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

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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 flow through the astrocyte syncytium. Water follows net osmotic transfers & metabolite build-up from EC to IC space.
- 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 of active tissue to the EC space of inactive tissue*

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 anaesthesia 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, Thiyagarajan, O’Donnell, Christensen, Nicholson, Ifft, Takano, Deane, Nederpapp
- Preparation: Mouse cortex

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

Do fluid shift from CSF 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.

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 of active tissue to the EC space of inactive tissue*

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 flow do seem to have more complex possibilities than one might have thought.

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 dispersed of EC markers.

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

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 osmotes 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.

Improved 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.

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.

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

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.

Electrical impedance changes would also be expected with changes of α, and were not found to be significant in Rano’s (‘96 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.