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Medical School, University of Thessaly, GREECE

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Dept. Neurosurgery, Marmarou Lab, VCU, USA

Living on the edge:
The functional neuroanatomy of the cortical subarachnoid space-brain surface interface

Aristotelis S. Filippidis M.D., Ph.D.
Postdoctoral Fellow

Neurohydrodynamics Meeting Series, Switzerland, EPFL, www.neurohydrodynamics.com, January 2012

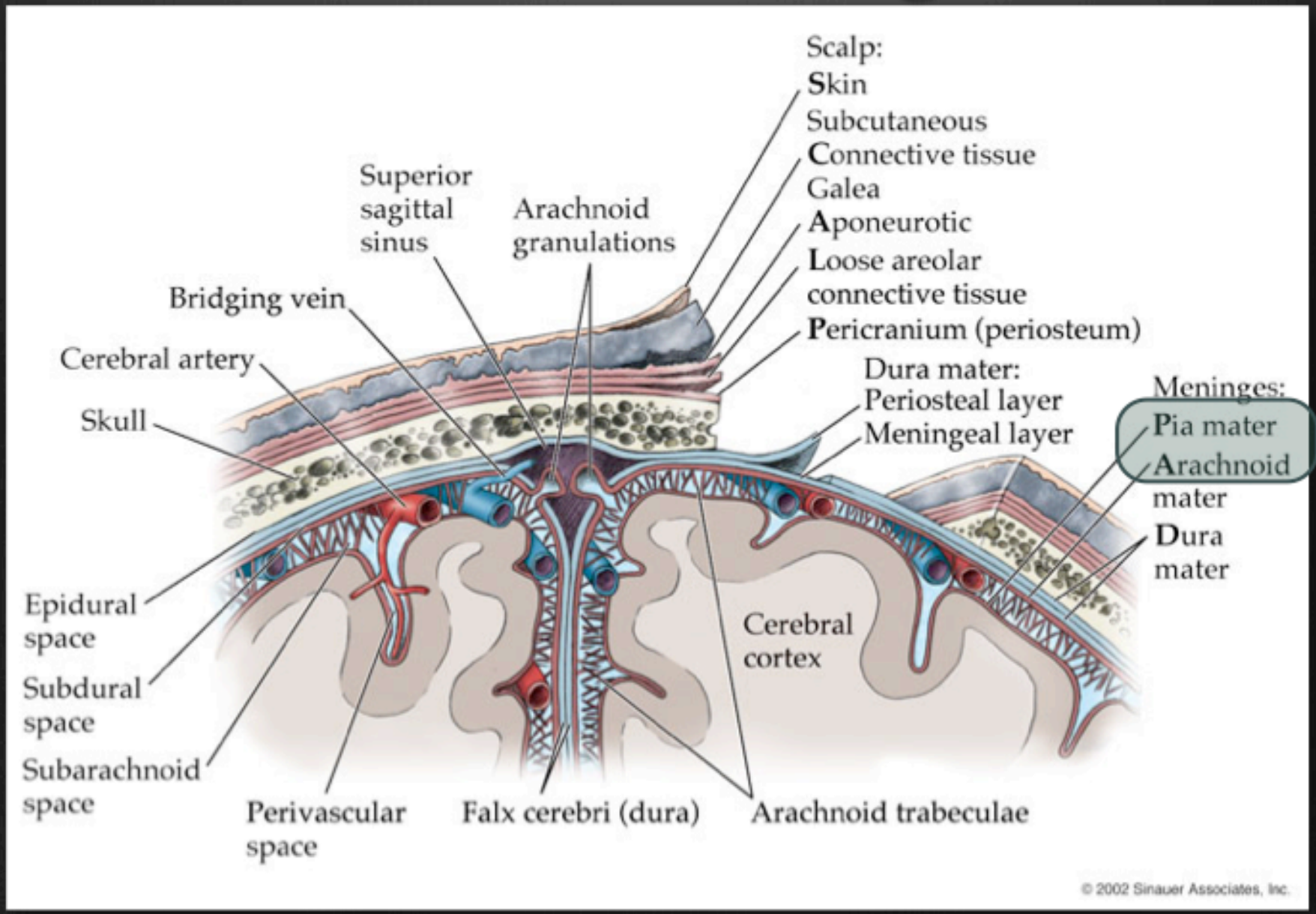
What is this and what is not ?

- THIS IS NOT about pure perivascular space anatomy
- THIS IS beyond structures, it is about solute-coupled water transport
- THIS IS about "Ion & Water mechanics"
- THIS IS about identifying analogies
- THIS IS about skimming for evidence
- THIS IS about teleology*

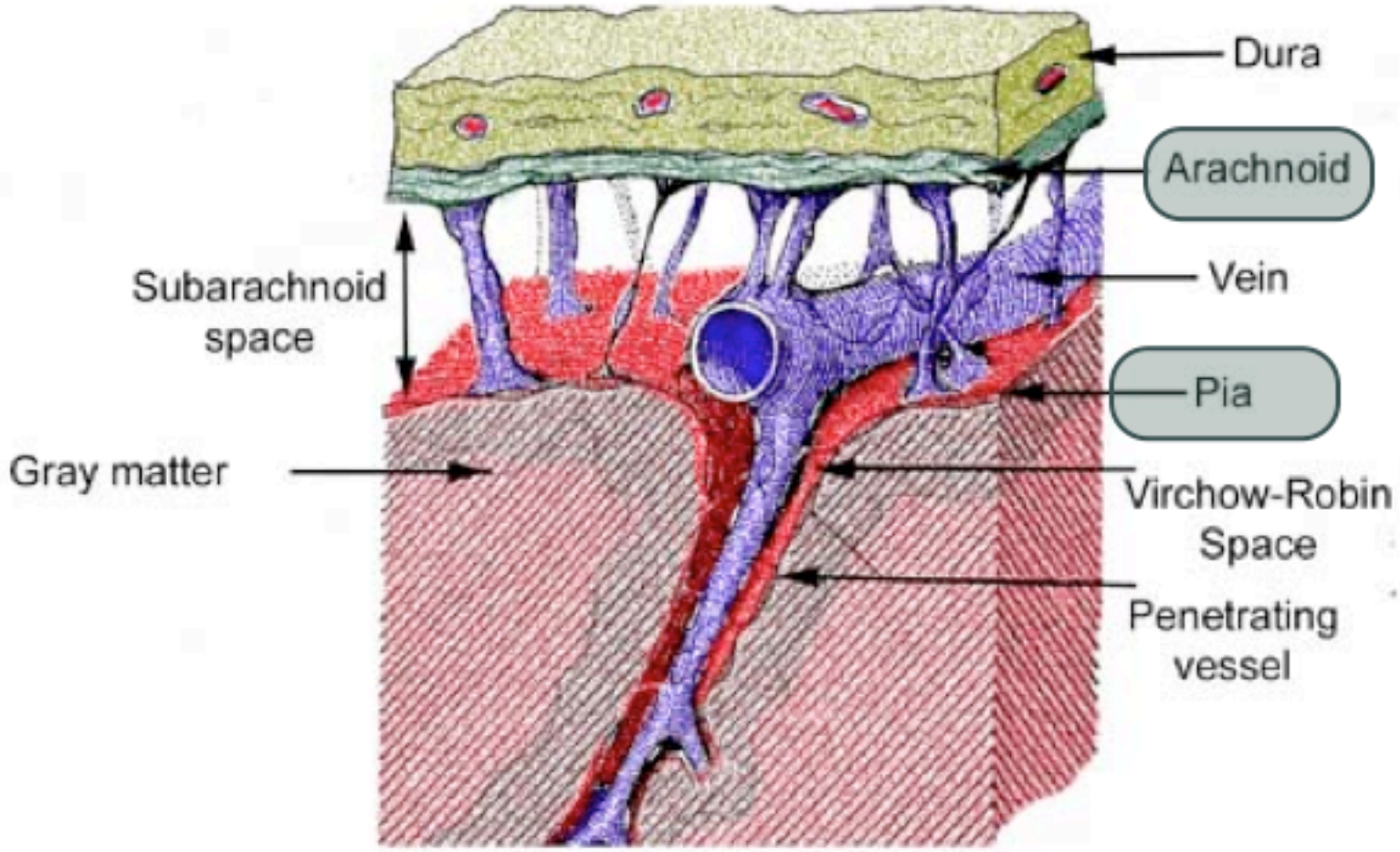
Plato and Aristotle, "The school of Athens", Raphael 1509

*Τελεολογία = teleology:
a definition induced in philosophy by *Plato* and *Aristotle* meaning that
the evolution of structures happens always with a purpose

Cortical Meninges



Cortical Subarachnoid Space



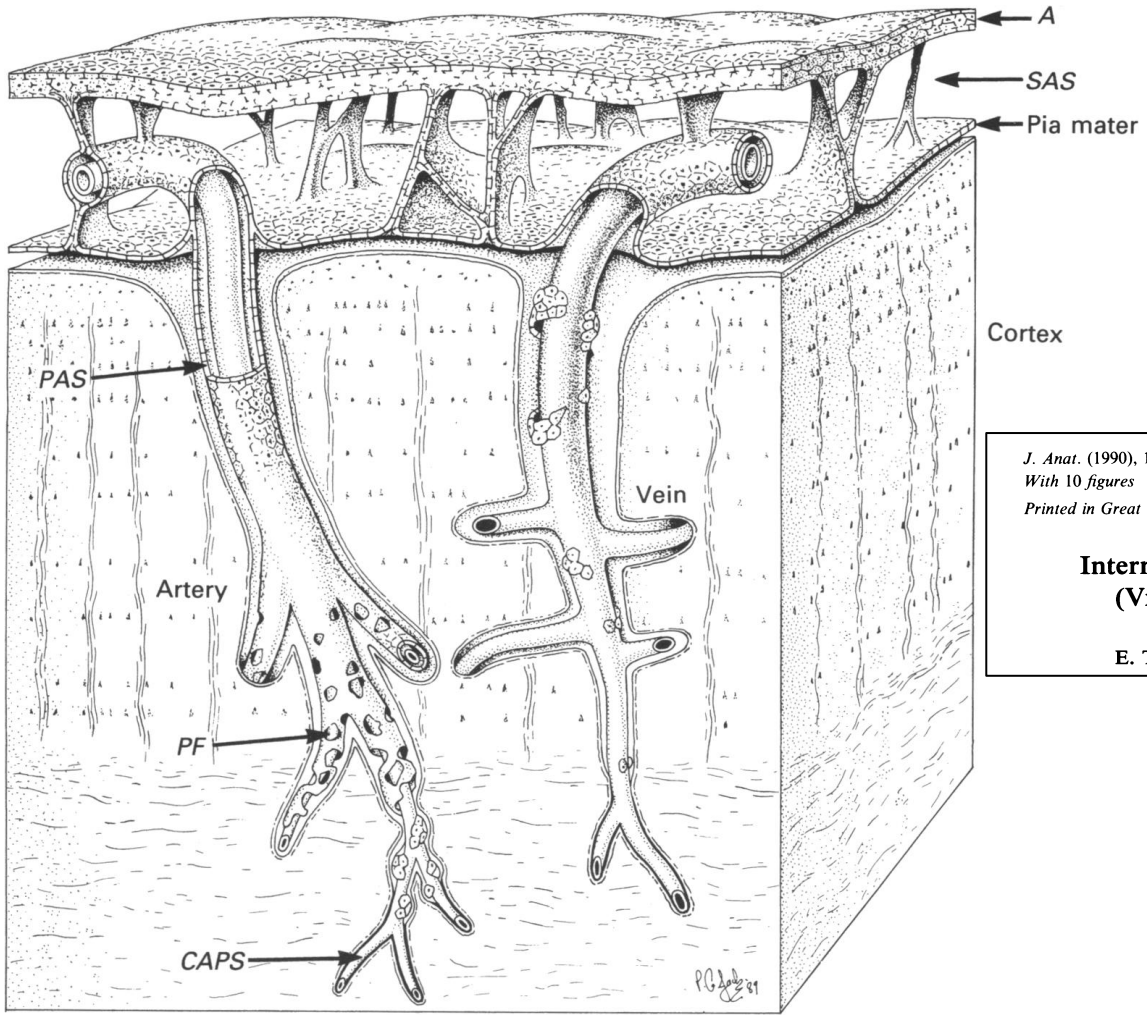
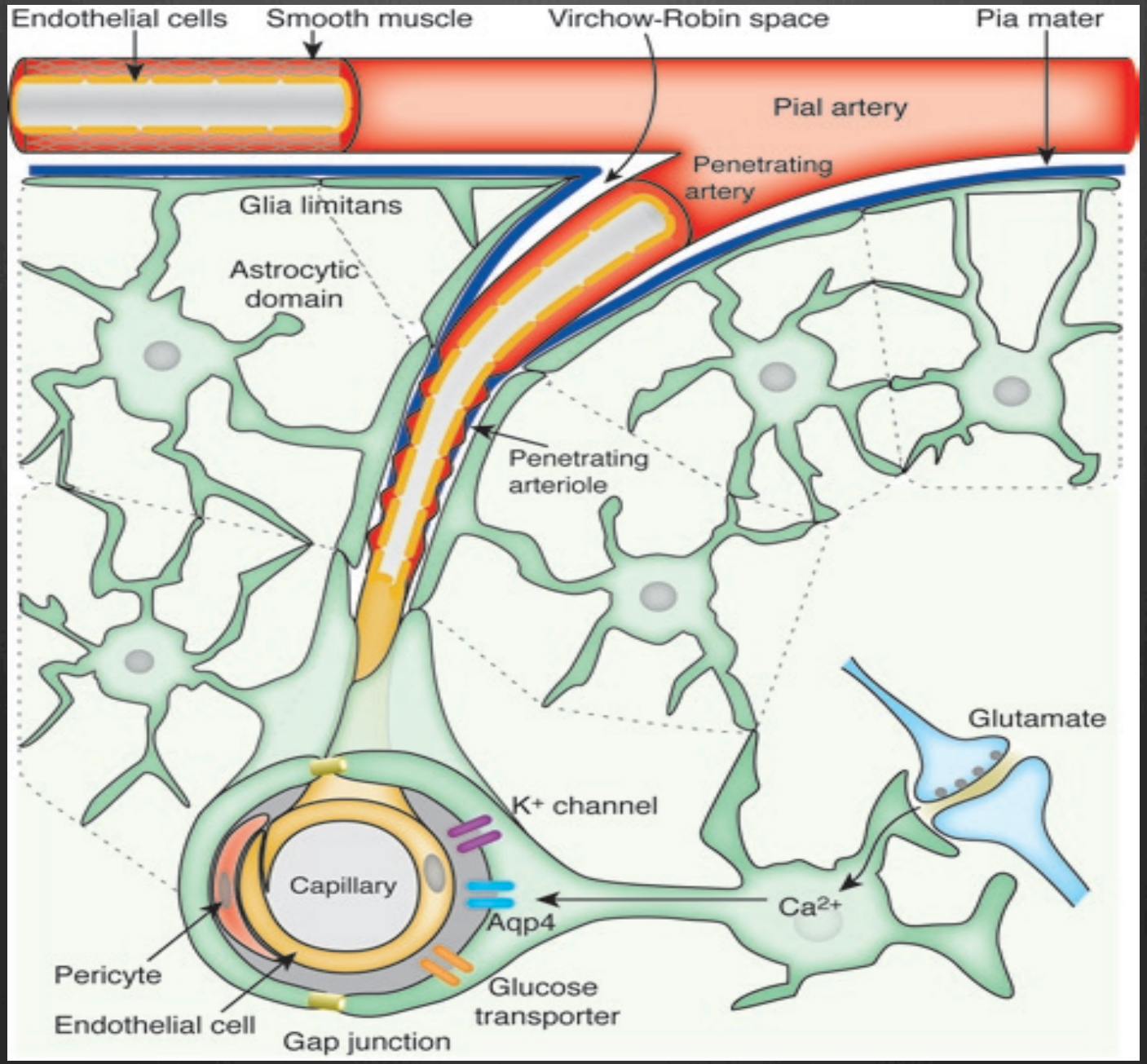


Fig. 10. Diagram demonstrating the relationships of the pia mater and intracerebral blood vessels. Subarachnoid space (*SAS*) separates the arachnoid (*A*) from the pia mater overlying the cerebral cortex. An artery on the left of the picture is coated by a sheath of cells derived from the pia mater; the sheath has been cut away to show that the periarterial spaces (PAS) of the intracerebral and extracerebral arteries are in continuity. The layer of pial cells becomes perforated (*PF*) and incomplete as smooth muscle cells are lost from the smaller branches of the artery. The pial sheath finally disappears as the perivascular spaces are obliterated around capillaries (*CAPS*). Perivascular spaces around the vein (right of picture) are confluent with the subpial space and only small numbers of pial cells are associated with the vessel wall.

J. Anat. (1990), **170**, 111–123
With 10 *figures*
Printed in Great Britain

Interrelationships of the pia mater and the perivascular (Virchow–Robin) spaces in the human cerebrum*

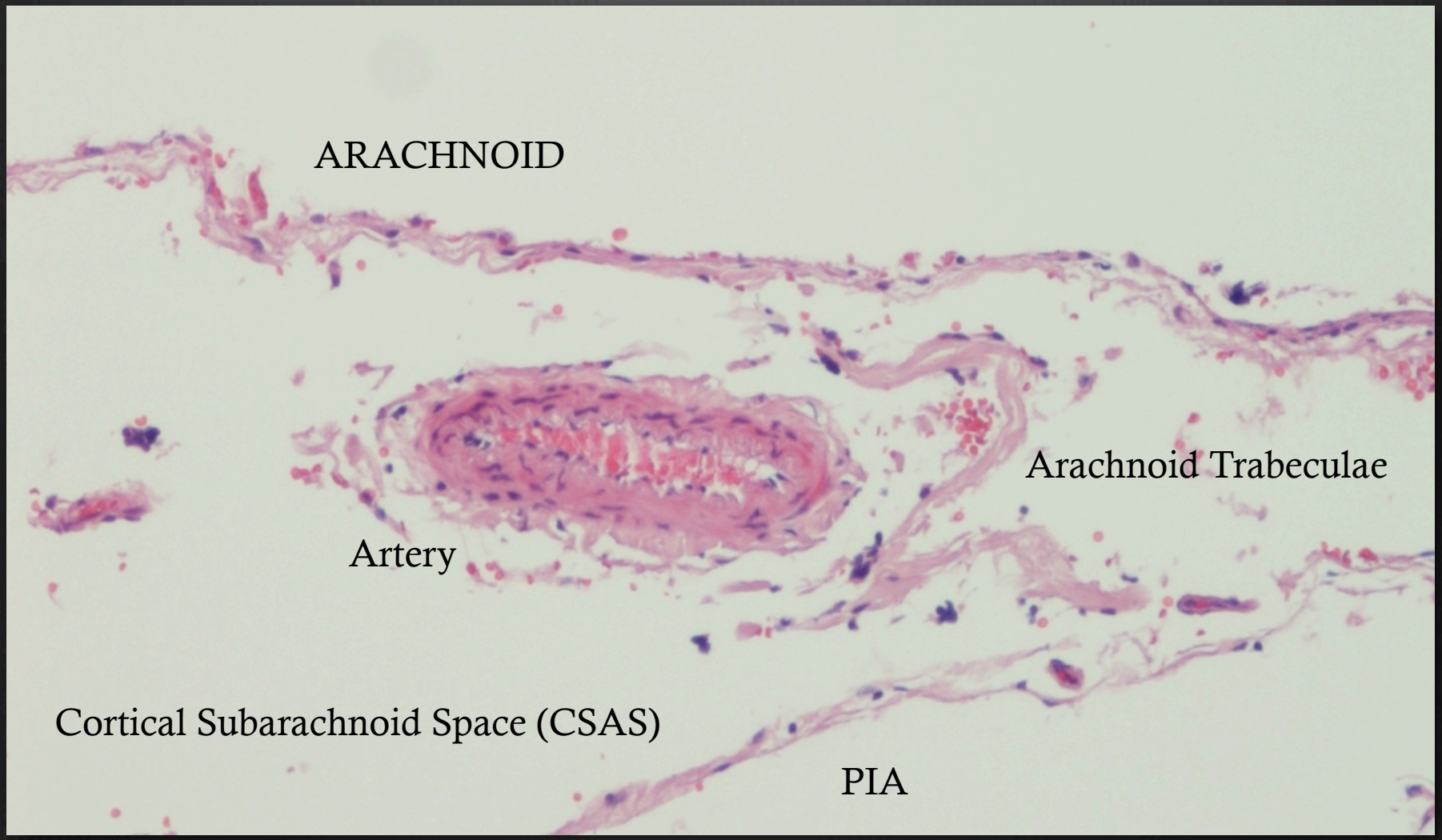
E. T. ZHANG,†‡ C. B. E. INMAN† AND R. O. WELLER†



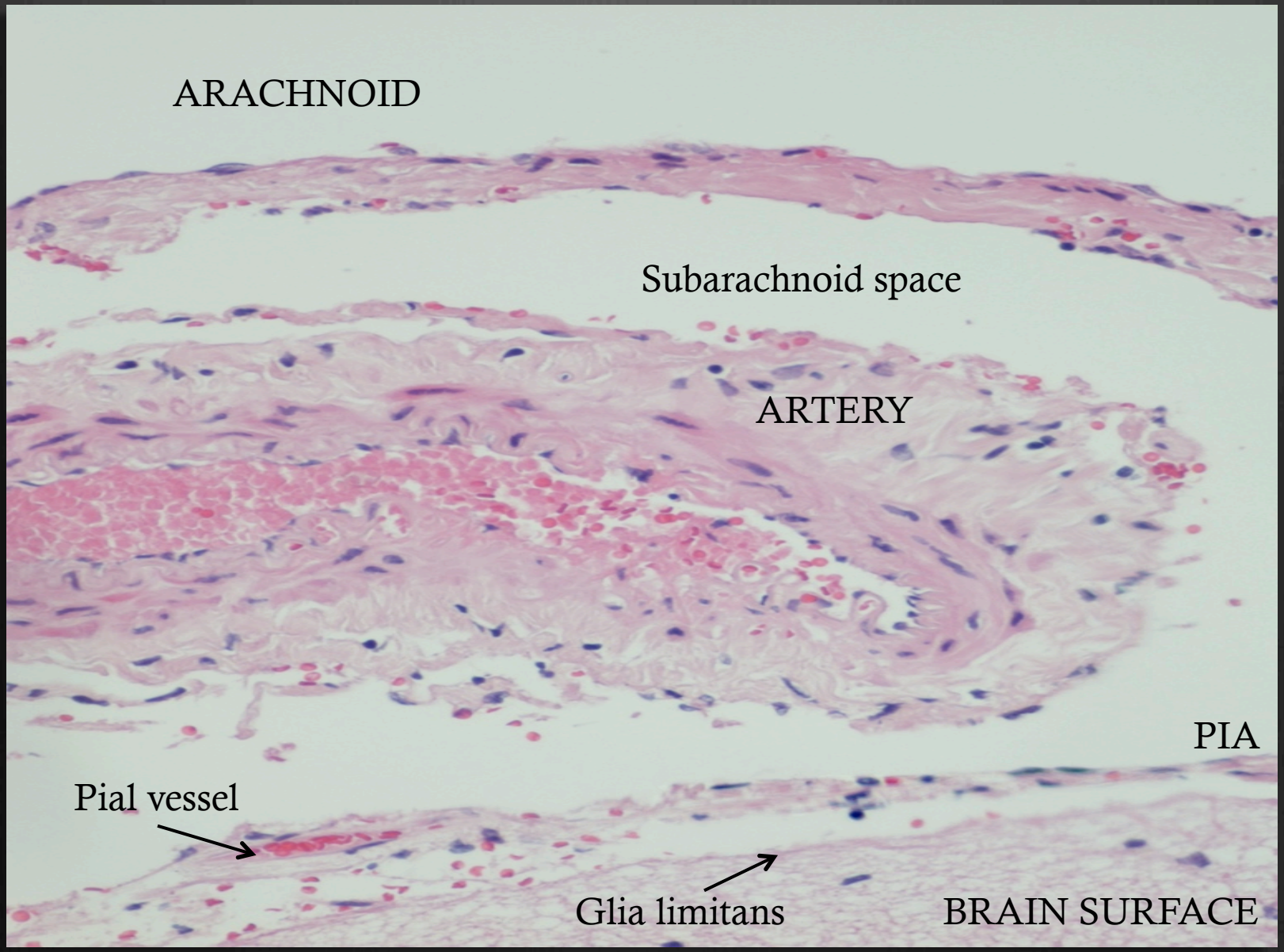
Costantino Iadecola & Maiken Nedergaard, ***Nature Neuroscience***, 2007

PIAL SURFACE

ARACHNOID SURFACE



Filippidis et al.
Transmembrane resistance and histology of isolated sheep leptomeninges
Neurological Research (2010) vol. 32 (2) pp. 205



Filippidis et al.
Transmembrane resistance and histology of isolated sheep leptomeninges
Neurological Research (2010) vol. 32 (2) pp. 205

Is CSAS important for neurohydrodynamics and CSF disorders ?

J Neurosurg Pediatrics 2:1–11, 2008

The importance of the cortical subarachnoid space in understanding hydrocephalus

Harold L. Rekate, M.D.,[1,2] Trimurti D. Nadkarni, M.Ch.,[3] and Donna Wallace, R.N., M.S., C.P.N.P.[1]

So…

The arachnoid and pia mater, line a preformed space (CSAS), with a biological fluid (CSF) which consists of 99% WATER.

We need to address the relationship of CSAS with Water…

Let's move on to the cellular level

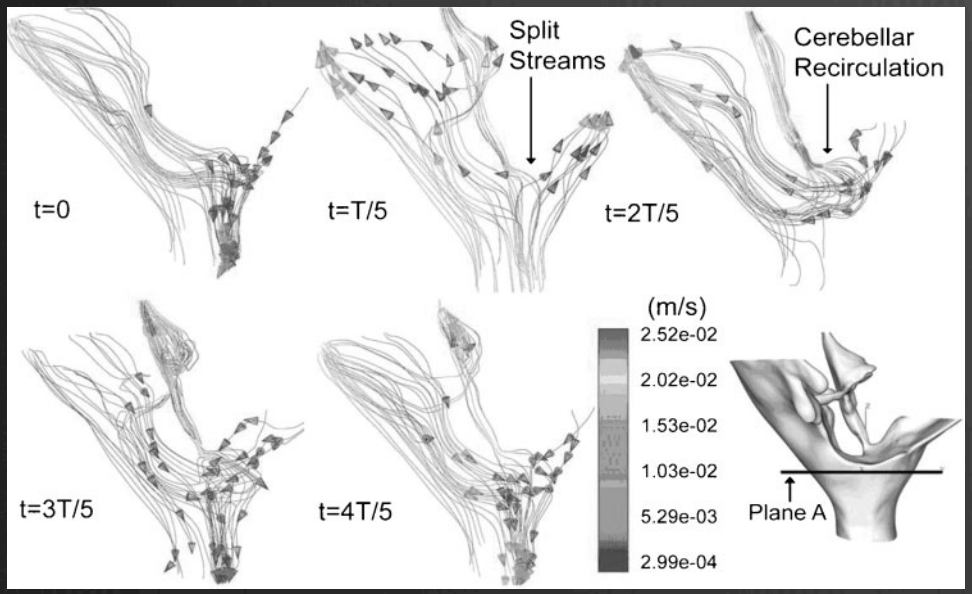
Let's talk about **solute-coupled transport of water**

Solute-coupled water transport: *the analogy*

Fluid movement, CFD

In Macro scale

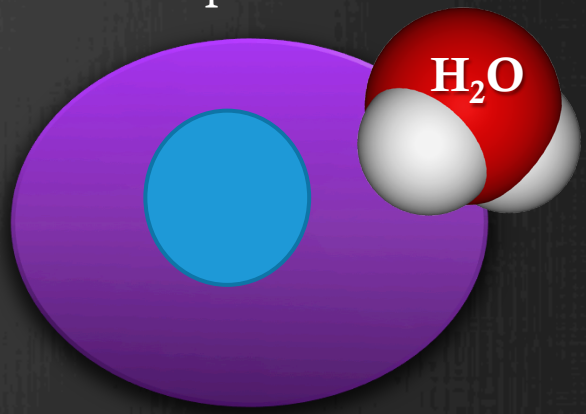
Pressure gradients & pulse amplitude important



Water movement

In Cellular scale

Osmotic gradient & cellular permeability important



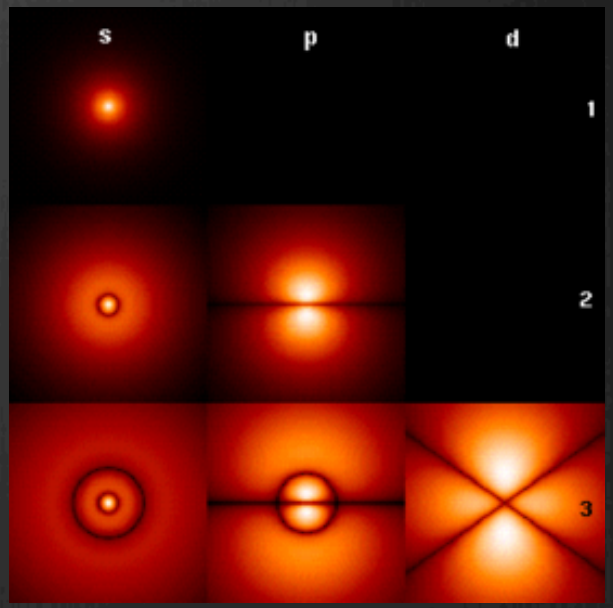
Schaffer N., Martin B., Loth F.
Cerebrospinal fluid hydrodynamics in type I Chiari malformation
Neurological Research (2011), 33:3, 247-260

"Ion & Water Mechanics"

Solute-coupled water transport: *analogy*

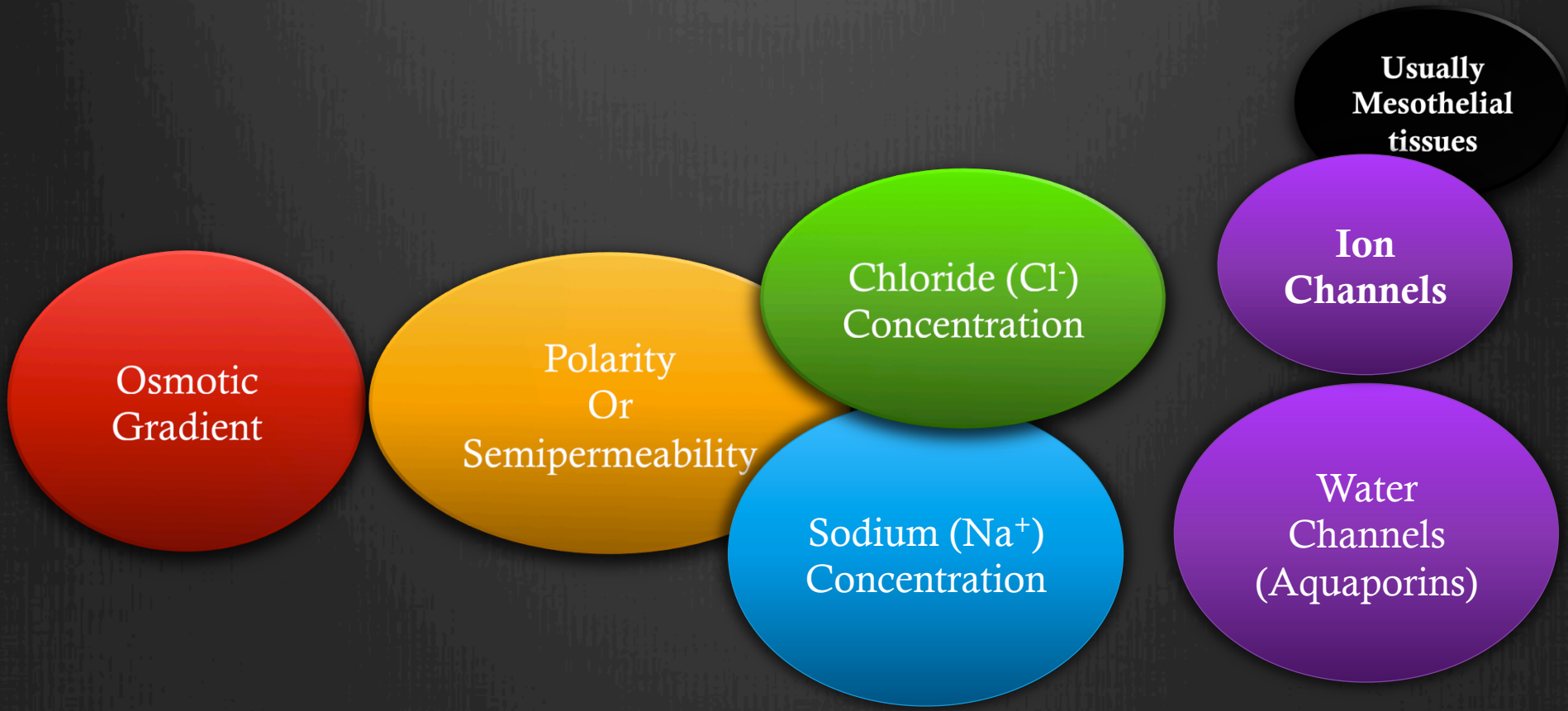
Newtonian Physics
Macro scale

Quantum physics
Subatomic scale



Thinking beyond structures ➔ "Ion & Water mechanics"

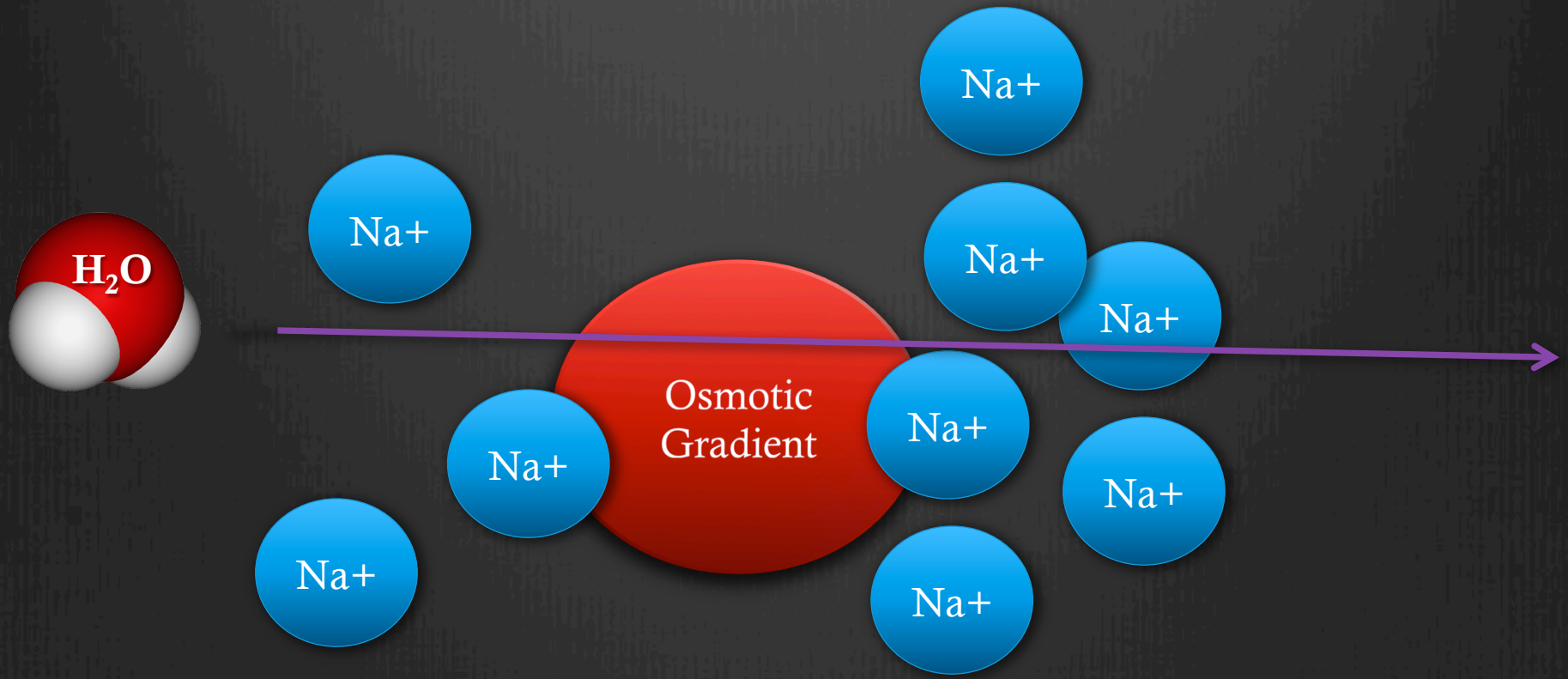
The Critical Mixture for solute-coupled transport



Thinking beyond structures → "Ion & Water mechanics"

Water FOLLOWS Sodium in polarized epithelia

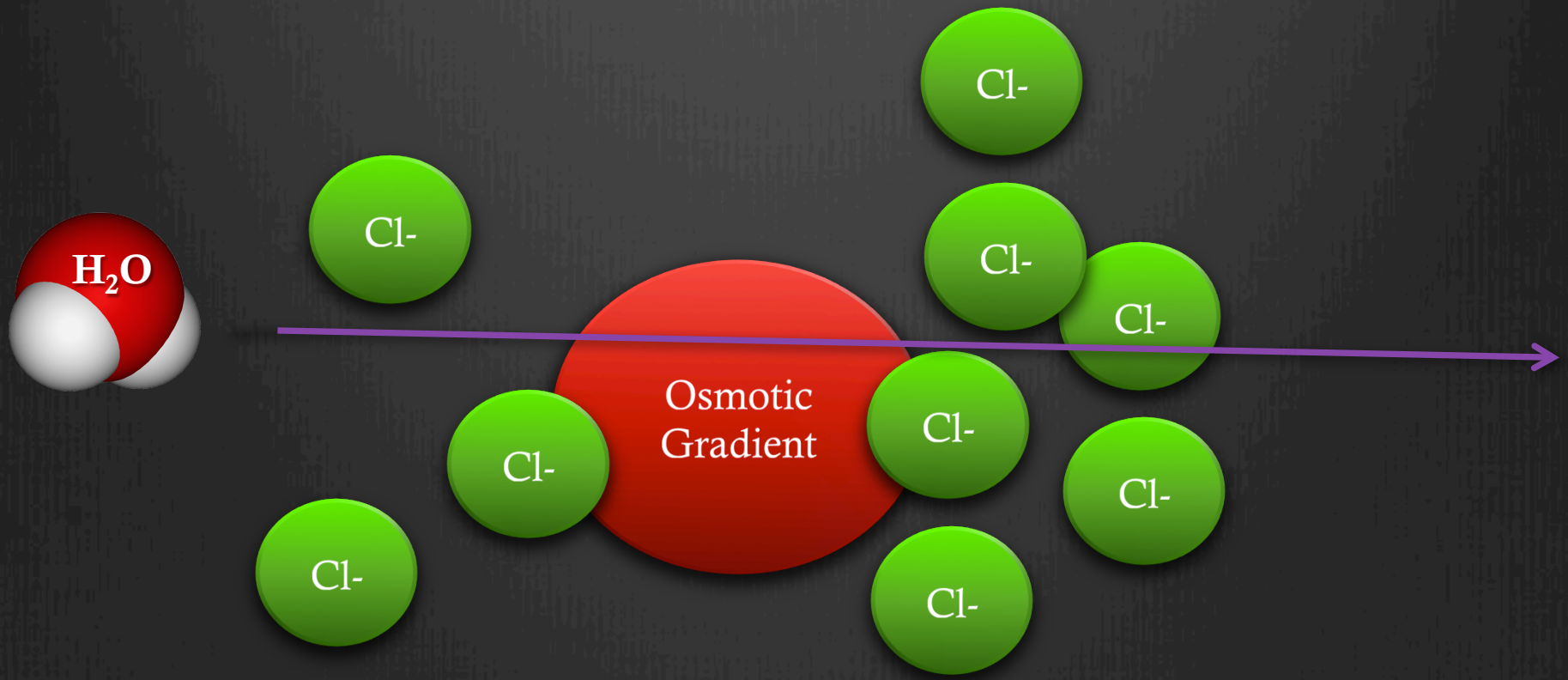
(e.g. choroid plexus, pleura, pericardium, omentum, nephron)



Thinking beyond structures → "Ion & Water mechanics"

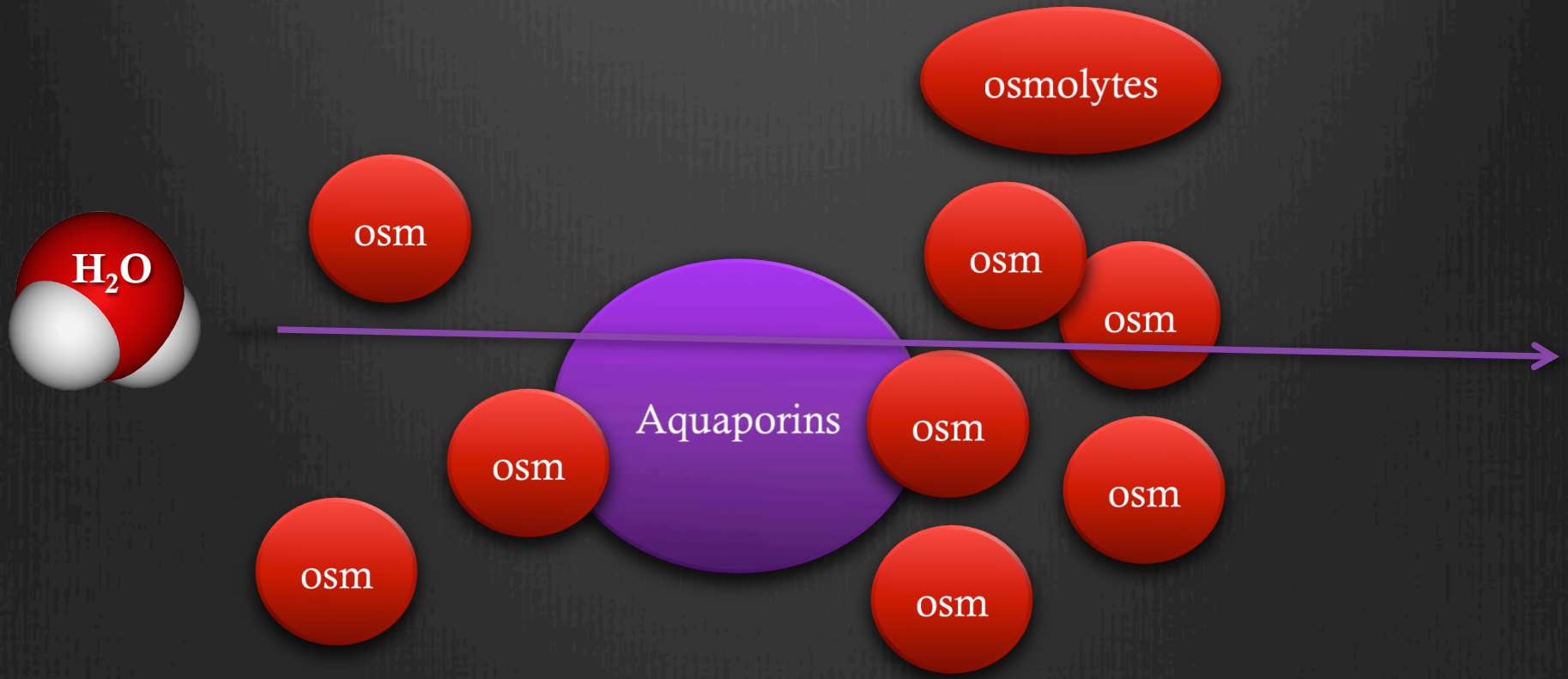
Water FOLLOWS Chloride in polarized epithelia

(e.g. sweat glands, salivary glands, bronchi)



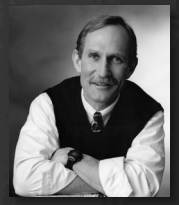
Thinking beyond structures → "Ion & Water mechanics"

Water FOLLOWS osmotic gradient of osmolytes through AQPs



AQUAPORINS

- Family of more than 13 water channel proteins
- First described in 1991 as aquaporin -1 (AQP1)
- Nobel prize in Chemistry 2003 *(Peter Agre)*

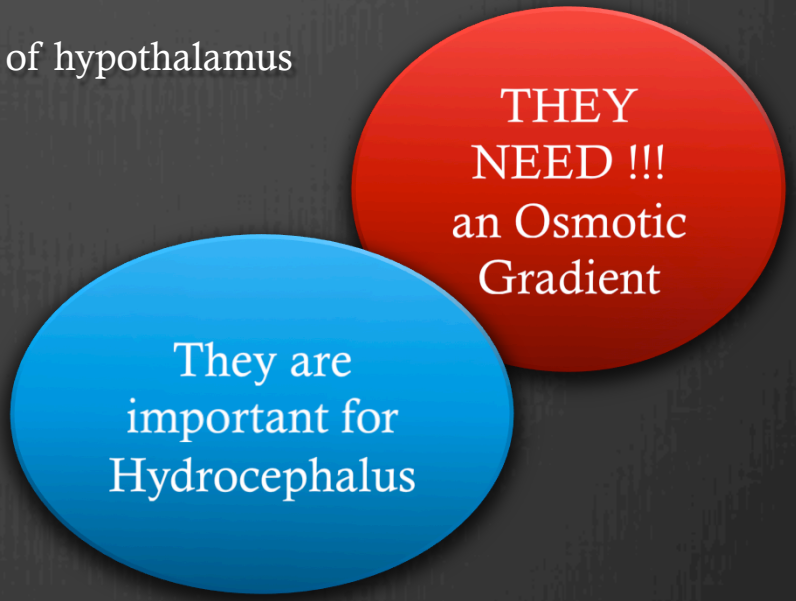


- Aquaporin-4 (AQP4) is the dominant form in the brain

Agre et al.
Towards a molecular understanding of water homeostasis in the brain.
Neuroscience (2004) vol. 129 (4) pp. 849-50

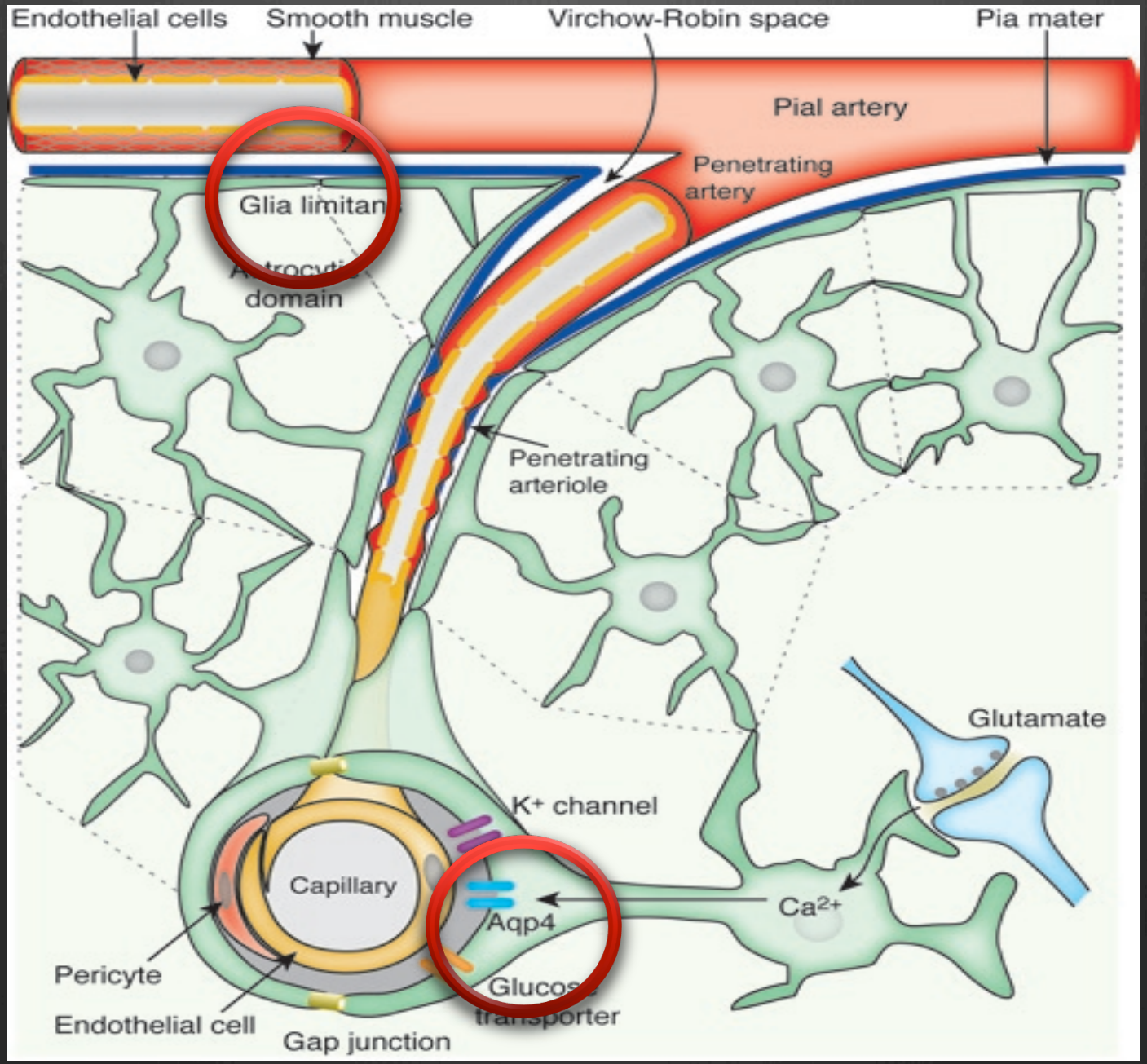
AQP4 LOCALIZATION

- **Glia Limitans**
- **Astrocyte foot processes around capillaries that form the Blood-Brain-Barrier (BBB)**
- Ependymal cells
- Supraoptic and suprachiasmatic nuclei of hypothalamus
- Cerebellum
- Hippocampal dentate gyrus,
- Hippocampal areas CA1-CA2
- Neocortex
- Nucleus of stria terminalis
- Medial habenular nucleus



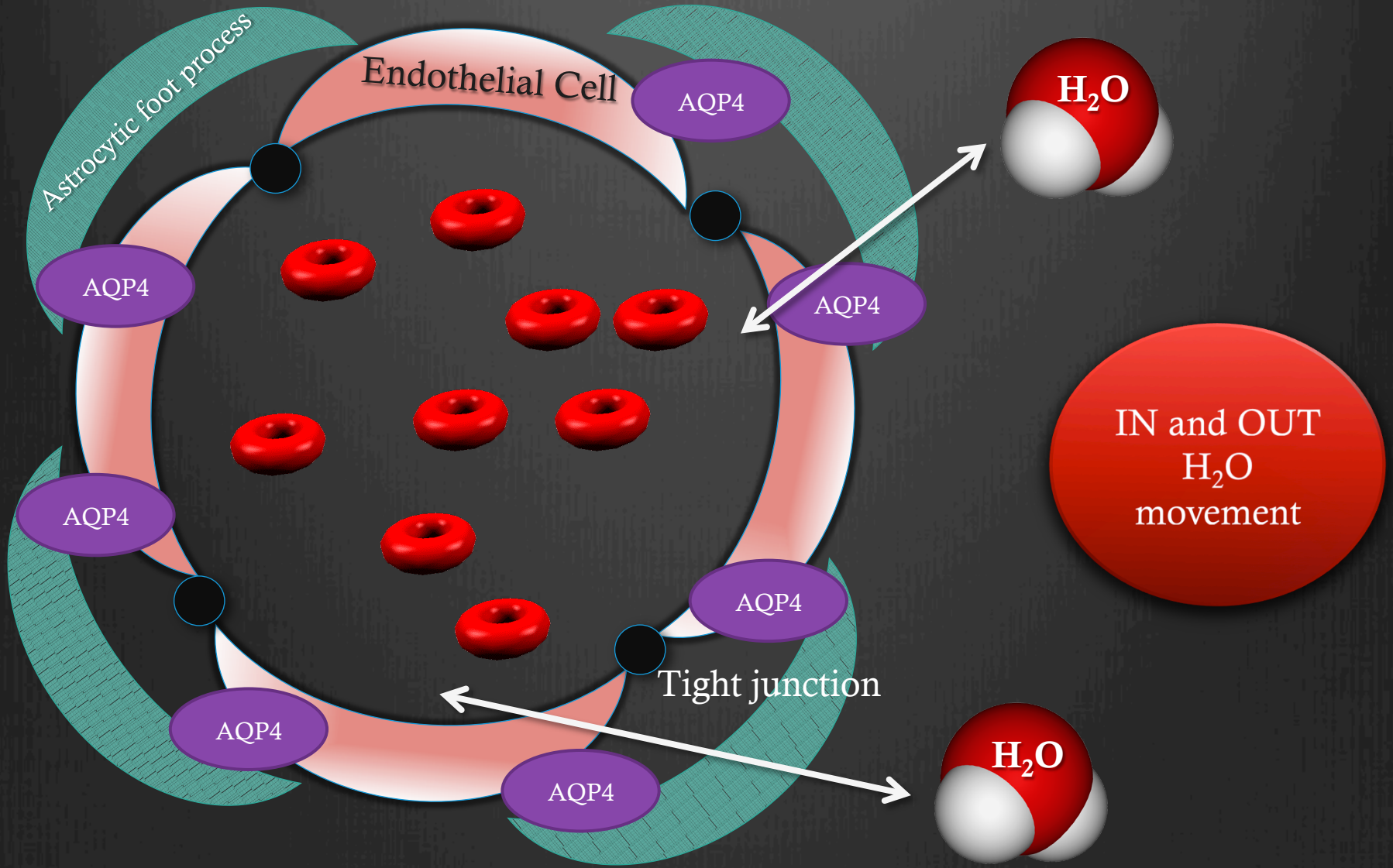
Badaut et al.
Aquaporins in brain: distribution, physiology, and pathophysiology.
J Cereb Blood Flow Metab (2002) vol. 22 (4) pp. 367-78

Filippidis et al.
Hydrocephalus and aquaporins: lessons learned from the bench.
Childs Nerv Syst. 2011 Jan;27(1):27-33. Epub 2010 Jul 13.

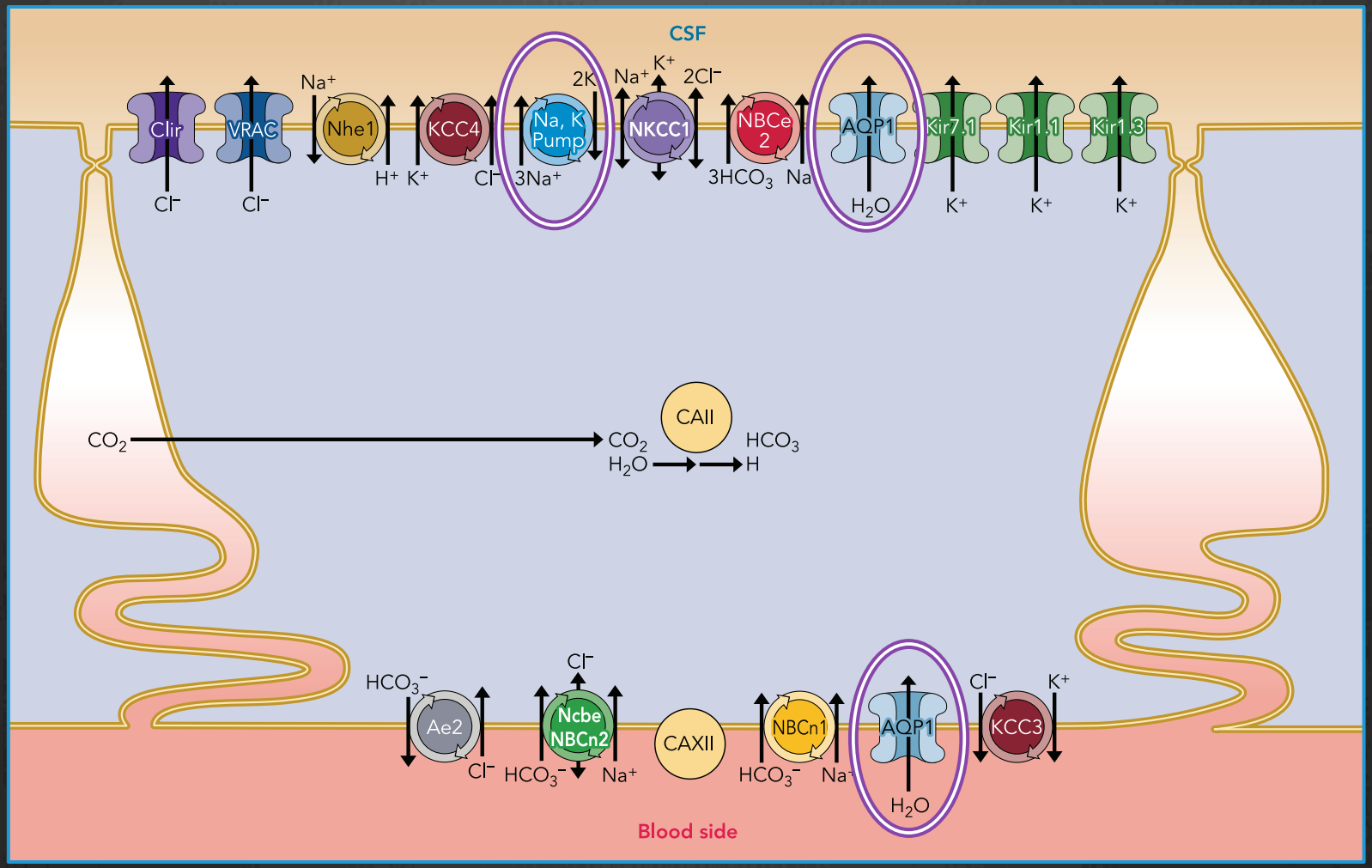


Costantino Iadecola & Maiken Nedergaard, ***Nature Neuroscience***, 2007

AQP4 and the Blood-Brain-Barrier and Cerebral vessels

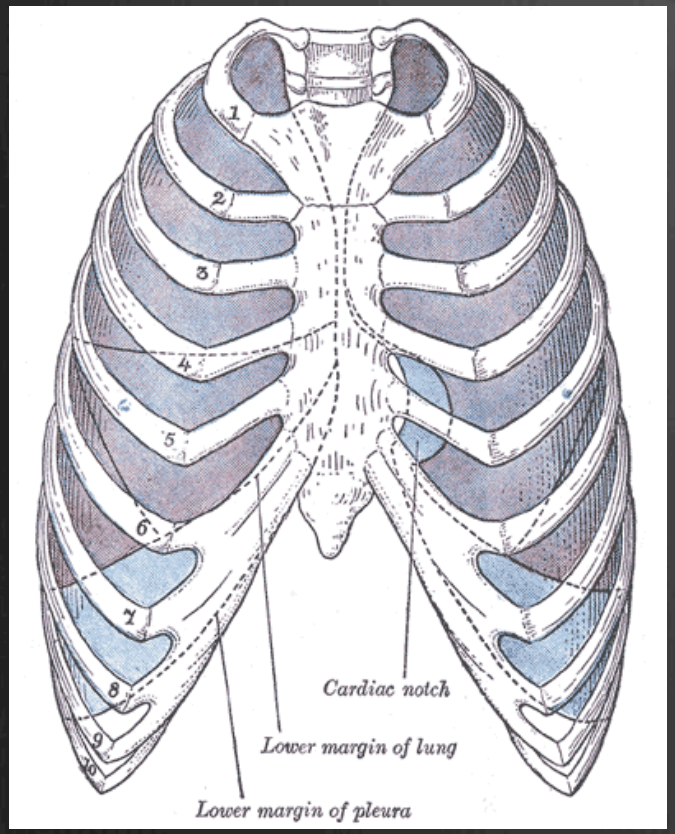


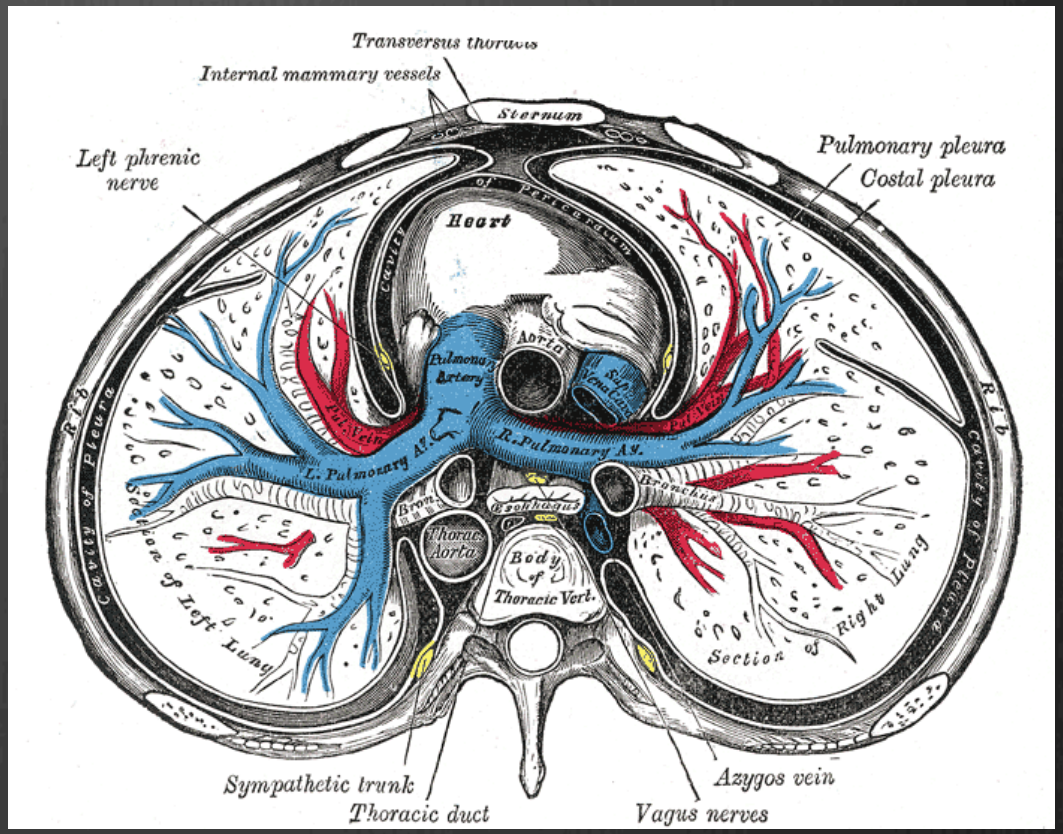
choroid plexus: analogy with CSAS ?



Damkier et al.
Epithelial Pathways in Choroid Plexus Electrolyte Transport.
Physiology (2010), 25, p 239-249

Pleura and mesothelial tissues: analogy with CSAS ?





A biological membrane that lines a preformed cavity-space and regulates the turnover of the pleural fluid.

Pleura, Pericardium, Peritoneum are MESOTHELIAL tissues ***SO WHAT ABOUT CSAS ???***

J Appl Physiol
90: 1565–1569, 2001.

Effects of SNP, ouabain, and amiloride on electrical potential profile of isolated sheep pleura

C. H. HATZOGLOU,[1] K. I. GOURGOULIANIS,[2] AND P. A. MOLYVDAS[2]

Dept. Physiology, Membrane permeability Lab
Medical School, University of Thessaly, GREECE

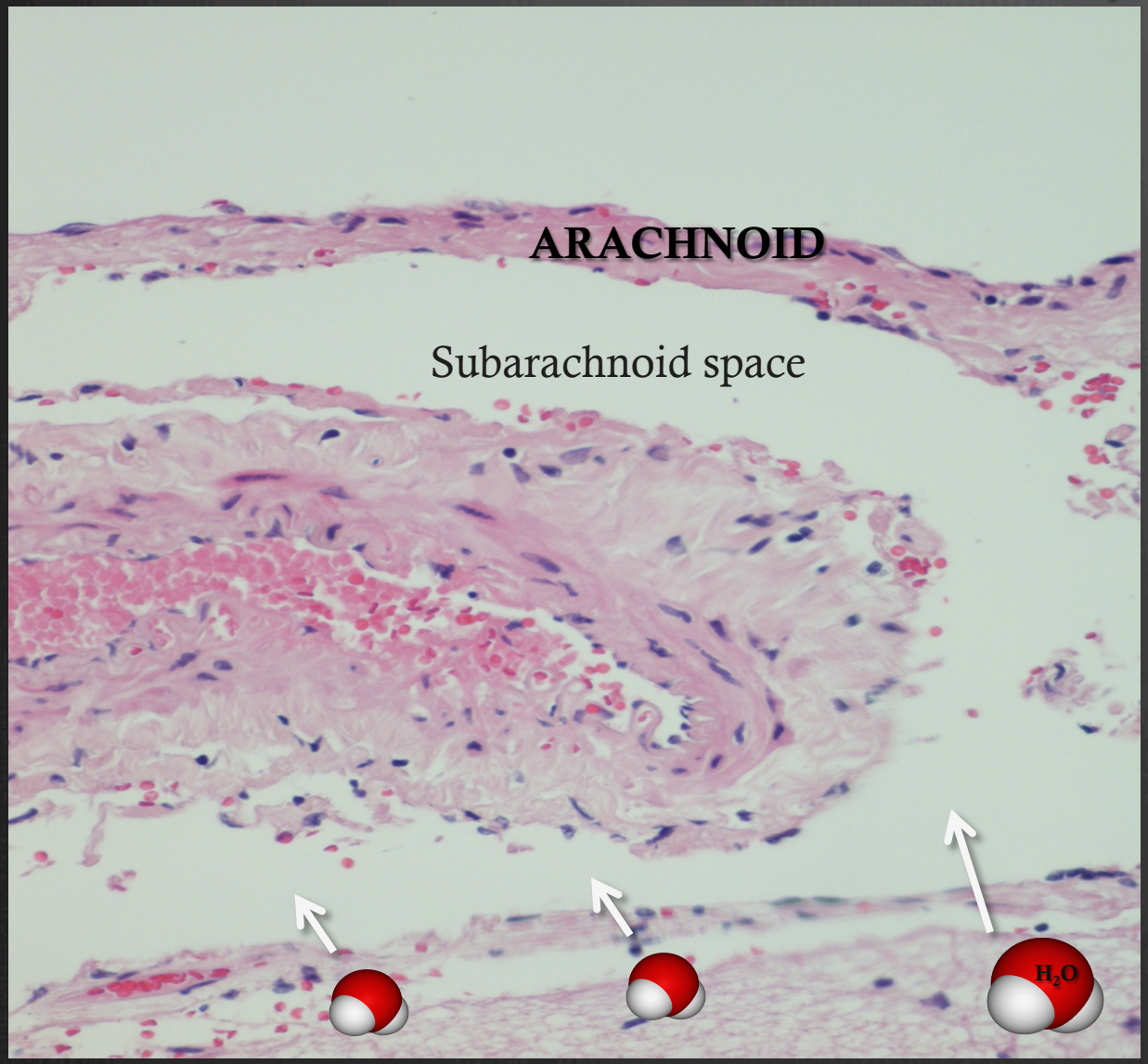
Could this be also the case for CSAS ?

Is Solute-coupled transport of water present ?

Skimming for Evidence…

Indirect evidence about brain edema (excess water) clearance at this interface

Glia limitans – subarachnoid space



Tait et al.
Water movements in the brain: role of aquaporins.
Trends Neurosci (2008) vol. 31 (1) pp. 37-43

Reulen et al.
Role of pressure gradients and bulk flow in dynamics of vasogenic brain edema.
J Neurosurg (1977) vol. 46 (1) pp. 24-35

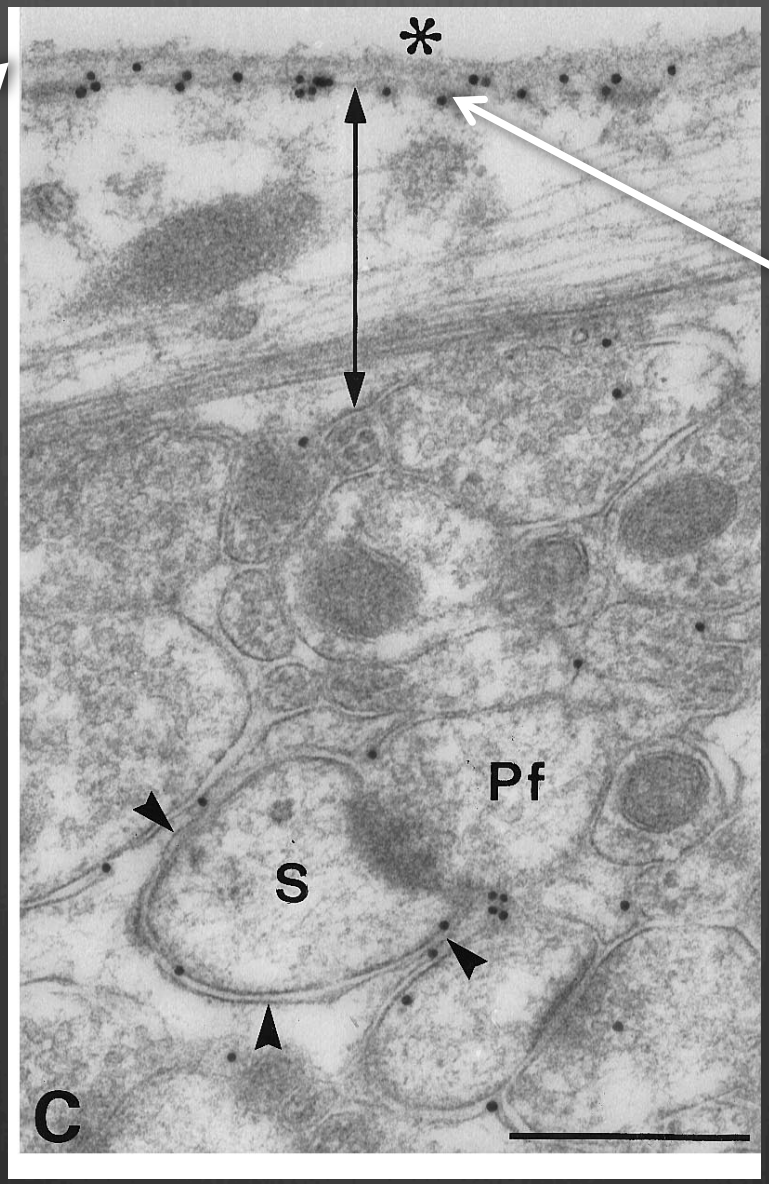
Cerebrospinal Fluid Production by the Choroid Plexus and Brain

Abstract. *The production of cerebrospinal fluid and the transport of ^{24}Na from the blood to the cerebrospinal fluid were studied simultaneously in normal and choroid plexectomized rhesus monkeys. Choroid plexectomy reduced the production of cerebrospinal fluid by an average of 33 to 40 percent and the rate of appearance of ^{24}Na in the cerebrospinal fluid and its final concentration were proportionately reduced. In both normal and plexectomized animals, ^{24}Na levels were found to be markedly greater in the gray matter surrounding the ventricles and in the gray matter bordering the subarachnoid space. That sodium exchanges in these two general areas of the brain may be linked to the formation of the cerebrospinal fluid is discussed here.*

CSAS-
brain surface interface !

Milhorat et al.
Cerebrospinal fluid production by the choroid plexus and brain
Science (1971) vol. 173 (994) pp. 330-332

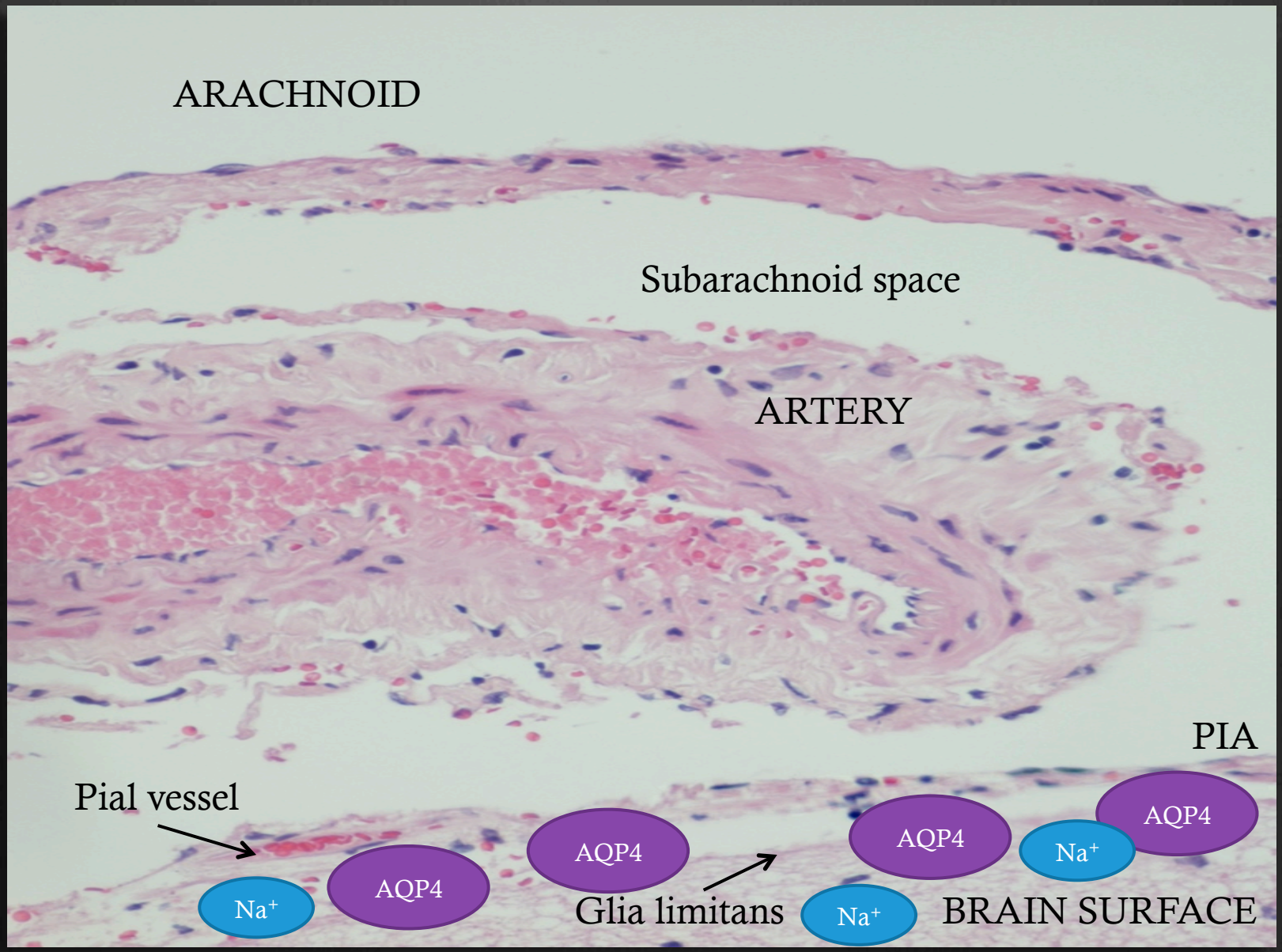
PIA mater - Glia Limitans
lower CSAS interface



Black dots ?
AQP4

Nielsen et al.
Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain
J Neurosci (1997) vol. 17 (1) pp. 171-180

Let us think with teleology in mind !



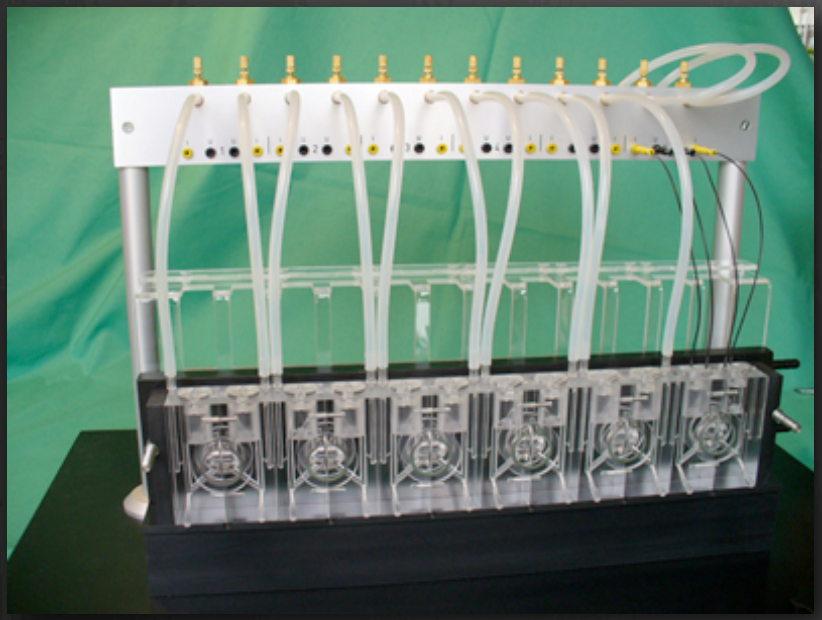
What is missing ?

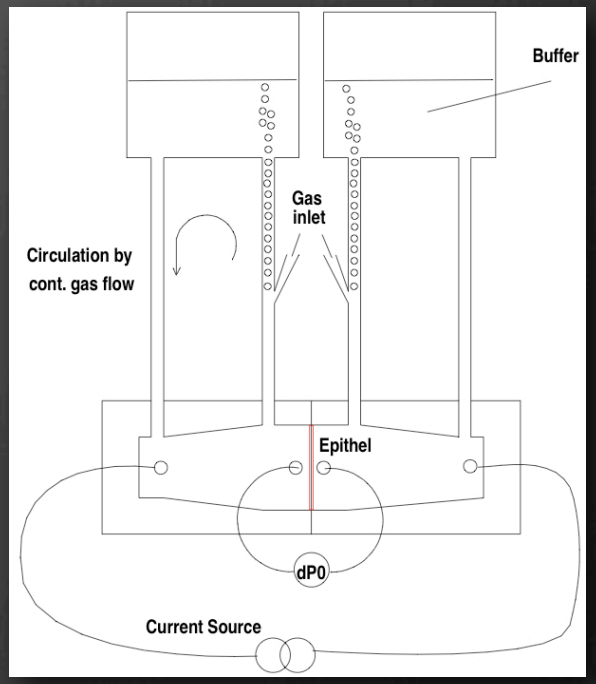
Water & Ion channels !

Solute-coupled transport

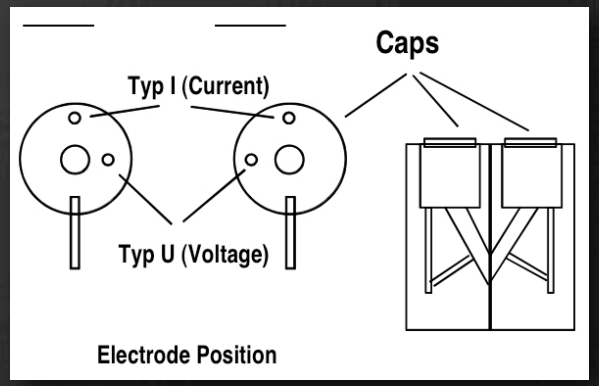
Membrane Electrophysiology

"Hans Ussing" chambers

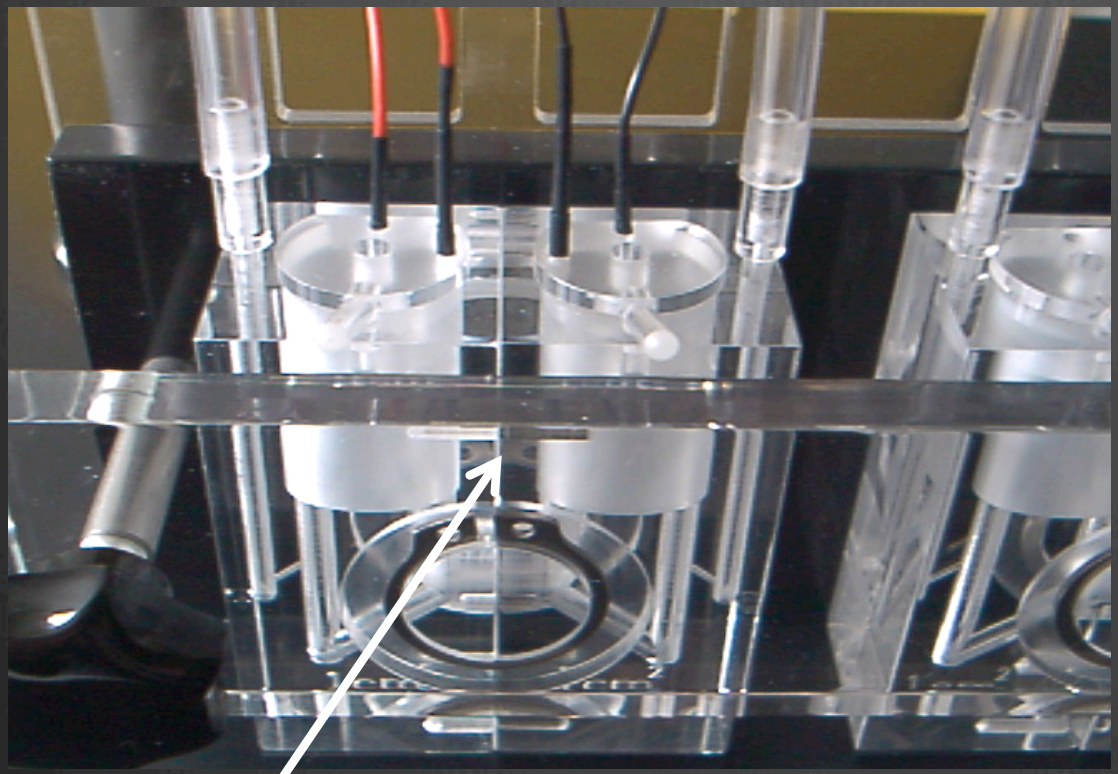




ESTABLISHED METHOD
FOR SOLUTE-COUPLED TRANSPORT STUDIES



Ussing HH, Zerahn K.
Active transport of sodium as the source of electric current in the short-circuited isolated frog skin.
Acta Physiol Scand. 1951 Aug 25;23(2-3):110-27.



Ex vivo CSAS model

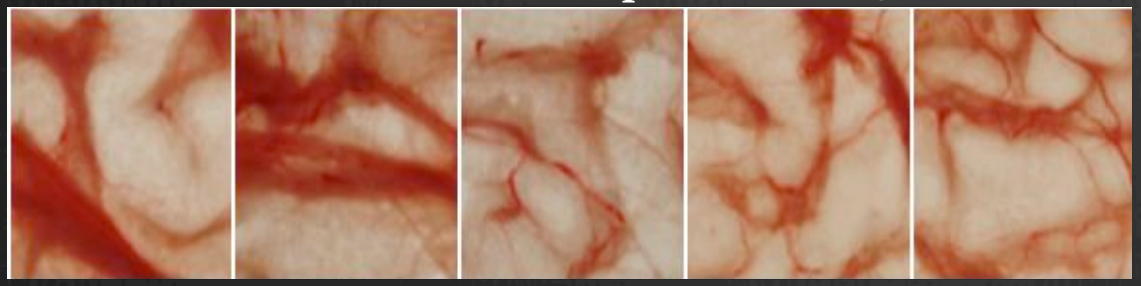
We get the:

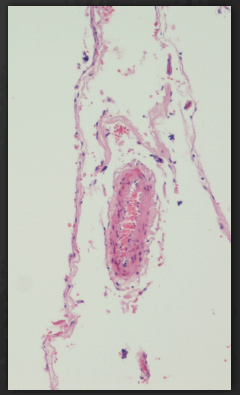
Transmembrane Resistance

R ($\Omega * cm^2$)

HIGH transmembrane resistance = LOW ionic permeability
LOW transmebrane resistance = HIGH ionic permeability

CSAS tissue profiles (facing hemichamber)





Orientation in between hemichambers

RAPID COMMUNICATION

Transmembrane resistance and histology of isolated sheep leptomeninges

Aristotelis Filippidis*, Sotirios Zarogiannis*, Maria Ioannou†, Konstantinos Gourgoulianis‡, Paschalis-Adam Molyvdas* and Chrissi Hatzoglou*

Neurol Res. 2010 Mar;32(2):205-8. Epub 2009 May 8.

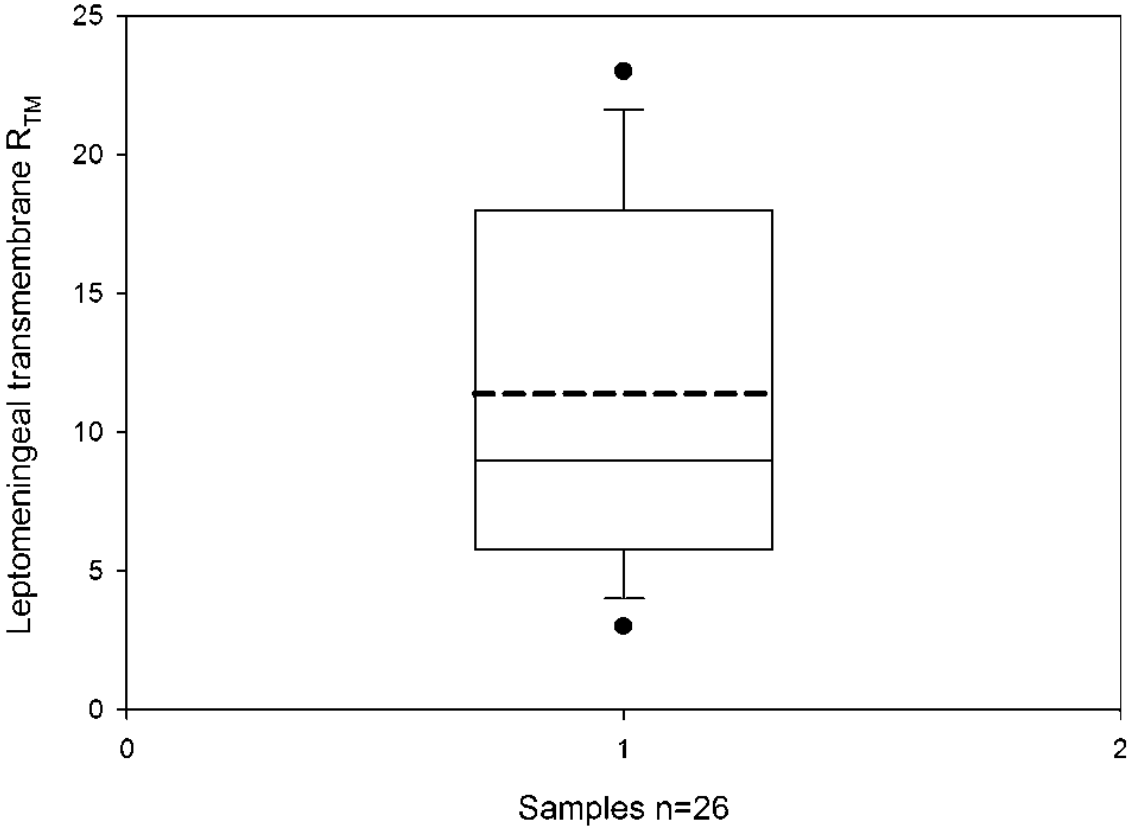


Figure 1 **Boxplot diagram describing the distribution of measured values of leptomeningeal transmembrane resistance in sheep along with mean value and outliers. Dotted line in the box represents the mean value of 11·38 Ω cm^2 obtained from 26 experiments**

CSAS

"It is a "leaky" epithelium which bears properties of mesothelium"

Filippidis A, Zarogiannis S, Ioannou M, Gourgoulianis K, Molyvdas PA, Hatzoglou C.
Transmembrane resistance and histology of isolated sheep leptomeninges.
Neurol Res. 2010 Mar;32(2):205-8. Epub 2009 May 8.

Childs Nerv Syst
DOI 10.1007/s00381-012-1688-x

ORIGINAL PAPER

Permeability of the arachnoid and pia mater. The role of ion channels in the leptomeningeal physiology

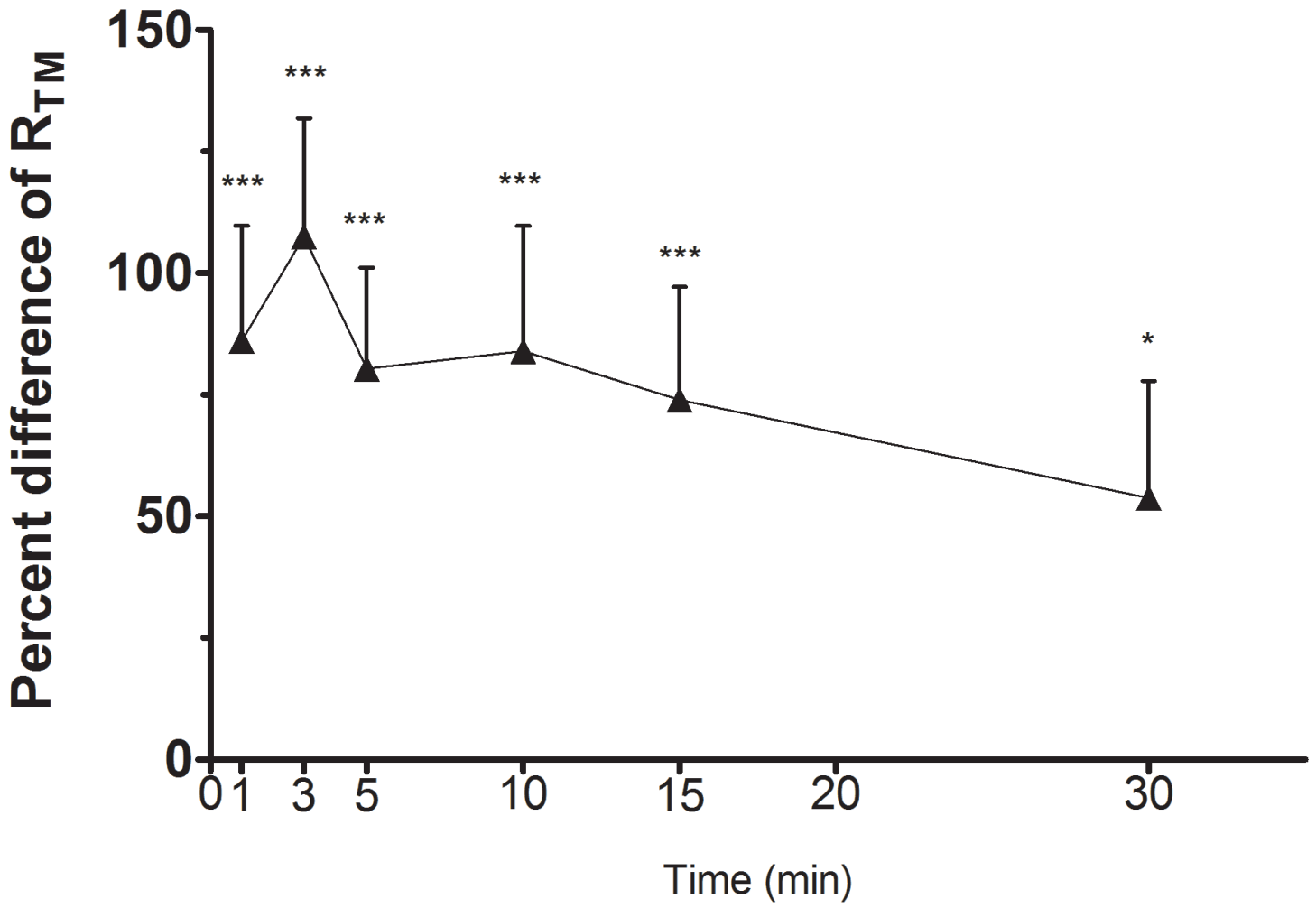
Aristotelis S. Filippidis · Sotirios G. Zarogiannis · Maria Ioannou · Konstantinos Gourgoulianis · Paschalis-Adam Molyvdas · Chrissi Hatzoglou

Sodium-Potassium-ATPase

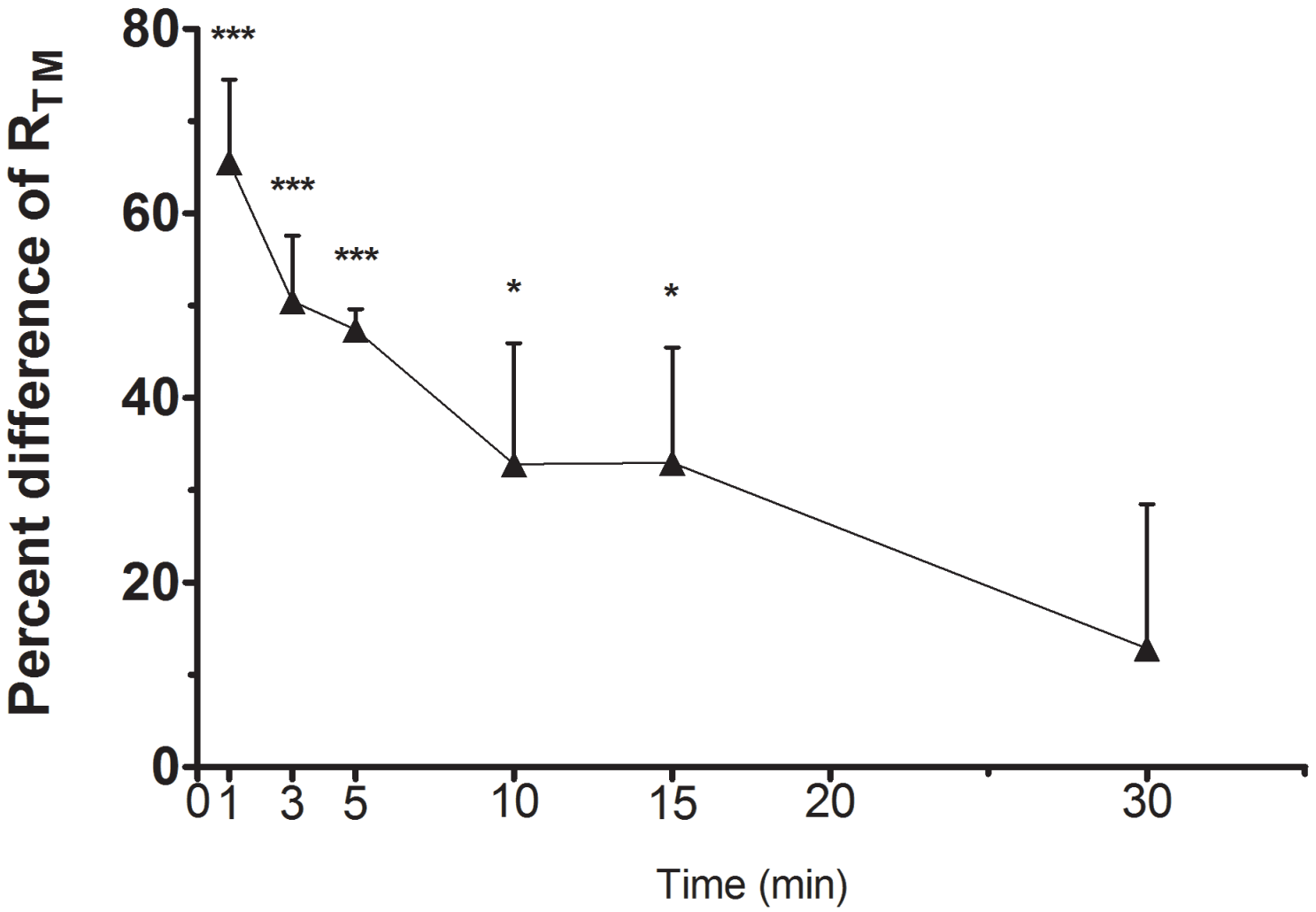
Main source of extracellular Sodium

We tested inhibition with OUABAIN

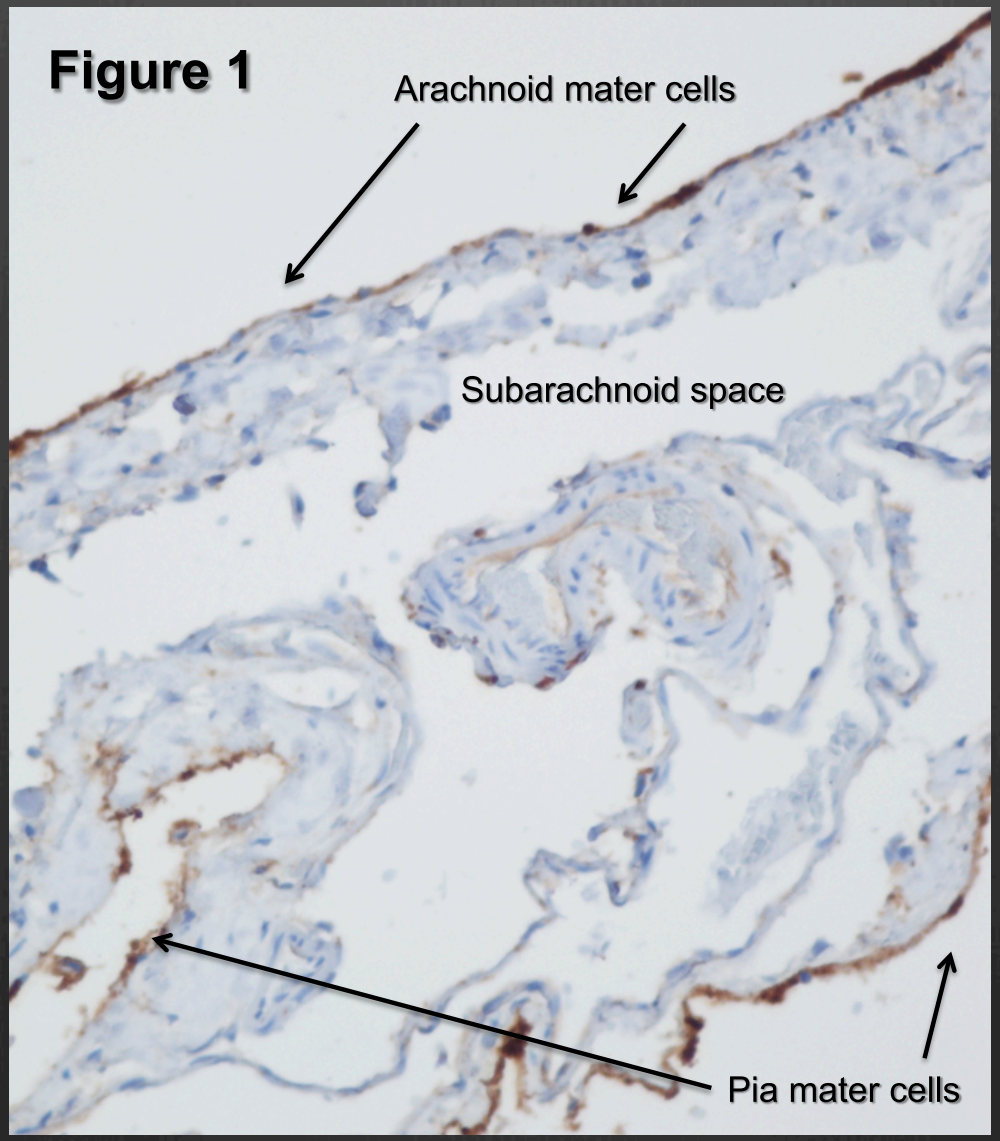
Leptomeninges Ouabain 10-3M Arachnoidal side



Leptomeninges Ouabain 10^{-3}M
Pial side



a1 subunit Sodium-Potassium-ATPase

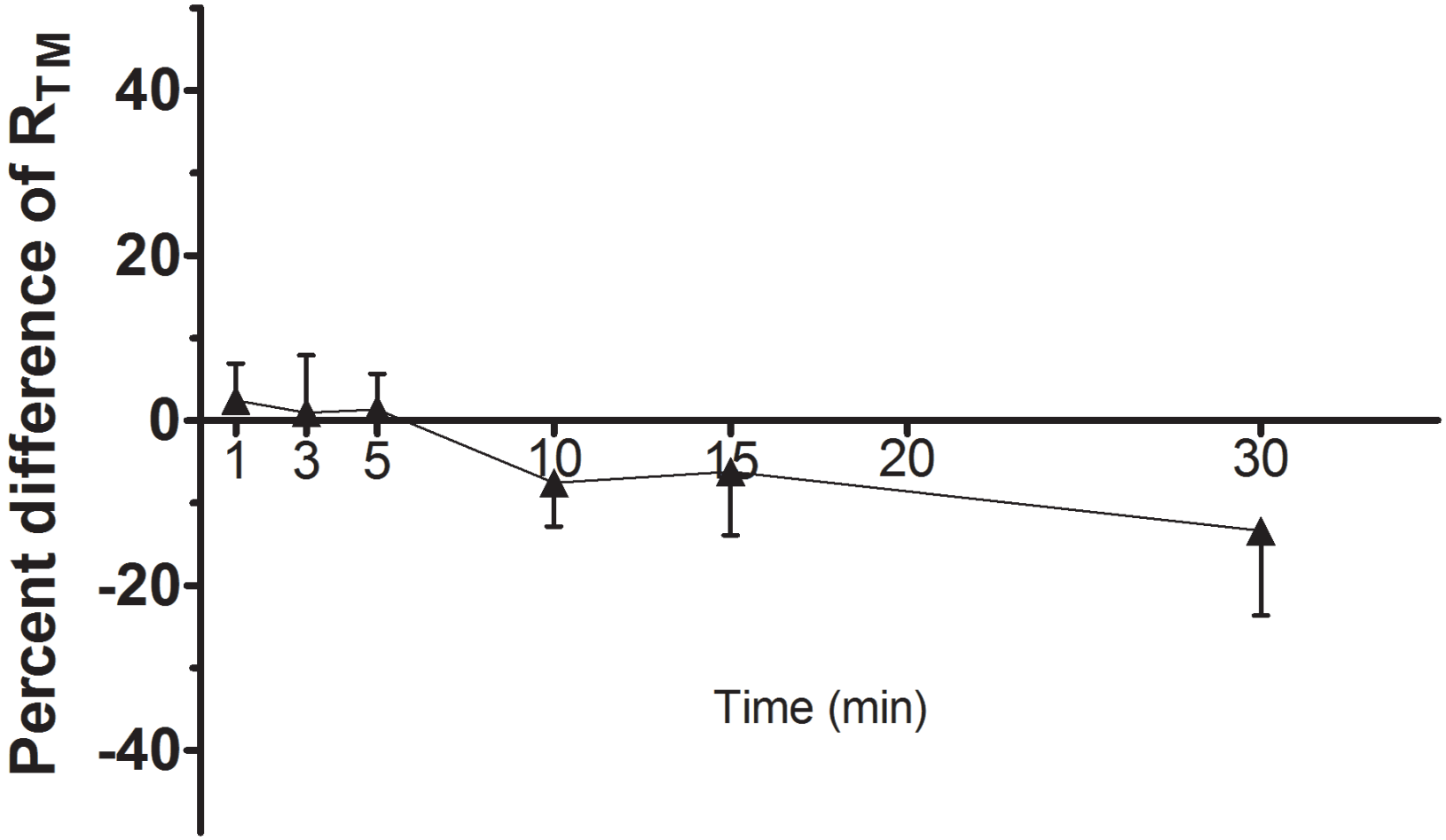


ENaC

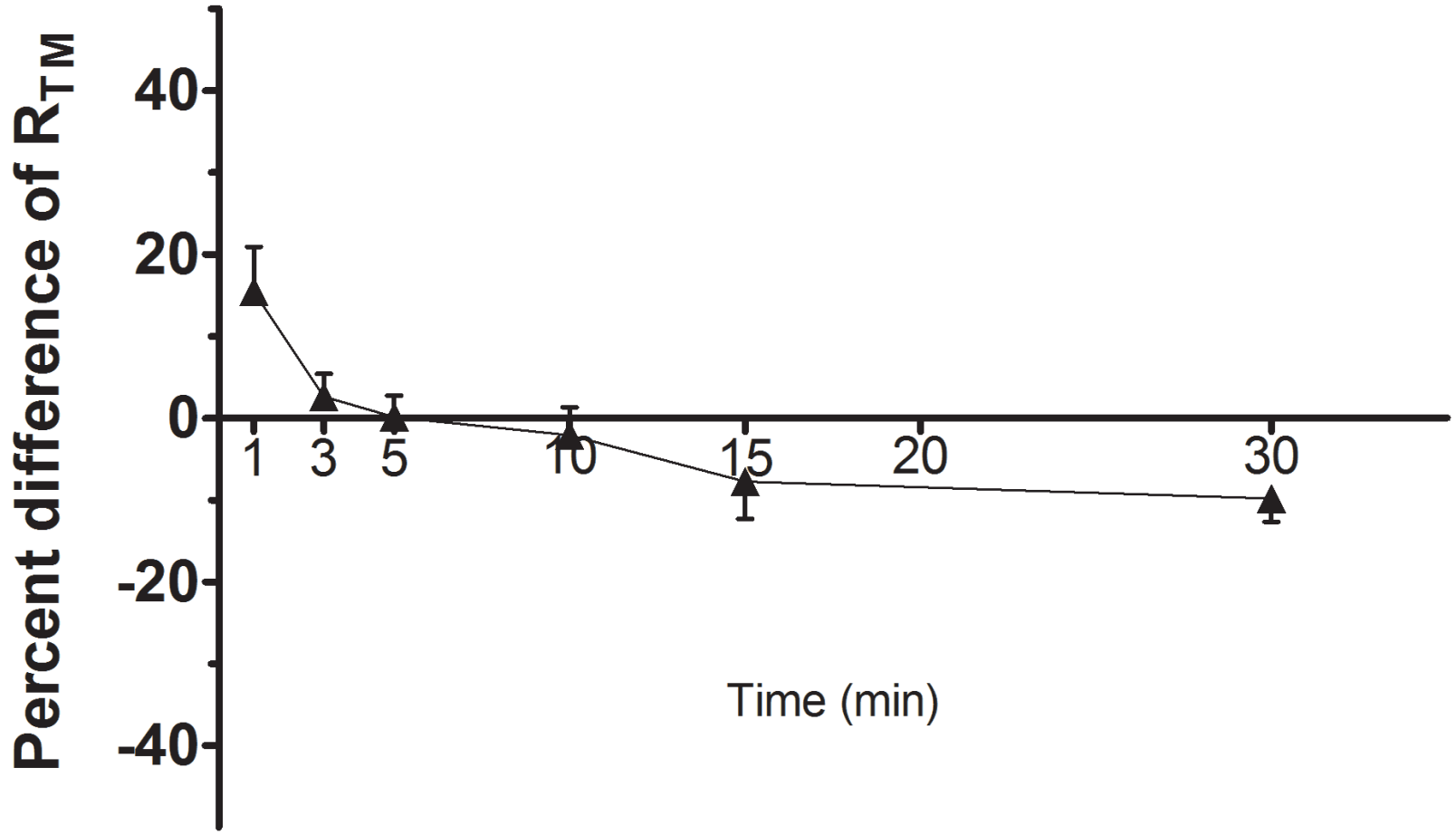
Epithelial Sodium Channel

We tested inhibition with AMILORIDE

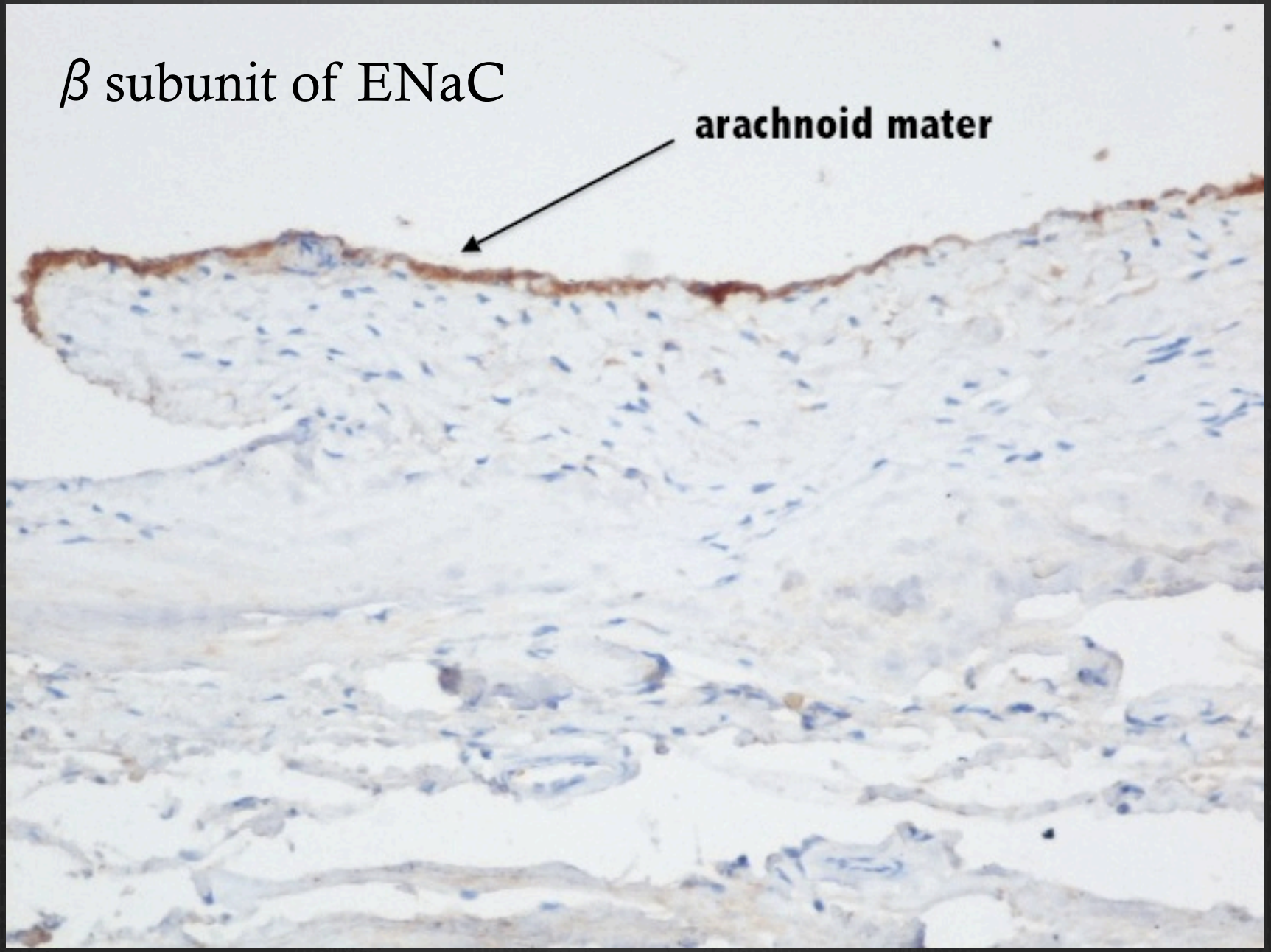
Leptomeninges Amiloride 10^{-5}M Arachnoidal side



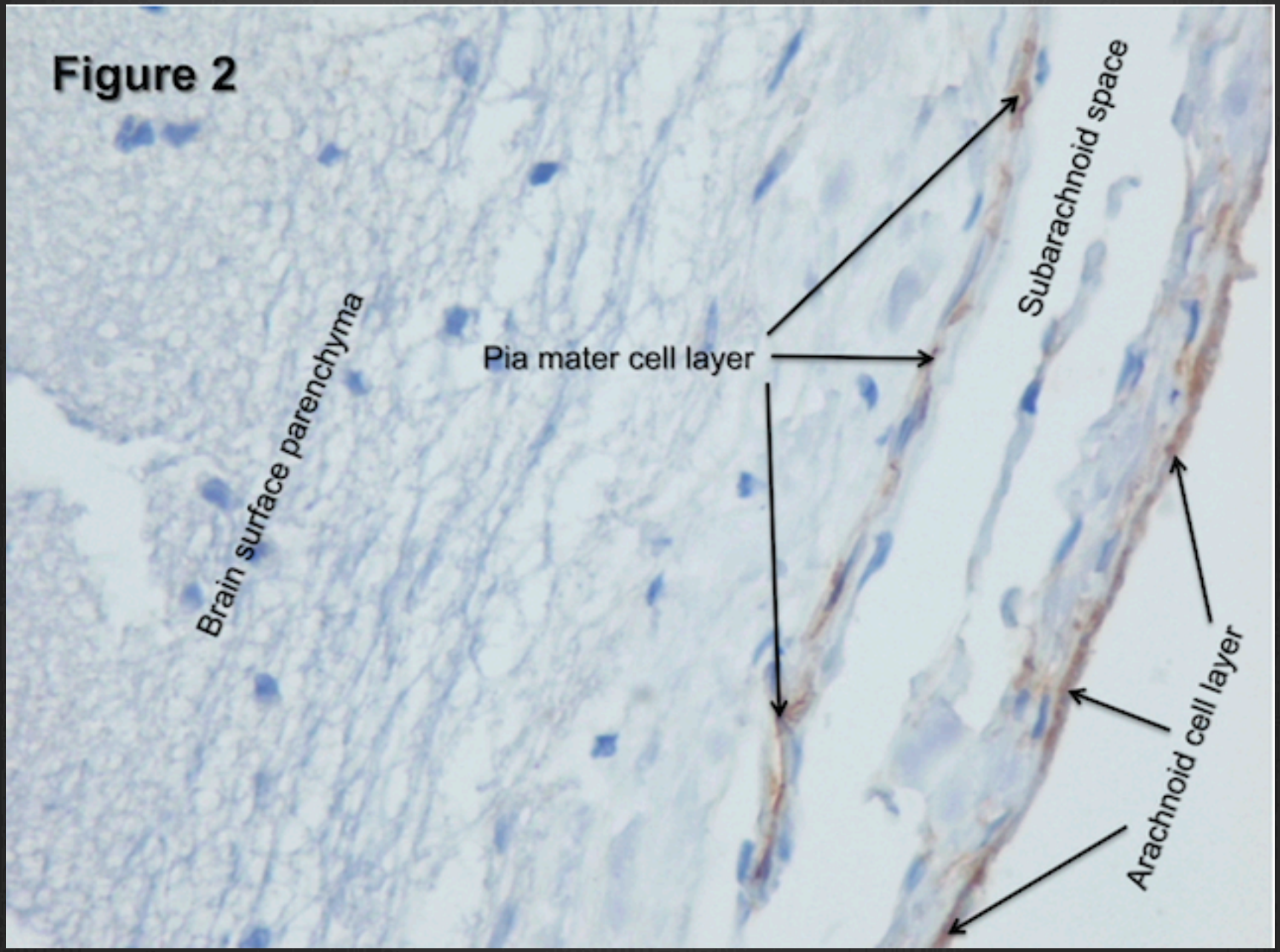
Leptomeninges Amiloride 10^{-5}M
Pial side



β subunit of ENaC



δ subunit - ENaC



Conclusions

- CSAS has a vibrant functional anatomy which becomes intriguing at the cellular level
- CSAS bears properties of mesothelial tissues
- CSAS it is a "leaky epithelium"
- Solute-coupled transport can potentially occur at this interface since key structures exist
- It shows polarity of ion channels
- We do not know if this property is related solely to CSF production or absorption.
- More studies needed to explore this new field.

"We believe that the CSAS-brain surface interface is an active member of the CSF turnover involved structures…and not just an inactive "bag of fluid". It's role needs to be defined and re-explored under a new prism."

Plato and Aristotle, "The school of Athens", Raphael 1509

"Η γὰρ γένεσις ἕνεκα τῆς οὐσίας ἐστίν, ἀλλ' οὐχ ἡ οὐσία ἕνεκα τῆς γενέσεως."

"For the process of evolution is for the sake of the thing evolved, and not this for the sake of the process."

It is all about "Teleology" in the end

THANK YOU !

Dept. Physiology
Membrane Permeability team:

Sotirios G. Zarogiannis, Ph.D
Maria Ioannou, M.D., Ph D.
Chrissi Hatzoglou, M.D., Ph.D.
Paschalis-Adam Molyvdas, M.D., Ph.D.
Konstantinos Gourgoulianis, M.D., Ph.D.