93. The control of cerebral blood flow, the cerebrospinal fluid, barrier systems of the brain.

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Quantitative data

- CBF (cerebral blood flow): 750 ml/min, constant
- 15% of resting CO (3% of maximal CO)
- CMRO$_2$ (cerebral metabolic rate for Oxygen): 45-50 ml/min, 20% of resting O$_2$ metabolism
- Mean perfusion: 0.5 ml/g/min
  - gray matter: 1.3 ml/g/min
  - white matter: 0.25 ml/g/min
Cerebral blood flow

- Supplies cerebral metabolism demanded by neuronal function
- Is required for the production and absorption of the cerebrospinal fluid (CSF)
- Transports hormones produced in the brain or delivers hormones regulating brain function
Factors determining cerebral blood flow

Under physiological circumstances, CBF is regulated through the local control of arteriolar diameter.
The cerebral arterial system

- 4 supplying artery (2 internal carotid artery and 2 vertebral artery)
- Anastomotic circle (Willis-circle)
- NO significant communication under physiological circumstances
The cerebral venous system

- Venous sinuses in the dura mater: their diameter is independent of blood pressure
- There are no valves in the cerebral veins

Features of cortical resistance vessels

- Extrinsic innervation of pial arterioles: 1. sympathetic, 2. parasympathetic, and 3. trigeminal sensory. Denervation does not increase flow (there is no vasoconstrictor tone)
- The intraparenchymal arterioles together with the endings of intrinsic neurons and glial cells comprise the so-called neurovascular unit!

The control of cerebral blood flow

- ~750 ml/min, ~15% of resting cardiac output, due to the profound autoregulation, it is largely independent of perfusion pressure between 60-160 mmHg, relatively stable value

- Changes in blood chemistry: 1. hypercapnia, 2. hipoxia, 3. hipoglycemia elicit arteriolar vasodilation and increase global cerebral blood flow.

- The distribution of perfusion among brain regions is variable.

- This can be assessed by positron emission tomography (PET) or functional MRI (fMRI) in awake humans.
Cerebral metabolic rate of glucose (CMRG) PET maps during different task, in man
CBF PET map during stimulation of the right visual field, in man
Simultaneous recordings of neural activity and hemodynamic (BOLD) responses in cerebral cortex

- **BOLD**: blood oxygen-level dependent signal
- **LFP**: local field potential (~synaptic activity)
- **MUA, SDF**: multi-unit activity, spike density function (~AP firing activity)
Flow-metabolism coupling

- LOCAL increases in neuronal activity lead to local increases in metabolism eliciting arteriolar vasodilation and LOCAL increases in blood flow.
- This is in fact an active (functional) hyperemia.
- First proposed by Roy and Sherrington (1890).
- The most important physiological regulatory mechanism, also essential in the progress of cognitive neuroscience!
Design and behavioral results.

A) Pre-session (including FMRI)

First-impression task (scanned)

How much would you like to date this person?
1 not at all 2 a little 3 somewhat 4 very much

Multi-rating task (not scanned)

How physically attractive is this person?
1 not at all 2 3 4 5 6 7 8 9 extremely

B) Speed-dating event layout (1-14 days later)

~40 participants
Equal #s M & W Each date 5 min

1 2 3 4 5 6 7 8 9

First-impression (FI)

Percentage of pursue decisions

Attr

Like

Neural predictors of subsequent decision compared with areas mediating judgments of physical attractiveness.

"Paracingulate cortex (circled) is the only activated region that significantly independently correlates with subsequent decision in a multiple regression.."

Mechanism of flow-metabolism coupling

- Rapid, within few seconds
- hypoxia, hypercapnia, and hypoglycemia DO NOT develop during coupling – actually increase in oxygen delivery exceeds increase in demand)
- The activation of excitatory glutamatergic synapses play an important role
- It is mediated by the specific contribution of the members of the neurovascular unit.
- Astrocytes may play unique role:
The astrocyte can signal the synaptic activation toward the arterioles!
Synaptic activation triggers a propagating intracellular Ca\(^{2+}\) signal in the astrocyte...
...and the perivascular glial end foot releases vasoactive substances (K⁺, PGE₂, EETs), in response to the Ca²⁺ signal
Summary of cerebral blood flow regulation

**METABOLIC**
- CBF vs. Neuronal activity
- Local!

**CHEMICAL**
- CBF vs. brain ECF pCO2
- (alkalosis) vs. (acidosis)

**AUTOREGULATION**
- CBF vs. Perfusion pressure
- (low) vs. (high)

**NEUROGENIC**
- CBF vs. sympathetic stimulation
The discovery of the blood-brain barrier: Paul Ehrlich and Edwin Goldmann (1913)

Paul Ehrlich (1854-1915)

Edwin Goldmann (1862-1913)

The dye does not cross from the blood to brain or conversely from brain to blood. The dye is stopped between the capillary endothelial cells.
The cerebral capillary

Layers:
1. Endothelium
2. Basal membrane (with pericytes)
3. Astrocyte-endfeet

100 cm²/g surface area, the endothelial cells comprise barely 0.1% of cerebral volume, mean intercapillary distance is ~40 μm
Molecular structure of the blood-brain barrier (BBB)

In the „tight junction“, integral structure proteins of adjacent cell membranes form homodimers (claudins, occludin) that are responsible for the low paracellular permeability. In the BBB, the junction is so tight that even water permeability is minimal.
Cerebral energy metabolism

Based on the aerobic oxidation of glucose

CMRO$_2$ (cerebral metabolic rate of oxygen):
$\sim50$ ml/min, 20% of O$_2$ consumption at rest

Cerebral blood flow has to deliver daily: $\sim72$ liters of oxygen, $\sim100$g glucose, simultaneously has to carry away $\sim72$ liters of carbon dioxide, $\sim50$ ml metabolic water and $\sim1500$ kJ thermal energy

Glucose + 6 O$_2$ $\rightarrow$ 6 CO$_2$ + 6 H$_2$O
Additional requirements of cerebral metabolism

- Amino acids required for protein synthesis
- Excretion of ammonia derived from amino acid degradation
- Essential, polyunsaturated fatty acids required for membrane synthesis
- Vitamins, iron
- Prevent the uptake of any endogenous or exogenous substance present in the blood plasma that can potentially interfere with neuronal function
Transport across the BBB

- mainly transcellular
- Simple diffusion: gases, lipid-soluble molecules (fatty acids, vitamins, alcohol), little water
- Facilitated diffusion: glucose, amino acids, ketone bodies, lactate
- Primary/secondary active transports: ions, $K^+$ secretion, glutamine-secretion, amino acids
- endocytosis, transcytosis: iron, proteins
Additional requirements of cerebral metabolism

- Amino acids required for protein synthesis
- Excretion of ammonia derived from amino acid degradation: GLUTAMINE secretion
- Essential, polyunsaturated fatty acids required for membrane synthesis
- Vitamins, iron
- Prevent the uptake of any endo- or exogenous substance present in the blood plasma that can potentially interfere with neuronal function
Glutamate/glutamine transport across the blood-brain barrier primarily serves cerebral ammonia homeostasis (daily glutamate uptake ~8 g, glutamine secretion ~12 g)


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Additional requirements of cerebral metabolism

- Uptake of amino acids required for protein synthesis
- Removing ammonia derived from amino acid degradation
- Uptake of essential, polyunsaturated fatty acids required for membrane synthesis
- Vitamins, iron
- Prevent the uptake of any endo- or exogenous substance present in the blood plasma that can potentially interfere with neuronal function
Many substances cannot pass the endothelial cells because they are either (1) degraded by enzymes located in the luminal membrane or (2) pumped back to the blood by multispecific active (ABC) transporters.

This barrier impedes greatly the delivery of medicines into the central nervous system.

The most important of such pumps are the P-glycoprotein (multidrug resistant protein MDR1), the MDR-related protein (MRP2), the organic anion transporter protein 2 (OATP2), breast cancer resistance protein (BRCP).
Cerebral blood flow

- Supplies cerebral metabolism demanded by neuronal function
- Is required for the production and absorption of the cerebrospinal fluid (CSF)
- Transports hormones produced in the brain or delivers hormones regulating brain function
The cerebrospinal fluid (CSF)

- The largest transcellular fluid compartment (140-150 ml)
- Functions: „water bath” effect (mechanical protection), lymphatic drainage, ICP control
- Composition: isotonic, similar to a protein-free plasma, however, NaCl concentration is higher, K⁺ concentration is lower than in plasma
- Production: 500-600 ml/day, 80-90% in the choroid plexuses, by active secretion
- There are no lymph vessels in the brain, the interstitial fluid (metabolic water + little filtrate, proteins) is drained toward the CSF
Organization of the ventricular system of the brain.

Helle H. Damkier et al. Physiol Rev 2013;93:1847-1892

Physiological Reviews

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Electrolyte transport in the choroid plexus epithelium

**Basolateral side:** $\text{Cl}^-$ uptake by anion exchanger 2 (AE2), $\text{Na}^+$ and $\text{HCO}_3^-$ uptake by the neutral $\text{Na}^+/\text{HCO}_3^-$ cotransporter (NBCn2), some $\text{HCO}_3^-$ is locally produced from $\text{CO}_2$ by carbonic anhydrase

**Luminal side:** $\text{Na}^+$ efflux: $\text{Na}^+/\text{K}^+$ ATPase, $\text{HCO}_3^-$ efflux by the electrogenic $\text{Na}^+/\text{HCO}_3^-$ cotransporter (NBCe2), $\text{Cl}^-$ efflux by the $\text{K}^+/\text{Cl}^-$ cotransporter (KCC4), water follows both transcellular and paracellular pathways (membranes possess aquaporins, TJ is water permeable)
Organic components of CSF

- Virtually protein free < 0.35 g/L
- Virtually cell free < 5 WBC/μL
- Glucose cc is ~ 2/3 of plasma level
CSF absorption

Passive
CSF-pressure dependent

Source: Ganong WF: Review of Medical Physiology, 22nd Edition:
http://www.accessmedicine.com

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Fluid compartments of the brain

Arterial blood

Blood-cerebrospinal fluid barrier (choroid plexus epithelium)

Blood-brain barrier (capillary endothelium)

Filtrate

Cerebrospinal fluid

„lymph“

Extracellular fluid

Ependyma

Arachnoid villi

Cerebral veins

Venous blood

Neurons

Glia

Metabolic water
The Monroe-Kelly principle

- The combined volume of the 3 intracranial fluid compartments (brain ICF + ECF 1400 ml, CSF: 140 ml, and CBV (cerebral blood volume): 75 ml) is constant because they are enclosed in a bony capsule.
- An enlargement of any of these compartments must be compensated by the other 2.
Outside the blood brain barrier:

**circumventricular organs (6)**
Hormone release (EM, NH), sensory function (OVLT, SFO, SCO, AP)

**Pineal gland**
Hormone release

**Choroid plexus:**
Cerebrospinal fluid secretion

EM eminentia mediana; OVLT organum vasculosum laminae terminalis; NH neurohypophysis; SFO subfornical organ; SCO subcomissural organ; PI pineal gland; AP area postrema