

Structure and Physiology of Blood Brain Barrier



정 용

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Structure and Physiology of Blood Brain Barrier

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Blood-Brain Barrier (혈뇌장벽)

brain

spinal cord

> 98 % of small molecule drugs do not cross the BBB	~100 % of large molecule drugs do not cross the BBB	<1 % of drug companies have a BBB drug targeting program	<1 % of academic neuroscience programs emphasize BBB transport biology
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Pardridge, 2005

BBB

- Concept: Sheltering or isolation CNS from the systemic circulation
- Substances: highly **specialized structures** composed by different cell types that controls the movement of molecules from blood to CNS or vice versa.
- The continuous endothelial membrane of the brain vasculature, which has **sealed cell-to-cell contacts** and is sheathed by **vascular mural cells** and perivascular **astrocyte end-feet**.

General capillary

Brain capillary

Intercellular cleft

Pericyte

Basement membrane

Astrocyte end-foot

Lumen

Endothelial cell

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Function of BBB

- Separate the circulating blood and brain compartments and strictly regulates blood-to-brain and brain-to-blood transport of solutes

Physical Barrier

Transport Barrier

Metabolic barrier

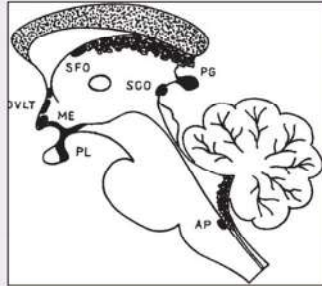
Immunologic barrier

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Areas without BBB

- Pineal gland (PG)
- Neurohypophysis (PL)
- Area postrema (AP)
: vomiting center
- Subfornical organ (SFO)
: angiotensin II sensing
- Vascular organ of lamina terminalis (OVLt)
- Median eminence (ME)

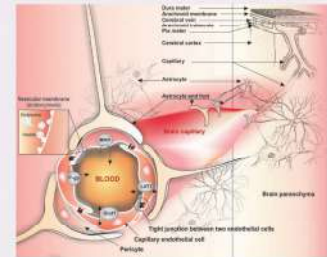


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Components of BBB

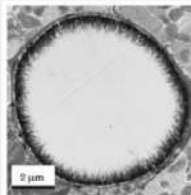
- Capillary endothelial cells
 - Glycocalyx layer
 - Tight junction
 - Adherens junction (zonula adherens, intermediate junction)
 - Membrane transporters
- Basement membrane
- Pericytes
- Astrocytes
- Neuron



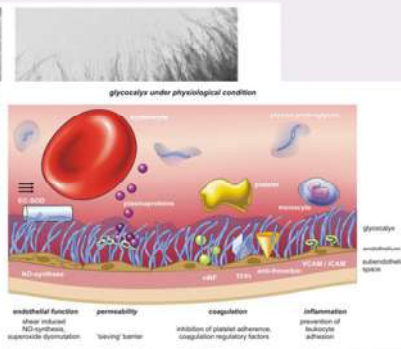
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Glycocalyx



Robertson and Wattman, 2013



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Cell junctions

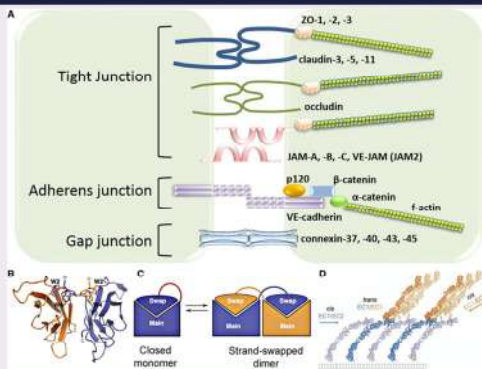
- Tight junction
 - Occludin
 - Claudin 1,3,5,12
 - ZO-1,2,3
 - Junctional adhesion molecules (JAMs): JAM-A,B,C
- Adherens junction
 - PECAM
 - VE-cadherin
- Gap junction

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Daneman and Prat, 2015

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Cell junctions



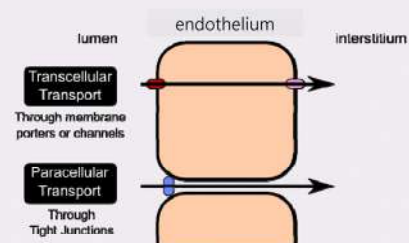
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Komarova et al., 2017

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Transport

- Paracellular transport
- Transcellular transport (Membrane transport)



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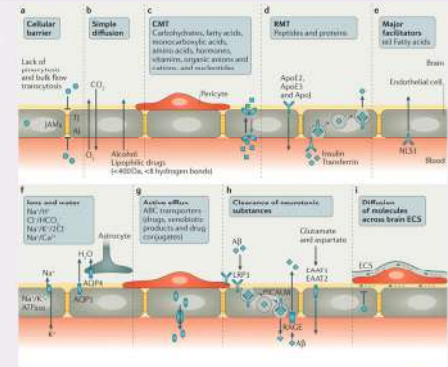
Membrane Transport

- Simple diffusion
- Carrier-mediated transport (CMT)
- Receptor-mediated transcytosis (RMT)
- Sodium-dependent lysophosphatidylcholine symporter 1 (NLS1, also known as major facilitator superfamily domain-containing protein 2a)
- ATP-binding cassette (ABC) transporters

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Membrane Transport



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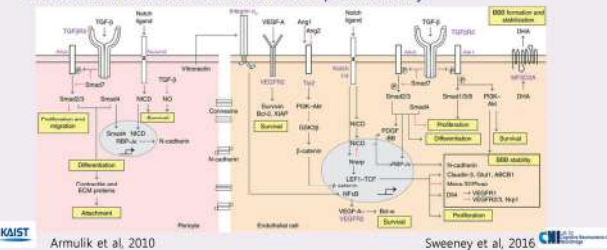
Sweeney et al., 2018

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Pericyte and BBB

- The percentage of endothelial cell coverage by pericytes is inversely proportional to the permeability of the BBB.
- Pericytes regulate TJ formation and influence transendothelial vesicular transport. (Dalkara and Alarcon-Martinez, 2015)
- Signals from pericytes regulate the expression of genes in the endothelial cells that influence BBB permeability.



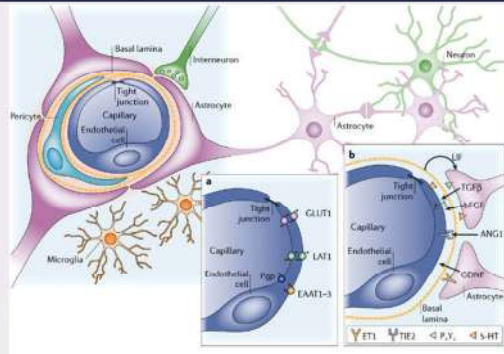
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Armulik et al., 2010

Sweeney et al., 2016

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Astrocyte and BBB



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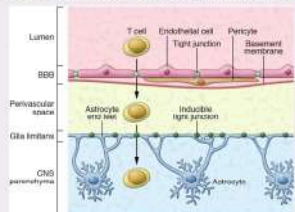
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Astrocyte and BBB

- Upregulate many BBB features, leading to tighter tight junctions: physical barrier (Dehouck et al., 1990; Rubin et al., 1991)
- Increase the expression and polarized localization of transporters, including Pgp and GLUT1: transport barrier (Schinkel, 1999; McAllister et al., 2001)
- Increase specialized enzyme systems: metabolic barrier (Haseloff, et al., 2005)
- Astrocyte tight junction limit the migration of inflammatory leukocytes: Immunologic barrier



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Hornig et al., 2017

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Summary

- BBB
 - Glycocalyx
 - Endothelial tight junction
 - Restricted paracellular transport
 - Controlled transcellular transport
- Regulation
 - Role of pericytes
 - Role of astrocytes
 - Role of neurons?
 - Interaction with metabolic system
 - Interaction with thrombotic or thrombolytic systems
 - Interaction with immune system
- Changes in Pathological conditions
- Drug delivery through BBB

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