Computational model of tracer transport reduction due to deletion of Aqp4

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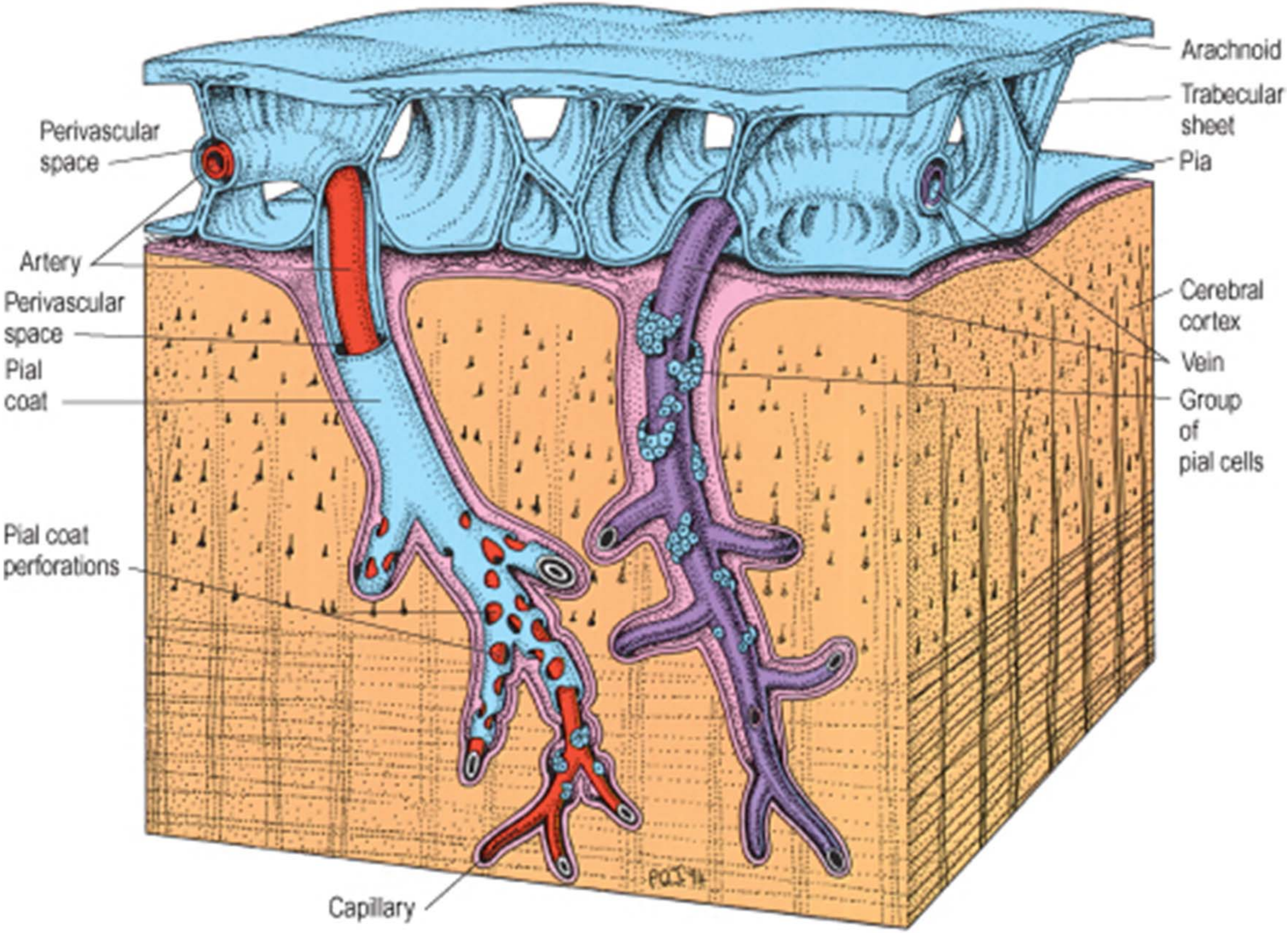
Paravascular and Interstitial Spaces



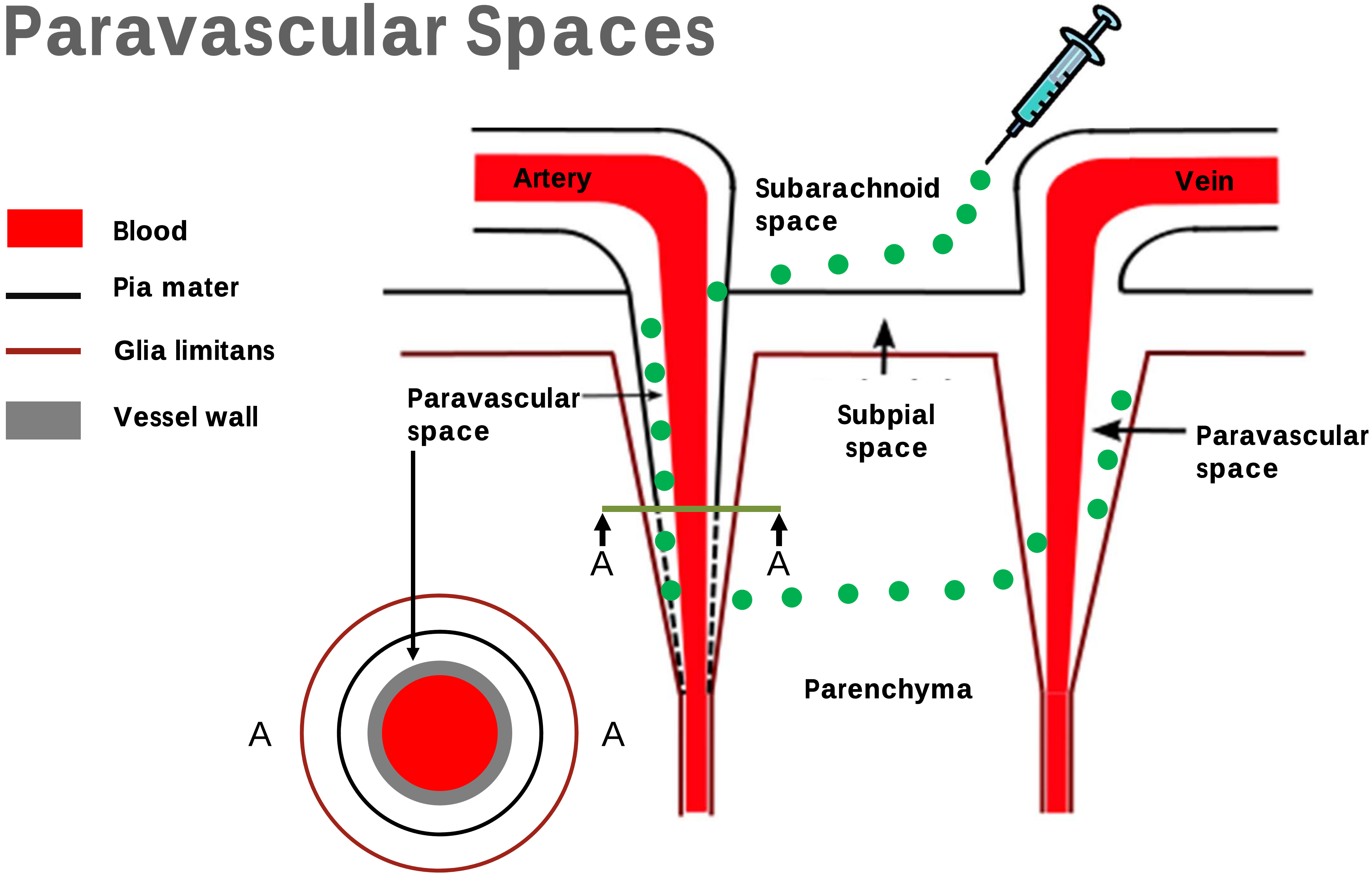
Elsevier Ltd., Gray's Anatomy 39th ed.

Cerebral Fluid Pathways

What do tracer studies tell us about cerebral water flow?

- Data on temporal and spatial changes in tracer signal intensity are used to infer the expected underlying fluid flow field
- However, there are generally a number of possible distinct flow fields that may yield the observed tracer distribution
- Therefore, tracer studies need to be supplemented with data from other sources to validate the inferred flow field

Paravascular Spaces



Adapted from and expanded: Zhang, Inman and Weller. Journal of Anatomy 170 p. 111 ff (1990)

Paravascular Fluid Pathways

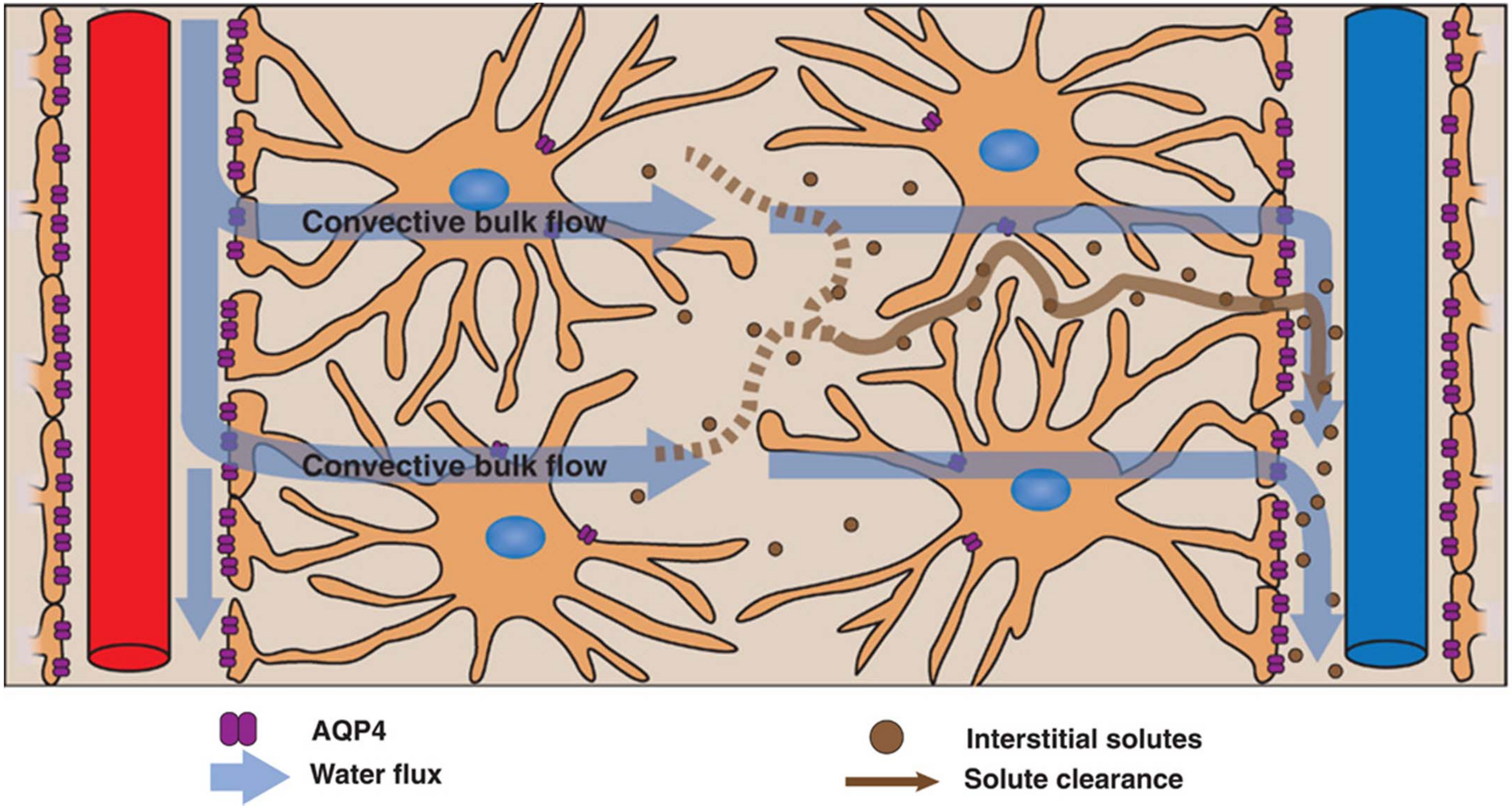
Main results of murine in vivo multi-photon tracer studies

- In mice lacking Aquaporin-4 (AQP4) water channels, tracer spread into the parenchyma is substantially reduced.
- During sleep, tracer spread into parenchyma is increased.

Iliff et al., Science Translational Medicine 4 (147) pp. 147ra111 (2012)
Xie et al., Science 342 (6) pp. 373-377 (2013)

Paravascular Fluid Pathways

Current interpretation of experiments



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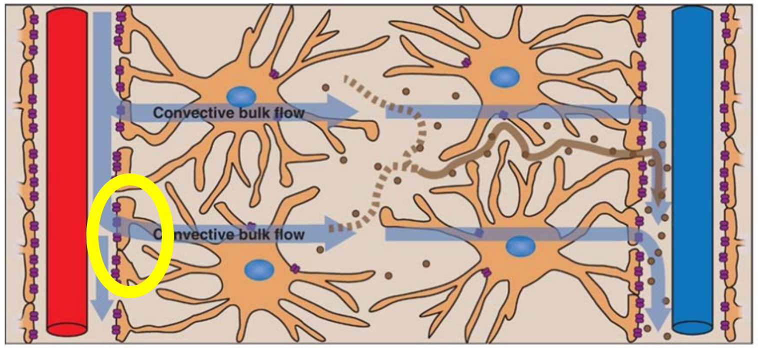
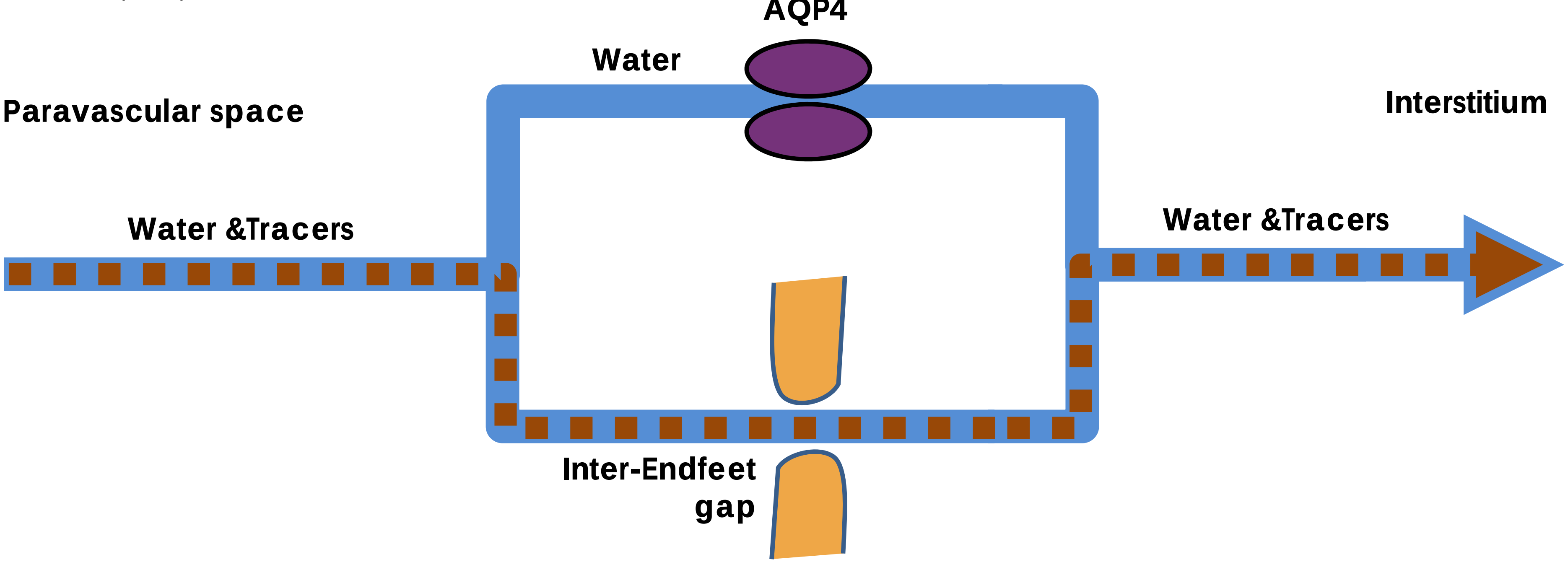
Paravascular Fluid Pathways

Current interpretation of experiments

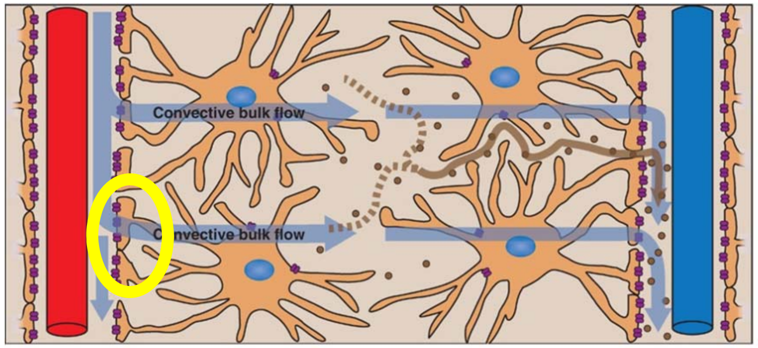


Iliff et al. (2012)

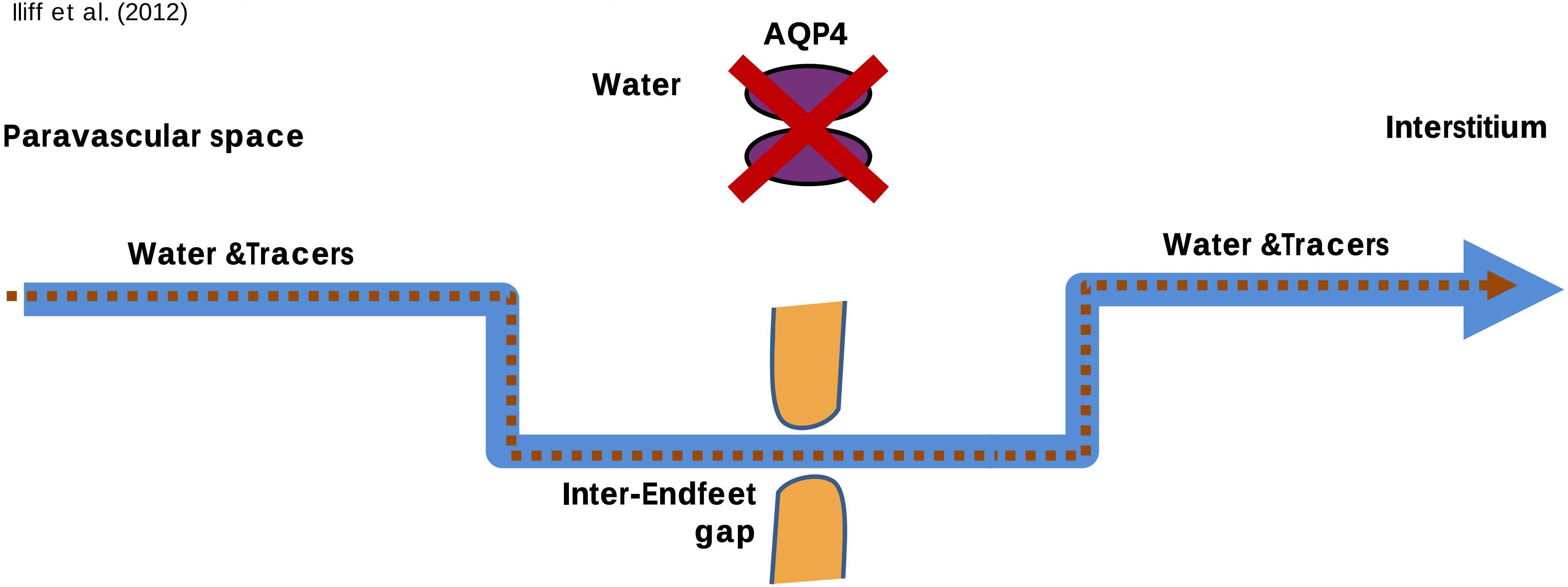


Paravascular Fluid Pathways

Current interpretation of experiments



Iliff et al. (2012)



New Interpretation of Experiments

Astrocyte networks serve as low resistance water pathways

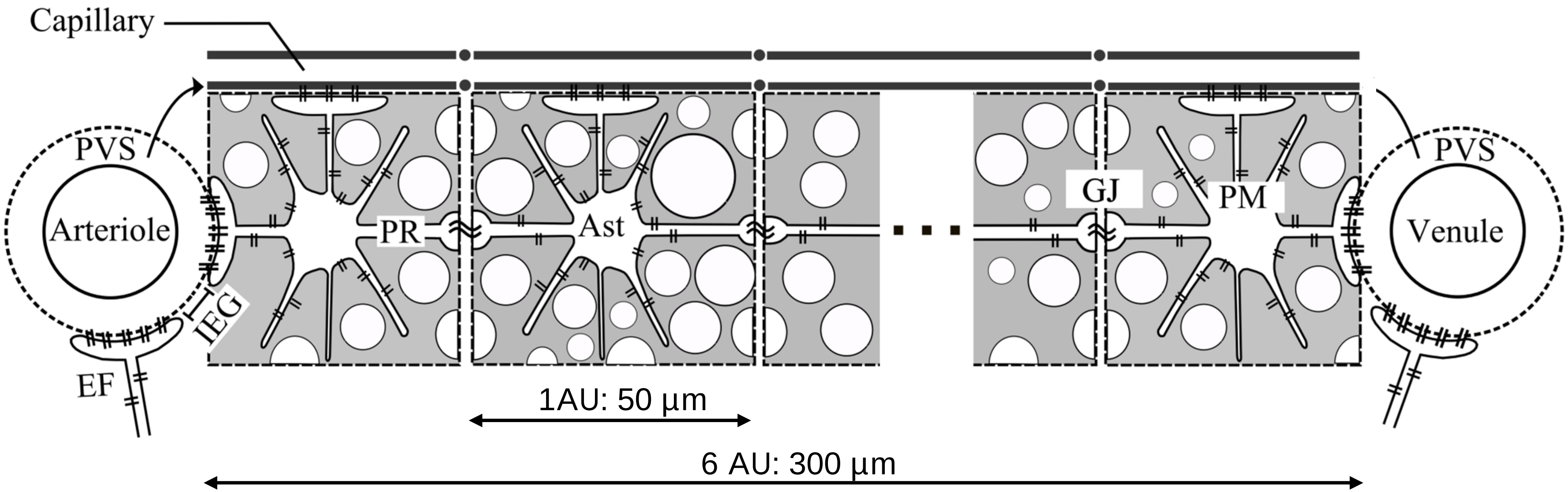
- Extracellular space (ECS) volume fraction is small (20%).

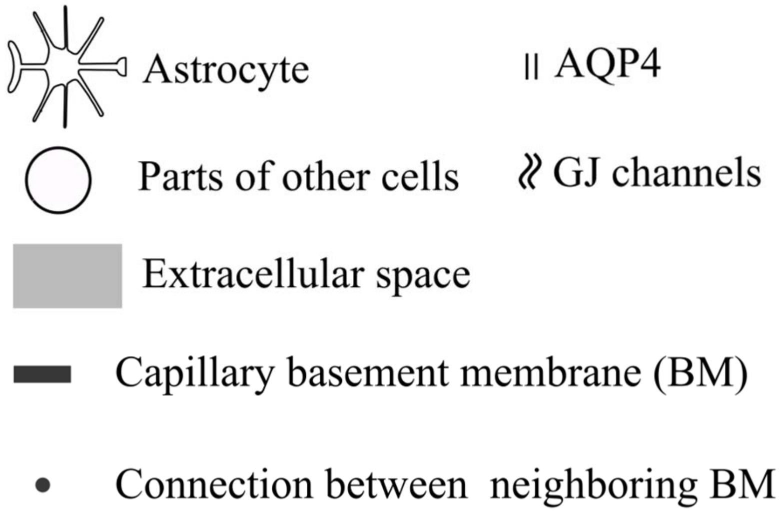
- Resistance to water flow through ECS is two orders of magnitude larger than through the intracellular space (ICS) of astrocytes.

- AQP4 is not only relevant on astrocyte endfeet, but also on the remainder of the astrocyte plasma membrane.

- AQP4 connects the high resistance ECS with the lower resistance ICS.

Water Flow through Astrocyte Networks





PVS: Paravascular space

EF: Astrocyte endfoot

IEG: Inter-endfoot gap

PR: Astrocyte process

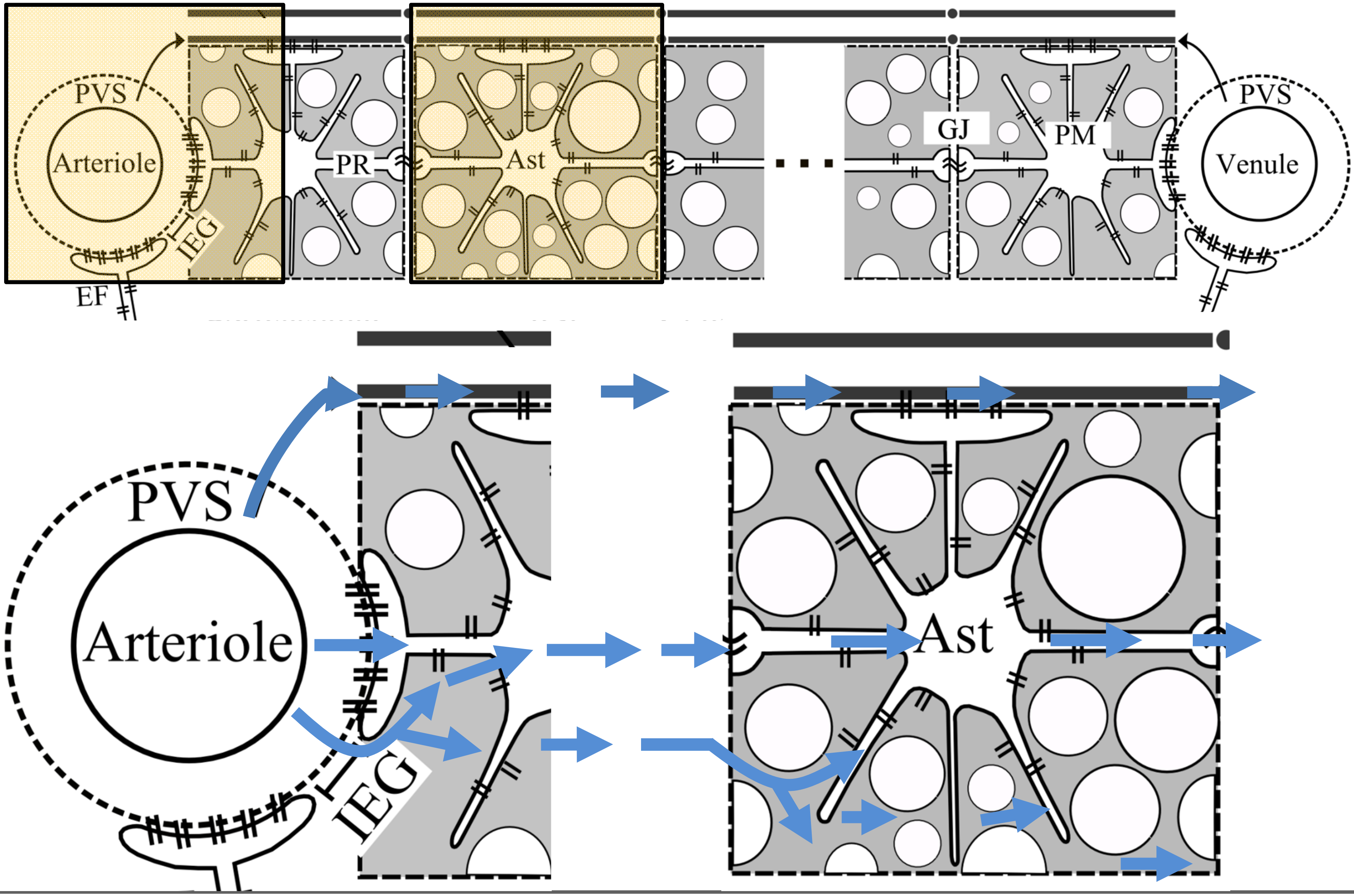
Ast: Astrocyte

AU: Astrocyte unit

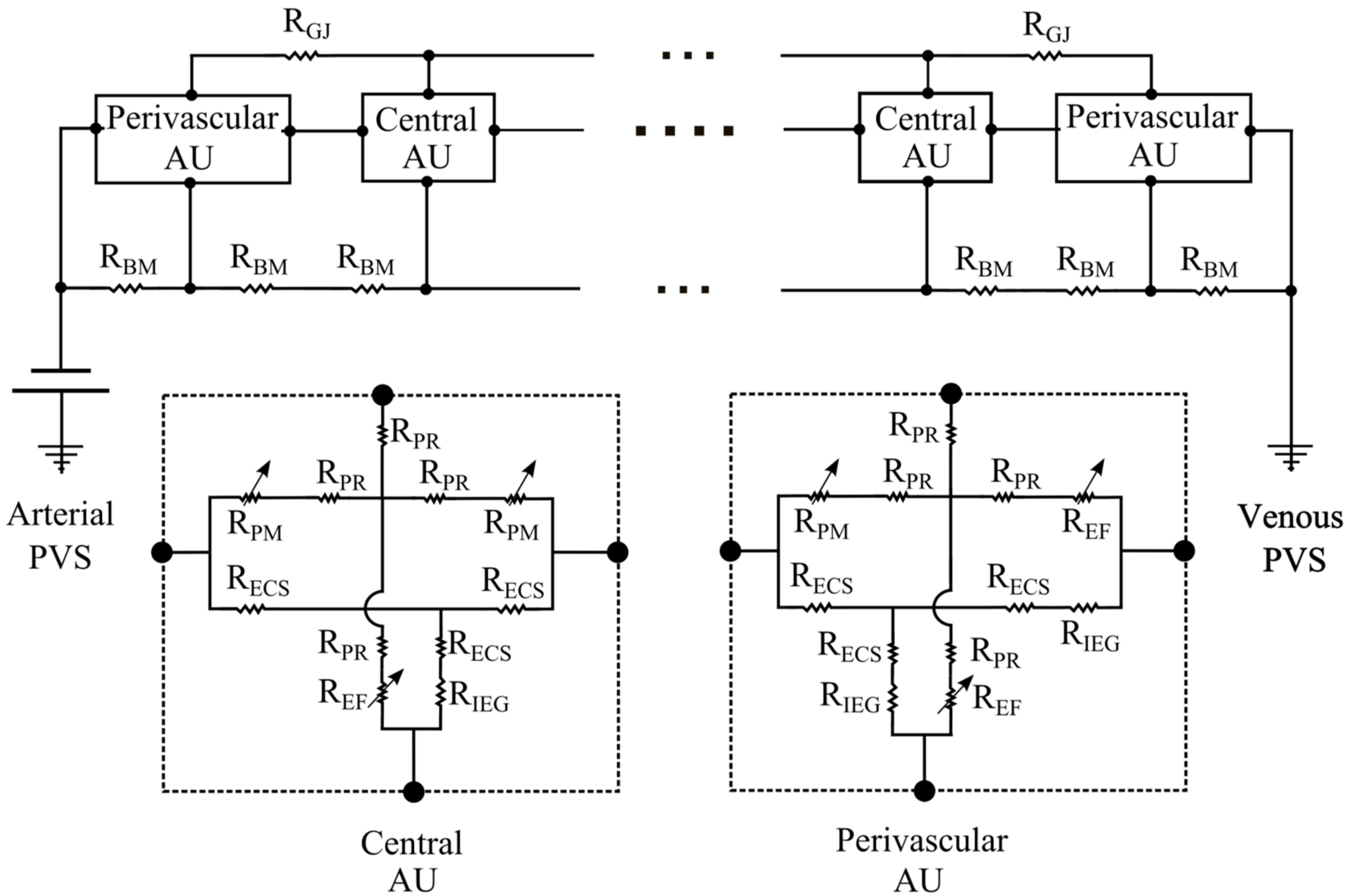
GJ: Gap junction

PM: Plasma membrane

Water Flow through Astrocyte Networks



Model of Astrocyte Network



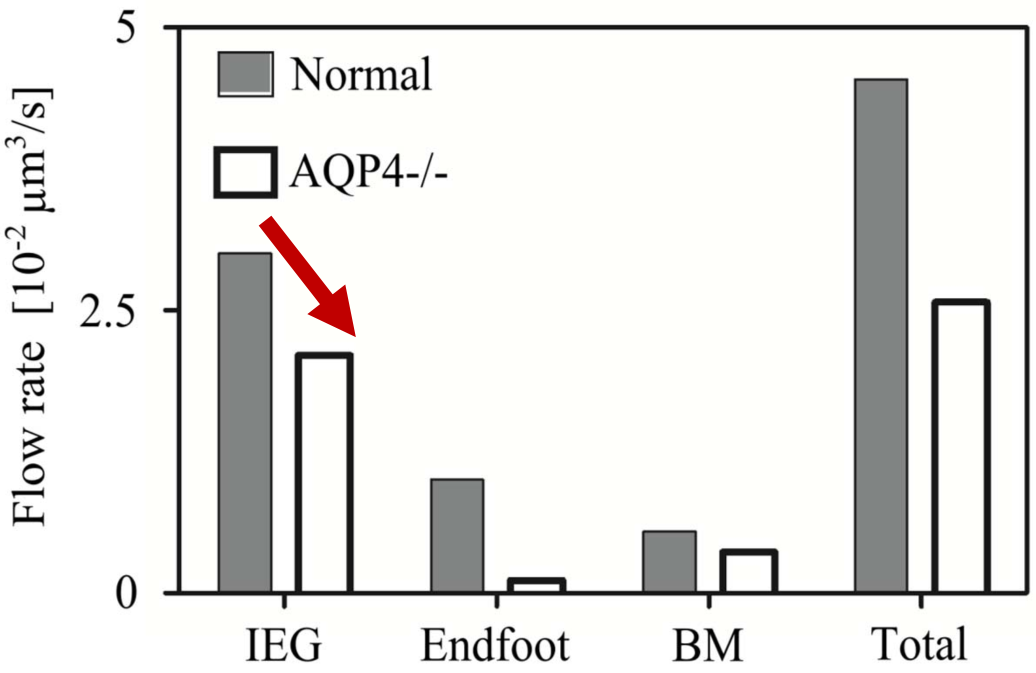
PVS:	Paravascular space	BM:	Basement membrane	PR:	Astrocyte process
AU:	Astrocyte unit	GJ:	Gap junction	EF:	Endfoot
R:	Resistance to water flow	ECS:	Extracellular space	IEF:	Inter-endfoot gap
		PM:	Plasma membrane		

Model Assumptions

- Driving pressure gradient from arterial to venous paravascular space
- Pressure gradient independent of changes in fluid path resistances, e.g. when AQP4 channels are removed
- Contribution of trans-membrane proteins other than AQP4 and gap junction proteins not taken into account

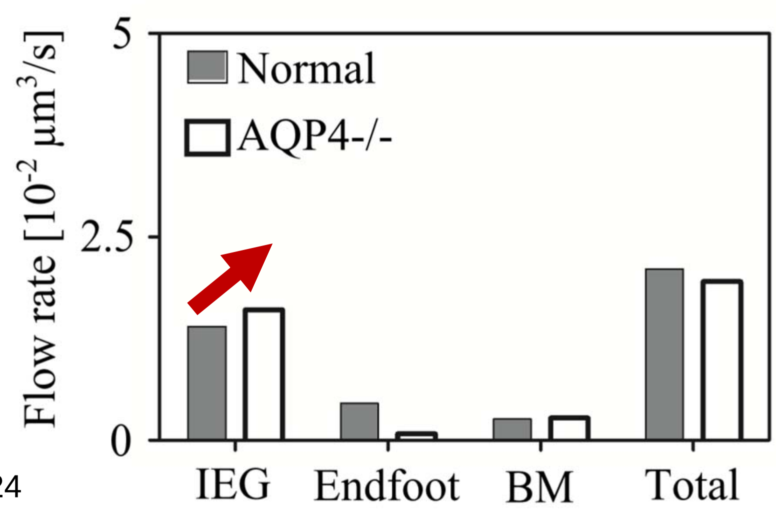
Results

Deletion of AQP4 reduces flow through inter-endfeet gaps



IEG: Inter-endfeet gap
BM: Basement membrane

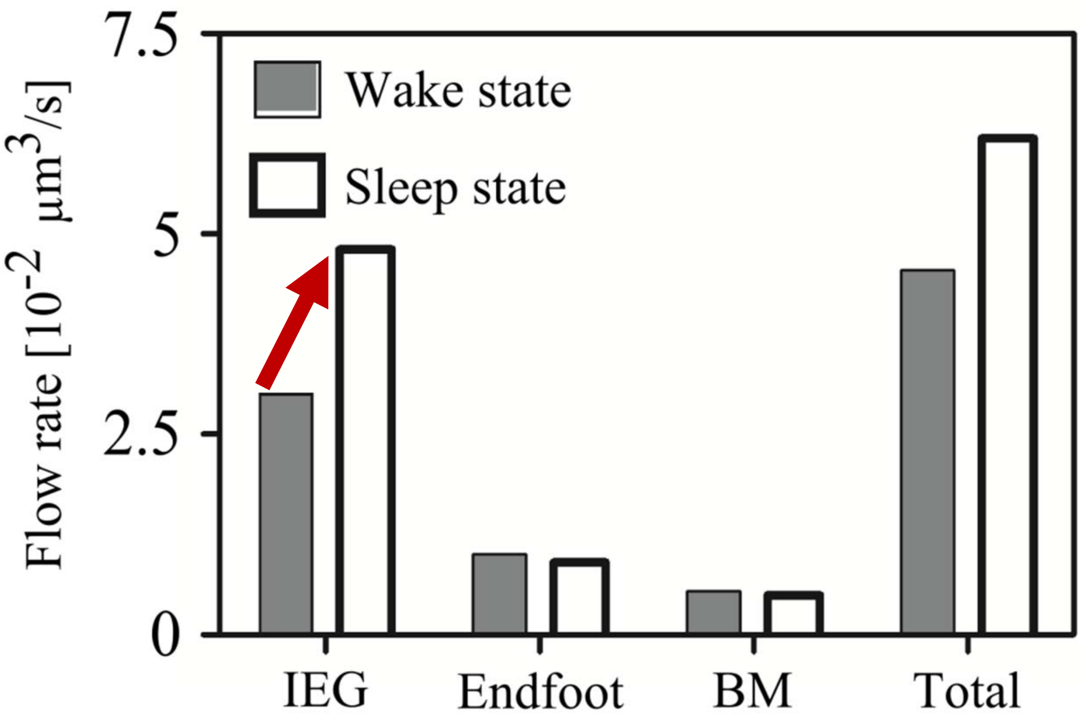
Without
astrocyte network



M. Asgari et al., Scientific Reports 5, 15024 (2015) doi:10.1038/srep15024

Results

Simulated sleep increases flow through intra-endfeet gaps



IEG: Inter-endfeet gap
BM: Basement membrane

M. Asgari et al., Scientific Reports 5, 15024 (2015) doi:10.1038/srep15024

Conclusions

- Parallel, interconnected intra- and extra-cellular water pathways can explain the tracer distribution patterns observed in vivo.
- AQP4 is likely to establish the connection between the parallel pathways.
- The assumption of a pressure gradient from arterial to venous paravascular spaces is consistent needs to be validated.

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