The challenge presented by altered brain interstitial fluid dynamics during slow wave sleep

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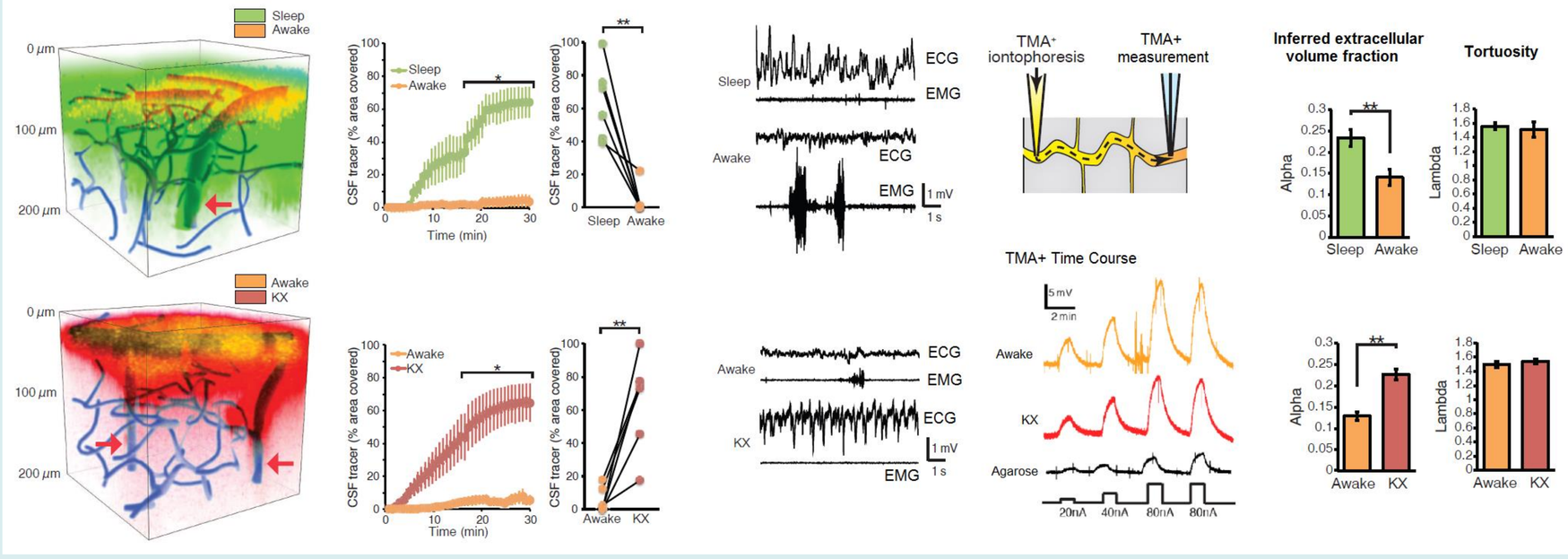
Data from Xie et al.* (2013) Science 342:373-377
Sleep Drives Metabolite Clearance from the Adult Brain

from their abstract:

"…. we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. …"

- Xie, Kang, Xu, Chen, Liao, Thiyagarajan, O'Donnell, Christensen, Nicholson, Iliff, Takano, Deane, Nedergaard
- Preparation: Mouse cortex



Enhanced influx of dextran (3kD) from CSF in sleep & ketamine + xylazine (KX) anaesthesia.

Extent of penetration to 100μm depth

ECG during sleep and KX anaesthesia

EC marker (TMA) dispersal yields estimates of EC volume & tortuosity.

Inferred EC volume & tortuosity in sleep & KX anaesthesia.

The potential importance of these data is for solute clearance: brain analogues of lymphatic drainage. The data are both interesting and (to me) surprising. The challenge is to understand their biophysical basis. This poster considers some possibly relevant mechanisms without new data, aiming to stimulate discussion and new experiments.

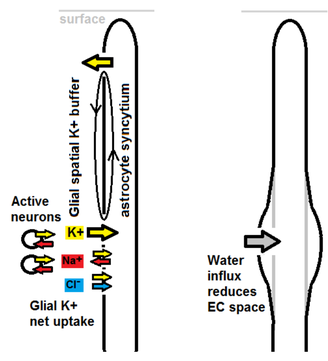
Does fluid shift from CSF or blood to interstitial space during sleep?

A widespread EC expansion from 14% to 22% without cell shrinkage would amount to an 8% swelling of brain tissue. Displacing this much of the CSF (ca. 10% of brain volume) or blood (ca. 5%) would be life threatening in other circumstances.

NB the data that indicate changes of EC space come from the superficial 300μm of mouse cortex. Even if limited to a fraction of brain tissue, it is a challenge to see what forces could cause such a shift within a time course of a few minutes.

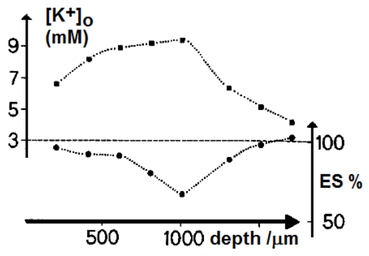
Activity basics

K+ released to EC space from active neurons undergoes net uptake into neurons & glia, and dispersal to remote regions with current flow through the astrocyte syncytium. Water follows net osmotic transfers & metabolite build-up from EC to IC space.



Do changes reflect reduced activity on cessation of waking?

Puzzling if so. Neural activity and spreading depression do cause neuronal & glial swelling and reduce EC space fraction (α). But such a large change (α ↓ by 40%) is usually accompanied by very large $[K^+]_o$ elevations and -ve field potentials that should have been evident if present during waking in these experiments. Both tend to be characteristic of sleep rather than waking.



[Dietzel et al. ('80) Exp Br Res 40,432-9]
Cat cortex, thalamic stimulation.

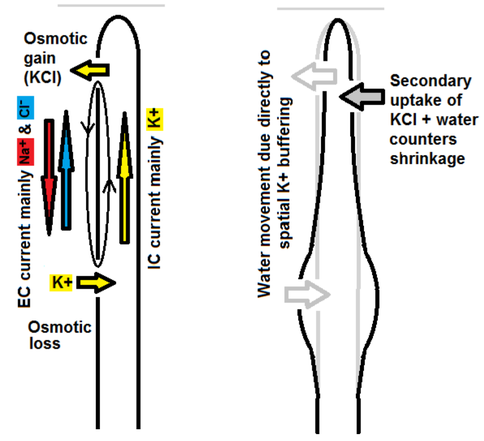
Electrical impedance changes would also be expected with changes of α , and were not found to be significant in Ranck's ('66: Exp. Neurol. 16,416-437) experiments on rats, during transition between quiet arousal and sleep - though he did see changes in deep subicular structures during REM sleep.

Could deep slow wave activity cause surface EC expansion through osmotic transfer?

Possibly, but it seems unlikely to be a big enough effect. The K+ spatial buffer currents effectively transfer osmoles (KCl) from active tissue to the EC space of inactive tissue*. This will tend to cause cells to shrink there. Shrinkage could be facilitated by AQP4 water channels in astrocyte membranes.

However, shrinkage in inactive tissue would be countered by KCl uptake into the cells on some timescale, and re-entry of water. Parameters are uncertain, but it seems difficult to envisage shrinkage being comparable in magnitude to cell swelling in active tissue.

*ca. 1.1 osmole per transferred mole of K+ [Dietzel et al., '80]

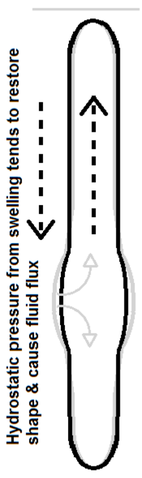


Could osmotic effects in active tissue cause fluid flux and solute convection through EC space?

Tissue osmotic pressure differences are mostly equilibrated by water movement across membranes or solute diffusion within fluid spaces. Transmembrane hydrostatic pressure gradients are normally negligible by comparison.

However, if coupled astrocytes are swollen in one region they may produce a significant small hydrostatic force (a form of elasticity) tending to push IC fluid away, pulling EC fluid towards the region and restoring normal geometry. This activity-driven fluid flux could enhance EC solute movement by convection (carriage along with fluid) and could also mimic an increase of EC space when measured by dispersal of EC markers.

The extent of this effect is frankly hard to estimate, without much information about mechanical or hydraulic parameters.



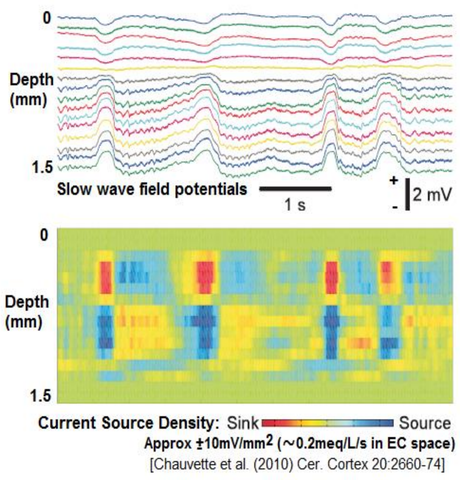
Evolution has taken advantage of sleep for many functions, and it is an intriguing possibility that sleep processes such as slow wave activity may have adapted to aid brain solute clearance. I don't think the data yet points to clear answers to the mechanism, but the biophysics of interstitial solute dispersal and fluid flux do seem to have more complex possibilities than one might have thought.

Fluid movement can disperse solutes faster, over long distances, than diffusion

Could 'sloshing' of EC fluid back & forth due to slow wave activity enhance solute dispersal significantly during sleep?

Alternating current sources and sinks occur during slow wave activity with separation of several 100μm, due to excitatory and inhibitory synaptic activity. As with glial currents, this must cause net movement of osmoles between EC space in different regions. Resultant variable swelling of both neurons and glia may lead to significant EC fluid fluxes. Desynchronised neural activity during waking, without such prolonged EC current flow, would have less effect. However, the contribution to solute dispersal, as with steady K+ spatial buffer currents, is uncertain.

Fluid flux caused by pressure gradients will disproportionately follow the widest available channels in EC space (unlike simple diffusion or electric current flow). This is a factor that may particularly enhance dispersal or clearance of large molecules by fluid flow convection.



[Chauvette et al. (2010) Cer. Cortex 20:2660-74]

ABSTRACT

- Recent data from Xie et al. (2013: Science 342:373-377) has shown enhanced dispersal of extracellular (EC) marker ions released iontophoretically into superficial cortex during slow wave sleep.
- This was consistent with a ca. 60% increase of EC volume during sleep, possibly contributing to enhanced clearance of waste solutes.
- If such a change were widespread, it would involve surprising shifts of osmotically active molecules between brain fluid compartments and/or the blood and csf.
- The poster considers alternative hypotheses that EC fluid may redistribute due to current loops associated with slow waves, either synaptic currents or glial (astrocytic) currents associated with spatial buffering of altered EC potassium.
- Since intracellular current is largely cation movement and extracellular current a more balanced flux of cations and anions, current loops shift osmoles from one tissue region to another.
- This may establish significant pressure gradients within the coupled astrocytic syncytium, causing fluid flow in opposite directions in IC and EC space.
- This could enhance dispersal of EC markers by convection: solutes carried with EC flow or 'sloshed' back and forth to enhance diffusion.
- It may also provide a mechanism for significant increases of EC space in some regions at the expense of others.