New view on the CSF circulation: CSF production and CSF absorption by brain capillaries

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Major differences between the new and old concept of CSF circulation
Normal CSF circulation old CSF bulk flow model

- There is bulk flow of CSF from the intraventricular plexus to the arachnoid granulations
Normal CSF circulation
New model

The CSF is produced and absorbed by the brain capillaries
The CSF is produced by the choroid plexus and absorbed by the arachnoid granulations.

The CSF is produced and absorbed by the brain capillaries.
Major routes of water flow into and out of the brain

Bulk flow model

- arachnoid granulation

New model

- blood-brain barrier

- choroid plexus
Major routes of water flow into and out of the brain

Bulk flow model
- arachnoid granulation

New model
- blood-brain barrier

- choroid plexus
New Concept of CSF Circulation

1. The CSF is absorbed by the brain capillaries

2. The major part of the CSF is produced by the brain capillaries
New Concept of CSF Circulation

1. CSF absorption by brain capillaries

2. CSF production by brain capillaries
The CSF bulk flow model is based on the assumption that the arachnoid granulations absorb all proteins and macromolecules in the CNS and that brain capillaries are impermeable to macromolecules!
Blood-brain barrier

Due to the tight junctions, the BBB is almost impermeable to water-soluble molecules.

Can they pass in the other direction from brain-to-blood?
Rapid elimination of albumin from the CSF

Rapid transport of albumin from CSF to plasma – half-time max in plasma occurs at 90 min

Rapid transport of albumin from the CSF into the brain
Inulin transport from CSF to blood

Rapid elimination of inulin from the CSF

Rapid transport of inulin from CSF to plasma – half-time max in plasma 60 min

Rapid transport of inulin from the CSF into the brain

Reed & Woodbury: J Physiol 1963
After i.v. injection, there is a small but significant transport of albumin from the blood to the CSF and to the brain.
Absorption of contrast medium from CSF to blood

At myelography in rabbits, there is a rapid transport of contrast from CSF to blood.

Peak concentration in blood occurs within 1 hour.

Fig. 5. Blood level curves from six rabbits injected in lumbar area.

Golman K: Neuroradiology 1979
At myelography in humans, there is a rapid transport of contrast from CSF to blood. Peak concentration in blood occurs within 2 hours. CT-cisternography (yellow): convexity-maximum occurs at 24h.
Rapid transport of contrast medium into the brain cortex

1 hour after i.c. injection in rabbit

Sage M: AJR 1983
At 3 hours, there is penetration of the contrast medium into the brain cortex.

At 24 hours, almost all contrast is located in brain tissue.
Blood brain barrier?

Conclusion: Non diffusible colour tracer

Ehrlich 1885 and Goldmann 1913
Conclusion:
Inulin, albumin, Iodine, contrast media
Reed & Woodbury 1963
Rapid transport from CNS to blood
D Greitz 1993
What is the biological substrate for the active transport at the BBB?

Tight junctions
Several brain to blood efflux transporters have been discovered at the BBB

- Betz discovered the first efflux transporter of amino acids (1978) – since then 40 different efflux transporters have been identified
transport numerous of endogenous and exogenous molecules from the brain to the blood
Brain-to-blood efflux transporters

Immuno-fluorescence study of P-glycoprotein

Löscher 2005
Recent advances in the brain-to-blood efflux transport across the blood–brain barrier

Ken-ichi Hosoya\textsuperscript{a,b}, Sumio Ohtsuki\textsuperscript{b,c,d}, Tetsuya Terasaki\textsuperscript{b,c,d,*}

Capillary wall

Multidrug transporter P-glycoprotein (fluorescence green)
The efflux transporters act as a detoxifying system for the brain
Half-time disappearance rate from brain:

12 min for PAH
The BBB is the only membrane that separates the brain from the blood.
Protein concentration in plasma is 200 times higher than in CSF
Protein concentration in plasma is 200 times higher than in CSF.

The low protein concentration in the CSF and ISF is maintained by active transport.
Further evidence of rapid transport and rapid absorption in brain tissue
Intracerebral transport of HRP

10 min post intracisternal injection !!

Frontal section of rat brain

Artery W-R space

Wagner: Acta Neuropathol 1974
Capillary absorption of HRP

Wagner: Acta Neuropathol 1974

Capillary after intracisternal injection

1h

24h triple dose
Intracerebral transport of HRP after intraventricular injection in mice

5 min postinjection

4 h postinjection

Banks & Broadwell: J Neurochem 1994
Brain to blood efflux of HRP and albumin after intraventricular injection

Half-time disappearance from brain:
44 min for HRP
42 min for albumin

Brain concentration curve
Thus: macromolecules are actively absorbed by the capillaries
To sum up:

- The CSF is absorbed by the brain capillaries
- Water-soluble molecules in the CSF are actively absorbed by the brain capillaries
New Concept of CSF Circulation

1. CSF absorption by brain capillaries
2. CSF production by brain capillaries
The CSF bulk flow model

is based on the assumption that the major part of the intracranial fluid is formed by the choroid plexus and that –

there is no fluid production in the brain capillaries!
Linear relation between CSF production and intracranial pressure (ICP)

Ekstedt 1975
The ICP is directly dependent on the CSF production in choroid plexus.
Intracranial pressure (ICP)

ICP = CSF_{prod} \times R

= 0

The bulk flow theory is based on the assumption that there is no fluid production in the capillaries!
Intracranial pressure (ICP)

\[ ICP = \text{Cap}_{\text{fluid prod}} \times R \]

If the fluid production in the capillary is significant – the ICP instead **must** be dependent on this production!
How much of the CSF formation is produced by the choroid plexus?
Experimental hydrocephalus in monkeys with and without plexectomy

<table>
<thead>
<tr>
<th>Ion</th>
<th>Content in 14 normal animals</th>
<th>Content in 16 plexectomized animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>158</td>
<td>156</td>
</tr>
<tr>
<td>K⁺</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>132</td>
<td>129</td>
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<tr>
<td>Ca²⁺</td>
<td>4.9</td>
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<td>PO₄²⁻</td>
<td>1.4</td>
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</tr>
<tr>
<td>Mg²⁺</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Protein</td>
<td>18.1</td>
<td>18.2</td>
</tr>
</tbody>
</table>
Measurement of CSF formation

- Infusion with a CSF tracer of known concentration and inflow rate
- With no CSF formation the outflow concentration equals inflow concentration

**Figure 4.** Counts of $^{131}$I albumin in influent ($C_i$)
Measurement of CSF formation

- With CSF formation, there is dilution in the outflow concentration
- CSF prod = inflow rate x dilution in %

\[
\text{dilution} = \frac{(\text{inflow conc} - \text{outflow conc})}{\text{outflow conc}}
\]
Subarachnoid CSF production:

(red arrows)
60% of total CSF production is produced in the subarachnoid space.

Fig. 1. Ventricular perfusion system.

Sato Bering 1965
CSF production

Subarachnoid CSF production:

(red arrows)
60% of total CSF production is produced in the subarachnoid space

Ventricular CSF production:

(via 2 ventricular needles)
Only 40% of total CSF production is produced in the ventricular system

Fig. 1. Ventricular perfusion system.
Sato Bering 1965
CSF production after plexectomy

Ventricular CSF production:

Only 40 % of total CSF is produced in the ventricular system

Fig. 1. Ventricular perfusion system.

Milhorat Science 1969
CSF production after plexectomy

Ventricular CSF production:
Only 40% of total CSF is produced in the ventricular system

Ventricular CSF prod. after plexectomy:
Only 30% of the ventricular CSF is produced in the choroid plexus
CSF production after plexectomy

Ventricular CSF production:
Only 40% of total CSF is produced in the ventricular system.

Ventricular CSF prod. after plexectomy:
Of the ventricular CSF production, only 30% is produced in the choroid plexus.
This indicates that: 12% of the total CSF is produced by the choroid plexus.

Fig. 1. Ventricular perfusion system.
CSF production after plexectomy

Ventricular infusion without plexectomy:
Only 40% of total CSF is produced in the ventricular system

Ventricular infusion after plexectomy:
Of the ventricular CSF production, only 30% is produced in the choroid plexus

Thus:
12% of the total CSF is produced by the choroid plexus
88% of the total CSF is produced by the brain capillaries

Milhorat Science 1969
Only a minor part of the CSF is produced by the choroid plexus
Major route of water flow into and out of the brain

Bulk flow model

- arachnoid granulation

New model

- blood-brain barrier
Conclusions

1. The major part of the CSF is produced and absorbed by the brain capillaries.

2. Brain capillaries actively transport water-soluble molecules from the brain.

3. Active transport from brain to blood is a prerequisite for brain homeostasis.