CEREBRAL BLOOD FLOW AND METABOLISM

Part 11.
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

What are the demands of cerebral metabolism?
Cerebral energy metabolism

- Glucose plays central role as an energy substrate in the brain
- Aerobic oxidation
- Cerebral Metabolic Rate of glucose ($\text{CMR}_{\text{glc}}$) - 30-70 µM/min/100g
- Cerebral Metabolic Rate of oxygen ($\text{CMR}_{\text{O}_2}$) - 3.3 ml/min/100g
The aerobic oxidation of glucose

\[ \text{Glucose} + 6 \, \text{O}_2 \rightarrow 6 \, \text{CO}_2 + 6 \, \text{H}_2\text{O} + 36 \, ?\text{ATP} \]

In fact, the measured \( \text{CMR}_{O_2} / \text{CMR}_{\text{glc}} \approx 5.5 \) and the respiratory quotient of the brain \( \text{RQ} = \frac{\text{VCO}_2}{\text{VO}_2} \approx 1 \)
Additional uses of glucose

- Pentose-phosphate shunt (2-5% of CMRglc) - produces NADPH - coenzyme for many enzymes
- Synthesis of glycolipids and glycoproteins
- Glycogen synthesis (astroglia)
- Amino acid synthesis: Ser, Gly, Ala, Glu, Gln
Additional uses of oxygen

- Cycloxygenase – prostanoid synthesis
- Tyrosin-hydroxilase – catecholamin synthesis
- Monoamino-oxidase – biogenic amin degradation
- NO-synthase – NO-synthesis
- Heme-oxygenase - CO-synthesis
- NADPH-oxidase
Cerebral energy metabolism

Glucose + 6 O₂ \rightarrow 6 CO₂ + 6 H₂O + 36?ATP

- **CMRO₂**: \(~50\text{ml/min}\), \(20\%\) of \(O₂\) consumption at rest
- Cerebral blood flow has to deliver daily:
  - \(~72\text{ liters of } O₂\)
  - \(~3\text{ M}\)
  - \(~0.5\text{ M} \sim 100\text{g glucose}\)
- CBF simultaneously has to carry away \(~72\text{ liters of } CO₂\)
  - \(~3\text{ M} \sim 50\text{ ml metabolic water}\)
  - \(~1500\text{ kJ\ thermal energy (21.2kJ/l } O₂)\)
Glucose transport in the brain

- All cell types express facilitative glucose transporters of the GLUT family.
- GLUT 1 is responsible for the transcellular transport of glucose through the blood brain barrier.

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Neuron-glia-capillary interactions in glucose metabolism
Alternative energy substrates

- **Ketone bodies**: in fetal life and at prolonged fasting – may contribute 50% of energy production

- **Fatty acids**: especially in infants while breastfeeding (maternal milk diet)

- **Lactic acid**?
The ketone bodies

- Acetone
- Acetoacetic acid
- β-hydroxybutyric acid
Ketone bodies are transported via facilitative monocarboxylate transporters (MCT)
Difficult task: getting rid of metabolic water

- Neurons produce \(~12\) times more water than the average cell
- Their membrane does not contain many aquaporins (water channel proteins)
- They must rely on molecular water pumps (MWPs) to get rid of the water
- MWPs operate through cycling of hydrated molecules
NAA – a likely MWP

Acetyl-CoA + Aspartate $\rightarrow$ N-acetyl-aspartate (NAA)

- synthesized in neurons in high concentration (~20 mM!)
- synthesis is coupled to glucose metabolism
- degraded in glial cells, acetate and aspartate recycles to neurons
- one cycle removes ~ 120 water molecules
NAA as an MWP of neurons

Neuron

Aspartate + Ac-CoA

\[ \text{NAA} + n\text{H}_2\text{O} \]

Glia

Aspartate + Acetate

\[ \text{NAA} + n\text{H}_2\text{O} \]

Aquaporin

\[ \text{nH}_2\text{O} \]

n~120
Metabolic water is drained towards the cerebrospinal fluid
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 endo- or exogenous substance present in the blood plasma that can potentially interfere with neuronal function
AMINO ACID TRANSPORT SYSTEMS

BLOOD

X-

BRAIN

L

A

N

ASC/B^o+

y^+

T

T3/T4

β

CAPILLARY ENDOTHELIUM

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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Summary of cerebral blood flow regulation

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

**CHEMICAL**
- CBF vs. brain ECF pCO2
  - CO₂ (alkalosis) vs. (acidosis)

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

**EXTRANSCIC NEUROGENIC**
- CBF vs. sympathetic stimulation
Neuronal activation and local CMRglc are tightly coupled

Studies with 2-deoxy-D-glucose:
first autoradiographic CMRglc and CBF determinations followed by positron emission tomography
Cerebral metabolic rate of glucose (CMRG) PET maps during different tasks, in man.
CBF PET map during stimulation of the right visual field, in man
PET and MRI (green: foot, red: hand, pink: tongue movements)
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.
Factors determining cerebral blood flow

Under physiological circumstances, CBF is regulated through the local control of arteriolar diameter.

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The neurovascular unit

- Morphological and functional unit of all cell types responsible for the metabolic homeostasis of the brain

- Microvascular cells: endothelium, vascular smooth muscle, pericytes

- Parenchymal cells: astrocytes, neurons
Proposed mechanisms of flow-metabolism coupling in the neurovascular unit

Neurology 2007;68:1730-1732
Mechanism of flow-metabolism coupling

- hypoxia, hypercapnia, and hypoglycemia DO NOT develop during coupling
- Neuronal and glial factors can affect the vascular smooth muscle
- **metabolites**: K⁺, lactate, adenosine
- problem with metabolites: coupling is faster than their release
- **local vasoactive mediators**: prostaglandins, NO, EET-s
Extrinsic and intrinsic innervation of blood vessels affect the neurovascular coupling
Summary of the regulation of cortical microvessels from cells located in subcortical areas and within the cerebral cortex

<table>
<thead>
<tr>
<th>SUB-CORTICAL AREAS</th>
<th>CEREBRAL CORTEX</th>
<th>VASOACTIVE MEDIATOR</th>
<th>RECEPTOR</th>
<th>VASOMOTOR RESPONSE</th>
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<tr>
<td>Interneuron</td>
<td>Microvessel</td>
<td>NO, ACh, VIP, GABA</td>
<td>–, M5, VPAC1</td>
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<td>NPY, SOM</td>
<td>Y1, SSR2/4?</td>
<td>Contraction</td>
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<tr>
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<td>NO</td>
<td>–</td>
<td>Dilatation</td>
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<td></td>
<td>20-HETE</td>
<td>?</td>
<td>Contraction</td>
</tr>
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Hamel, E. J Appl Physiol 100: 1059-1064 2006;
doi:10.1152/japplphysiol.00954.2005
Mechanism of flow-metabolism coupling

- hypoxia, hypercapnia, and hypoglycemia DO NOT develop during coupling
- Neuronal and glial factors can affect the vascular smooth muscle
- metabolites: $K^+$, lactate, adenosine
- local vasoactive mediators: prostaglandins, NO, EETS
- Intrinsic innervation may modify the local function of the neurovascular unit, special local coupling neurons? (VIP, NO)
Increases in blood flow and glucose transport rate occur simultaneously in the neurovascular unit upon neuronal activation!
Cellular elements of the neurovascular unit