Novel experimental and clinical findings challenging the classical concepts of CSF physiology -a literature research-

Thomas Brinker M.D.

Current understanding of CSF physiology

A half-liter of cerebrospinal fluid is produced each day. It is secreted at the choroid plexus and move through the cavities of the four ventricles over the surfaces of the brain and spinal cord to be rapidly absorbed at the arachnoid granulations.

There is evidence for solute movement from CSF to brain parenchyma via transport through the Virchow-Robin spaces surrounding the penetrating arteries at the pial surface. However, the CSF microcirculation is not a quantitatively important pathway for drug distribution into the brain from the CSF compartment.

"Drug that is injected into the CSF compartment is rapidly transported out of brain to the blood. Following the ICV injection of drug, it moves through the CSF flow tracks, and is absorbed into the peripheral bloodstream across the arachnoid villi to enter the general circulation."

Pardridge W 2011, Drug Transport in brain via the cerebrospinal fluid.

Fluids and Barriers in the CNS

Cell-based delivery of peptides to the CSF is efficacious in neurological disorders

TBI: Heile, A.M.B., et al., Cerebral transplantation of encapsulated mesenchymal stem cells improves cellular pathology after experimental traumatic brain injury. Neurosci Lett, 2009.

AD: Klinge, P.M., et al., Encapsulated native and glucagon-like peptide-1 transfected human mesenchymal stem cells in a transgenic mouse model of Alzheimer's disease. Neurosci Lett, 2011

ALS: Knippenberg, S., et al., Intracerebroventricular injection of encapsulated human mesenchymal cells producing glucagon-like peptide-1 prolongs survival in a mouse model of ALS. PLOS one 2012

Glioma: Kleinschmidt, K., et al., Alginate encapsulated human mesenchymal stem cells suppress syngeneic glioma growth in the immunocompetent rat. J Microencapsul, 2011

Radiolabeled water studies

- CSF Production: Intravenous injection of Deuterium water, assessment of half life of equilibrium between blood and CSF at the ventricles, cranial SAS and spinal canal (Bering 1952).

  Bateman 2011: MRI based volume assessments of ventricles, SAS and spinal canal. Re-calculation of Bering's data → 22ml water leaves the CNS per minute, CSF turn over rate 175 / day.

- CSF absorption from ventricle: Intraventricular infusion of 3H water. No flow to the subarachnoid space, but rapid transventricular absorption into periventricular capillaries. Bulat et al. 2008

  Absorption at the capillaries was suggested. Capillary CSF absorption was already proposed by Dandy WE & Blackfan KD (1914) and Dandy WE (1929).

CSF flow through the aqueduct

MRI findings in humans indicate that there might be no net-flow along the aqueduct:

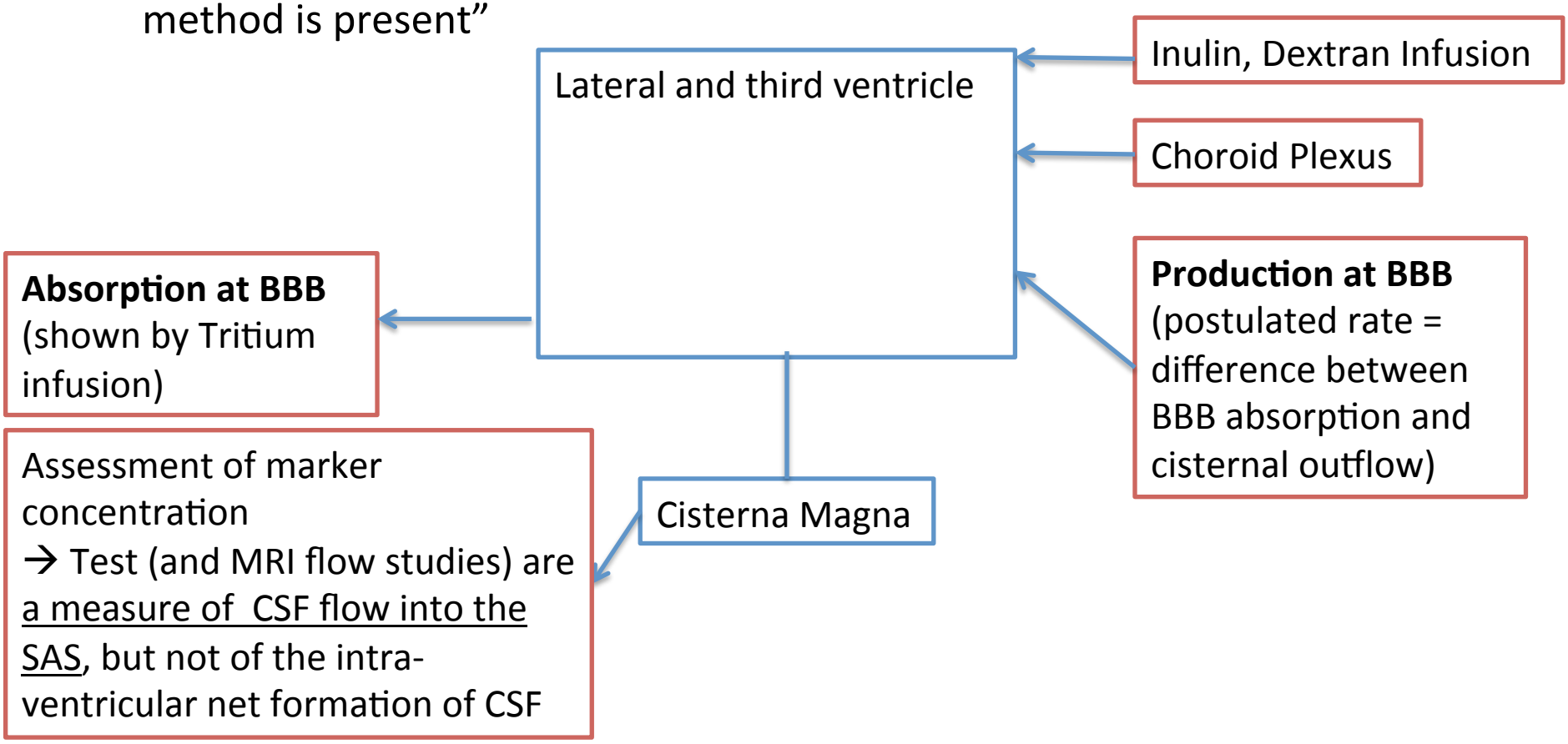
- Bradley et al 1986a. Comparison of MR cardiac-gated aqueductal flow velocity measurements in healthy individuals and in patients with hydrocephalus. Radiology 161 (P), 194.
- Bradley, W.G. et al, 1986b. Flowing cerebrospinal fluid in normal and hydrocephalic states: appearance on MR images. Radiology 159, 611–616.
- Enzmann et al, 1991. Normal flow patterns of intracranial and spinal cerebrospinal fluid defined with phase-contrast cine MR imaging. Radiology 178, 467–474.
- Batemann & Brown 2012 The measurement of CSF flow through the aqueduct in normal and hydrocephalic children: from where does it come. Child's Nervous System 28, 55-63

Experimental study:

Following cannulation of the aqueduct in cats, CSF permanently pulsated near the external end of the plastic cannula but **not a single drop of CSF was observed**. Oreskovic & Klarica 2010

Ventriculo-cisternal perfusion test

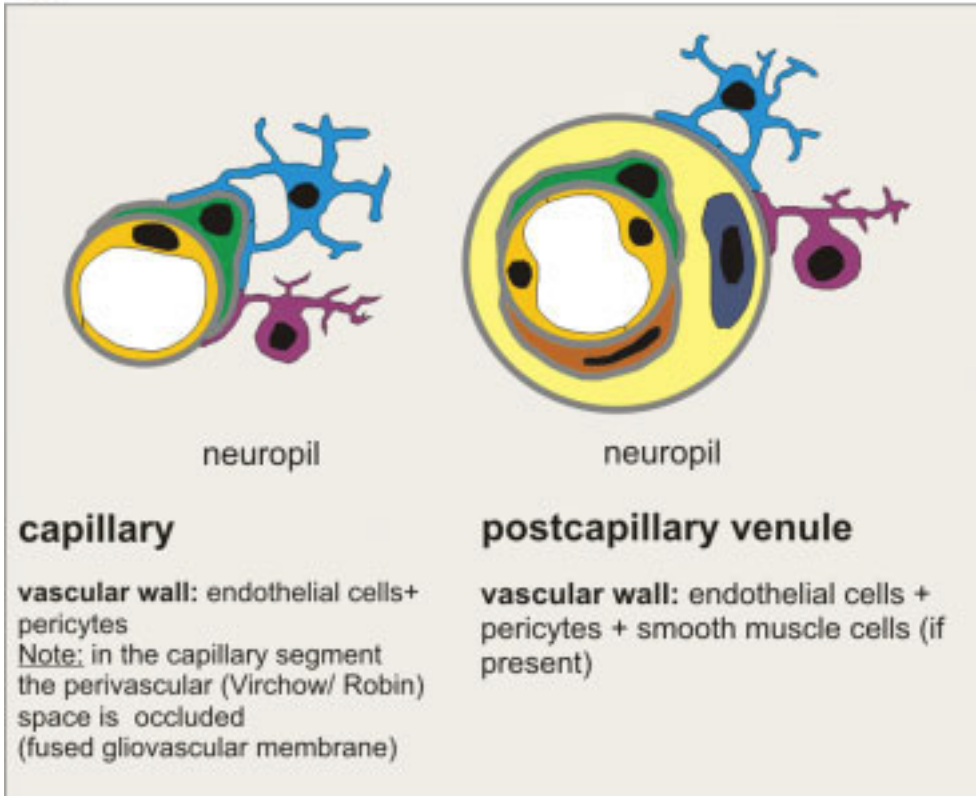
- Heisey 1962: Intraventricular infusion of inulin into the lateral ventricle in the goat. Inulin may not cross the ependymal layer of the ventricles. Rate of net formation of CSF is computed from inulin clearance: Vf = Vi (ci-co)/co .
- Orescovic & Klarica 2010 "Test must be wrong… an inherent defect in the method is present"



Vascular anatomy

There are > 100 billion capillaries in the human brain comprising a total length of approximately 400 miles. The inter-capillary distance in brain is about 40 µm, which is space for 2 neurons. Thus, every neuron in the brain is perfused by its own blood vessel.

Cited from Pardridge, Fluids Barriers CNS 2011; 8: 7.



The perivascular space connects the brain parenchyma with the subarachnoid space.

CSF absorption may be limited to the venules, CSF production to the capillaries.

Fig. from: Krueger & Bechmann 2010 : CNS Pericytes: Concepts, Misconceptions, and a Way Out.

CSF production and absorption at the blood brain barrier

Suggested mechanisms:

- Starling Forces: Hydrostatic pressure gradient (blood-CSF), osmotic (not just the oncotic) gradient (Kimelberg 2004)
- Aquaporin transporters (Anderson 2011, Owler 2010)
- Cellular components of the neurovascular unit?

CSF flow at the BBB must be highly regulated, determines brain homeostasis, likely involved in the pathophysiology of acute and chronic brain diseases including hydrocephalus.

→ Physiology and pathophysiology remains to be investigated.

Understanding the role of the BBB for CSF formation and absorption may be key for a more rational treatment of Hydrocephalus.

Recent experimental studies demonstrate the potential of **dynamic contrast enhanced (DCE) MRI** for investigation of the blood-brain barrier in hydrocephalus (Fanea et al 2013 and 2012) and in Alzheimer's disease (Anderson et al. 2011).

Aquaporin studies may be most important since these transporters regulate transmembrane water permeability in response to osmotic gradients. In the brain, AQP4 is localized to tissue-fluid interfaces: in the glia limitans (pia-subarachnoid CSF), the ependyma (ependymal lining-ventricular CSF), and at the BBB in the astrocyte foot processes and, to a lesser extent, the endothelium (reviewed by Anderson et al 2011).

→ **Need for appropriate experimental and clinical studies.**