1 (inwardly rectifying K^+ channel).
Pain	Inflammatory pain alters BBB tight junction protein expression and BBB permeability.
Glaucoma	Opening of the BBB, possibly through diffusion of endothelin-1 and matrix-metalloproteinase-9 into peri-capillary tissue.
Lysosomal storage diseases (LSD)	May show changes in BBB permeability, and/or transport, depending on specific LSD

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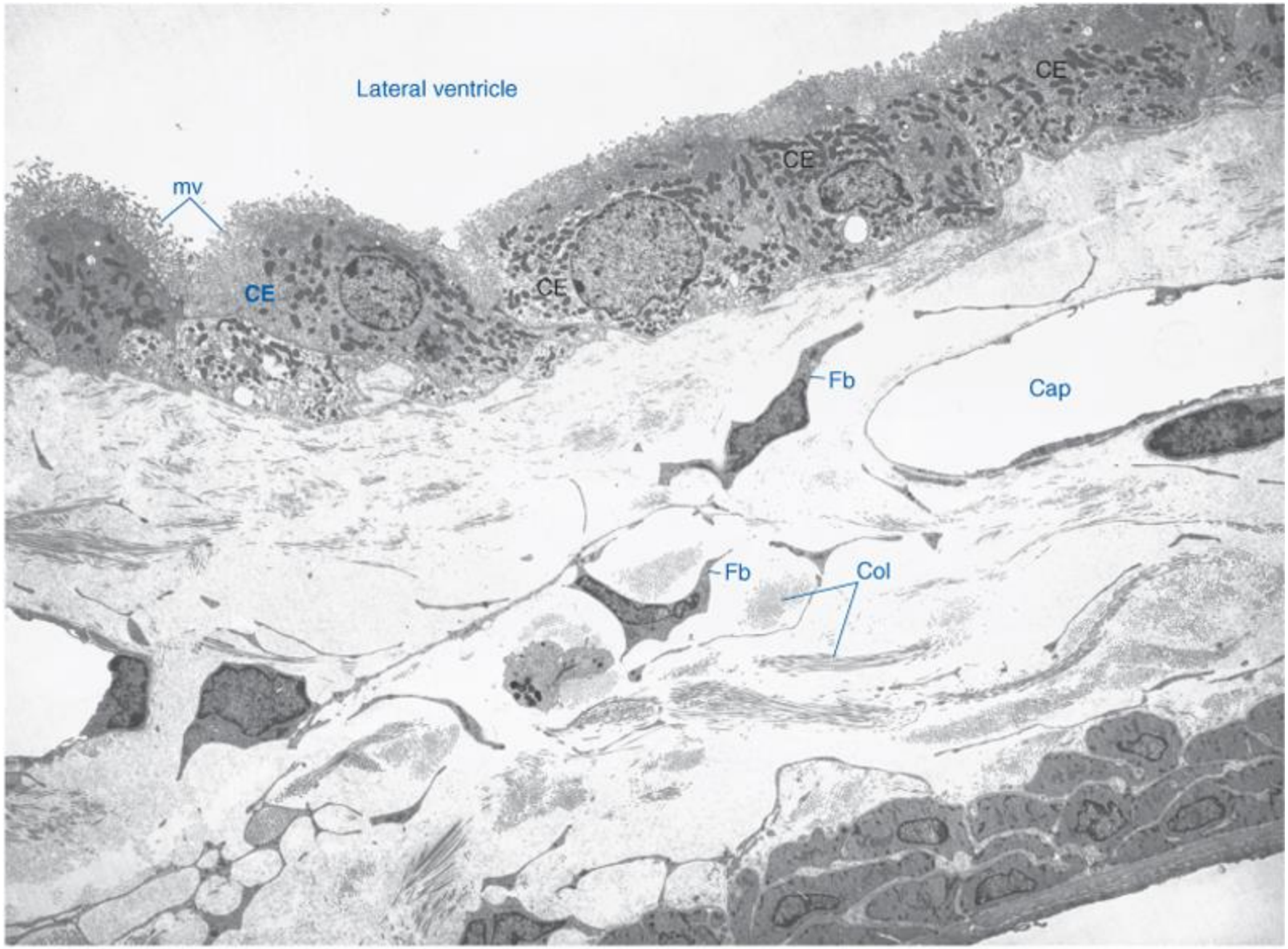
A choroid plexus



A

Nolte: The Human Brain.
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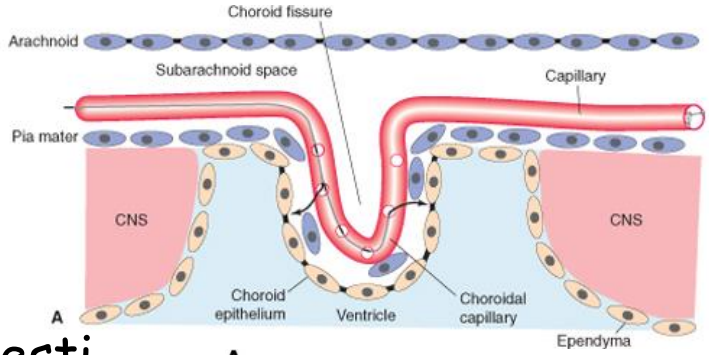
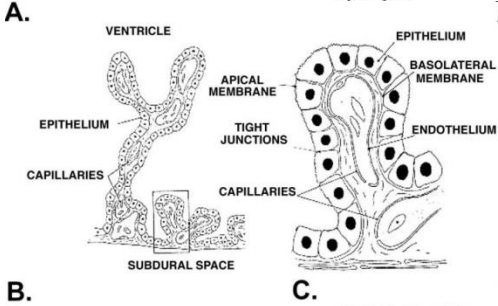
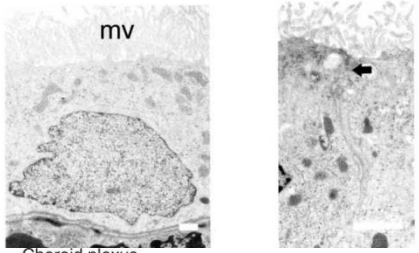
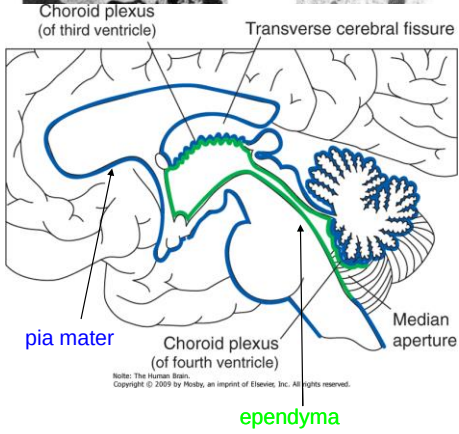
A vér-liquor gát [BCSFB]

- 1885, Ehrlich: i.v. adott festék az agyi parenchimát nem, de a CP-t és a CVO (*circumventricular organ*)-t festi
- 1913, Goldmann: CSF-be adott festék az agyi parenchimát igen, de a CP-t és a CVO-t nem festi
- choroid plexus (CP): kitüremkedő pia – ependima – kapilláris komplex
  - fő funkció a CSF szekréciója
  - ➢ fenesztrált kapilláris endotél
  - ➢ részben fragmentált pia (kollagén)
  - ➢ zárt choroid epitélium
    - ependimával folytonos
    - „leaky" (~vese, bél: transzporthám)
      - TJ összetétel a BBB-hez hasonló, de más claudin-típusok: kevésbé szelektív
    - alaphártyával kapcsolódik (+tanicita, pituicita)
    - mikrovillusok



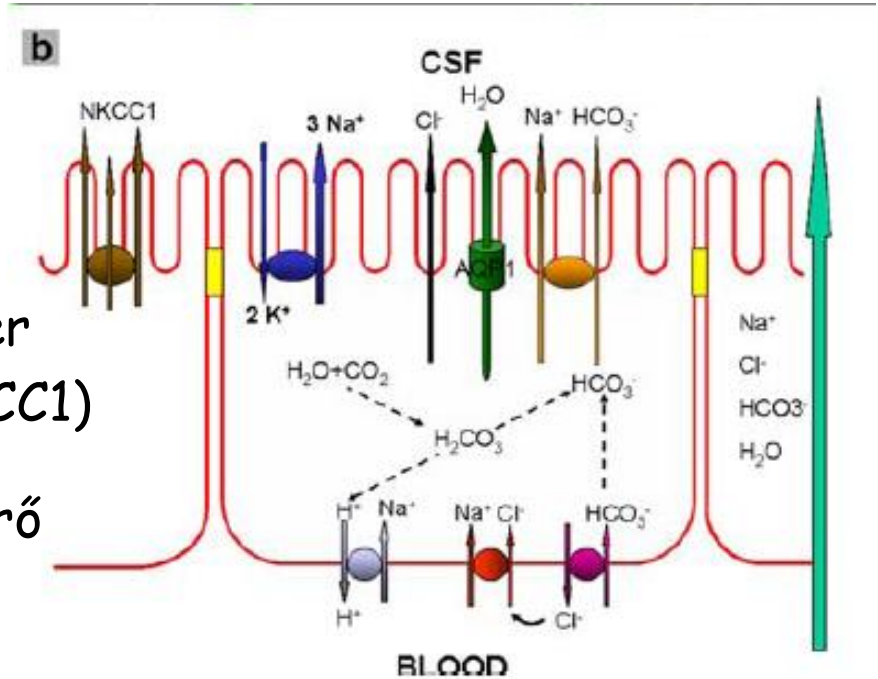






A vér-liquor gát [BCSFB]

- CSF szekréció: szekréciós hám
  - speciális transzporter-lokalizáció
    - apikális K-Na ATPáz
    - apikális Na-HCO_3^- kotranszporter
    - $Na^+/K^+/2Cl^-$ kotranszporter (NKCC1)
  - lumenben magas ozmotikus hajtóerő
  - aquaporin (AQP1) csatornák ; folyadékáramlás a CSF-be



- [retina-vér külső gát: AQP1 szintén az apikális membránban, de a folyadékáramlás a szubretinális térből befelé történik <- transzporterek fordított működése]

+ circumventrikuláris szervek (CVO), hipotalamo-hipofizeális rendszer: neuroendokrin hatás

Plazma és liquor összetétel

- vérplazmához képest magasabb Mg^{2+} és Cl^{-}, alacsonyabb K^{+} és Ca^{2+} szint
- állandó összetétel
- 0,5 l/nap, vérnyomástól független

Table 1
Typical plasma and cerebrospinal fluid concentrations for some selected solutes. From Begley (2007).

Solute	Units	Plasma	CSF	Ratio
Na^{+}	mM	140	141	~1
K^{+}	mM	4.6	2.9	0.63
Ca^{++}	mM	5.0	2.5	0.5
Mg^{++}	mM	1.7	2.4	1.4
Cl^{-}	mM	101	124	1.23
HCO_3^{-}	mM	23	21	0.91
Osmolarity	mOsmol	305.2	298.5	~1
pH		7.4	7.3	
Glucose	mM	5.0	3.0	0.6
Total amino acid	μM	2890	890	0.31
Leucine	μM	109	10.1–14.9	0.10–0.14
Arginine	μM	80	14.2–21.6	0.18–0.27
Glycine	μM	249	4.7–8.5	0.012–0.034
Alanine	μM	330	23.2–32.7	0.07–0.1
Serine	μM	149	23.5–37.8	0.16–0.25
Glutamic acid	μM	83	1.79–14.7	0.02–0.18
Taurine	μM	78	5.3–6.8	0.07–0.09
Total protein	mg/ml	70	0.433	0.006
Albumin	mg/ml	42	0.192	0.005
Immunoglobulin G (IgG)	mg/ml	9.87	0.012	0.001
Transferrin	mg/ml	2.6	0.014	0.005
Plasminogen	mg/ml	0.7	0.000025	0.00004
Fibrinogen	mg/ml	325	0.00275	0.000008
α2-macroglobulin	mg/ml	3	0.0046	0.0015
Cystatin-C	mg/ml	0.001	0.004	4.0

szerin proteáz inhibitor → Cystatin-C

Ábrák

A vér-agy gát [BBB]

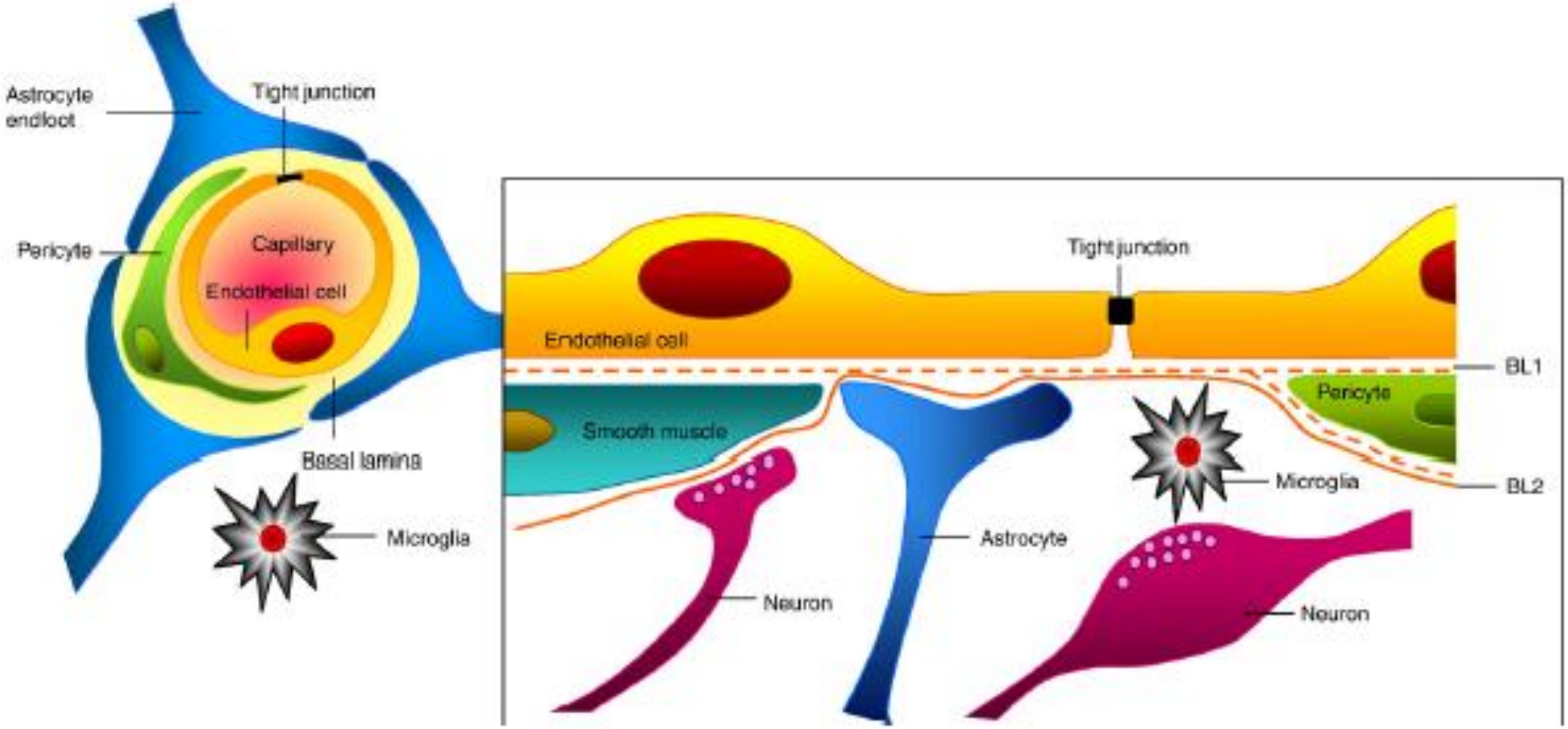


Fig. 2. The cell associations at the BBB. The cerebral endothelial cells form tight junctions at their margins which seal the aqueous paracellular diffusional pathway between the cells. Pericytes are distributed discontinuously along the length of the cerebral capillaries and partially surround the endothelium. Both the cerebral endothelial cells and the pericytes are enclosed by, and contribute to, the local basement membrane which forms a distinct perivascular extracellular matrix (basal lamina 1, BL1), different in composition from the extracellular matrix of the glial endfeet bounding the brain parenchyma (BL2). Foot processes from astrocytes form a complex network surrounding the capillaries and this close cell association is important in induction and maintenance of the barrier properties. Axonal projections from neurons onto arteriolar smooth muscle contain vasoactive neurotransmitters and peptides and regulate local cerebral blood. BBB permeability may be regulated by release of vasoactive peptides and other agents from cells associated with the endothelium. Microglia are the resident immunocompetent cells of the brain. The movement of solutes across the BBB is either passive, driven by a concentration gradient from plasma to brain, with more lipid-soluble substances entering most easily, or may be facilitated by passive or active transporters in the endothelial cell membranes. Efflux transporters in the endothelium limit the CNS penetration of a wide variety of solutes (based on Abbott et al., 2006).

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