Neurophysiology

Synchronized neurons drive waste clearance

Lauren Hablitz & Maiken Nedergaard

Active neurons can stimulate the clearance of their own metabolic waste by driving changes to ion gradients in the surrounding fluid and by promoting the pulsation of nearby blood vessels. **See p.149 & p.157**

The brain is responsible for how humans interact with the world. The firing of thousands of neurons in complex codes generates and integrates movement, thought and behaviour. This electrical activity is energy dependent and, much like fish in an aquarium making the water dirty, neuronal activity fills the brain's fluid with waste. But brain tissue lacks the waste-clearance network that is present in the rest of the body — the lymphatic system. Instead, the brain has developed an equivalent network of passageways alongside blood vessels (perivascular spaces), known as the glymphatic system[1]. On pages 149 and 157, respectively, Murdock *et al.*[2] and Jiang-Xie *et al.*[3] provide direct evidence that neuronal activation can accelerate glymphatic waste clearance from the brain.

The glymphatic system enables the cerebrospinal fluid that surrounds the brain to enter perivascular spaces alongside arteries. Cerebrospinal fluid can then mix with the interstitial fluid that surrounds electrically active neurons, which, in addition to waste, dump out ions, neurotransmitters, and other molecules that modulate neuronal activity, such as neuropeptides. This 'dirty' interstitial fluid can then exit through perivascular spaces that surround the veins and run along nerves[4].

This process is dependent on the protein aquaporin-4, which is expressed in cells that support neuronal function called astrocytes. Astrocytes form contacts (known as vascular endfeet) with blood vessels, and it is at these structures that aquaporin-4 acts as a channel to enable water to be exchanged between the perivascular space and brain tissue[5]. Ultimately, dirty interstitial fluid is cleared to the meningeal and deep cervical lymphatic system in the head and neck, outside the brain (Fig. 1).

Despite rapid growth in the field of glymphatics in the past decade, there are still sizable gaps in scientists' understanding of this homeostatic system. Because of technical limitations, researchers in the field have largely been stuck characterizing drivers of cerebrospinal-fluid influx into the tissue without an adequate understanding of how fluid in the tissue is flushed out to the peripheral lymphatic system. At a cellular level, the structure of the perivascular space is well-understood. Endothelial cells that line blood vessels and pericytes that wrap around endothelial cells are ensheathed by astrocytes, which form a border between the perivascular space and neurons. But cell-type-specific contributions to glymphatic function have yet to be dissected. The current studies[2,3] bring fresh insights to the field of glymphatics, and address a key question that has arisen in the past few years: does synchronized neuronal firing promote glymphatic clearance, and if so, how?

Jiang-Xie *et al.* show that inhibiting neuronal firing in the hippocampus region of the brains of mice prevents localized waste clearance, and that synchronized neuronal firing at multiple frequencies can drive changes in ion concentration in the interstitial fluid that facilitate fluid movement and the clearance of molecules from the interstitial space. A noteworthy feature of these experiments is that the authors repurpose a classic neuroscience technique for monitoring electrical activity outside cells, known as extracellular electrophysiological recording, to infer the movement of ions in the interstitial space. This approach is years ahead of its time because researchers are not yet able to visualize interstitial fluid or ion flow in the brain in real time. The innovative use of a known technique enables the authors to conclude that "neurons that fire together 'shower' together".

Murdock *et al.* expand on previous work from researchers in the same lab, which demonstrated that audio and visual stimulation oscillating at a frequency of 40 hertz

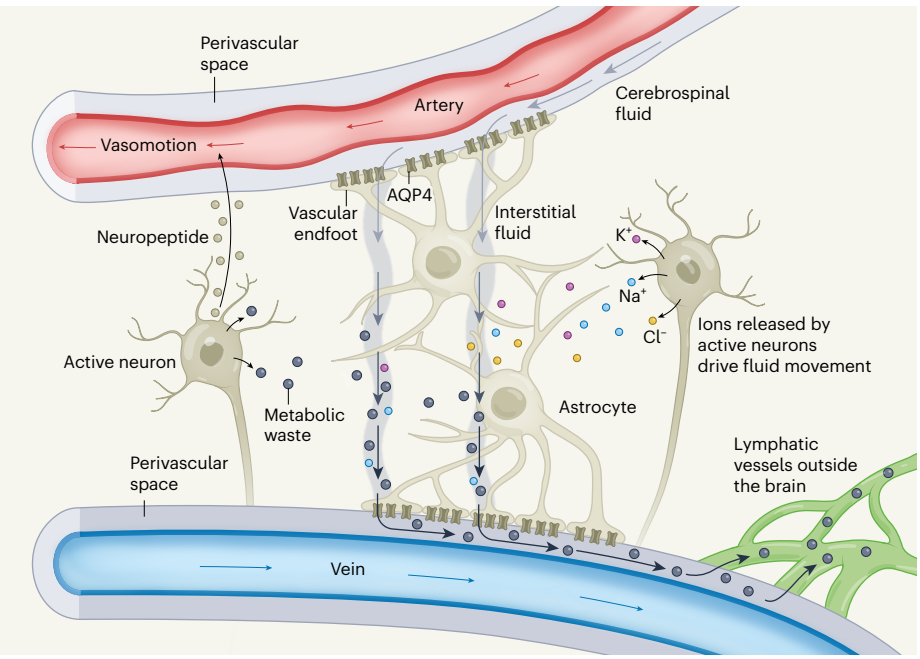

Figure 1 | Synchronized neuronal activity drives waste clearance in the brain. The brain clears metabolic waste through the glymphatic system, a network of fluid-filled perivascular spaces alongside blood vessels. 'Clean' cerebrospinal fluid from the brain flows along perivascular spaces next to arteries and disperses into the interstitial space surrounding neurons. Water movement is facilitated by the protein aquaporin-4 (AQP4), a water channel expressed on the vascular 'endfeet' of supporting cells called astrocytes. Ions (K^+, potassium; Na^+, sodium; Cl^-, chloride) and waste molecules released by active neurons dissolve in the interstitial fluid, and this 'dirty' fluid is flushed out along perivascular spaces next to veins and through lymphatic vessels to the body's waste-clearance system. Jiang-Xie *et al.*[3] show that waves of ion movement driven by synchronized neuronal firing can boost the clearance of interstitial fluid. Murdock *et al.*[2] find that audiovisual stimulation at 40 hertz induces neuronal firing and the release of a neuropeptide, which increases rhythmic movement of arteries (vasomotion) and enhances the flow of incoming cerebrospinal fluid. Both pathways could act in parallel to facilitate neuronal-activity-dependent waste clearance.

(gamma stimulation) can clear protein plaques (a hallmark of neurodegeneration) in mouse models of Alzheimer's disease[6,7]. Gamma stimulation has been heralded as a non-invasive treatment for neurodegeneration and has already moved into clinical trials[8–10]. The cellular mechanisms that underpin the effects of this therapy are unclear, although there are some links to activation of microglia — the immune cells of the central nervous system[7]. In the latest study[2], the authors show that gamma stimulation enhances glymphatic clearance, most noticeably in the brain's cerebral cortex. Gamma stimulation increases aquaporin-4 localization along the vascular endfeet of astrocytes and widens the diameter of meningeal lymphatic vessels, driving increased fluid flow through the tissue and clearance from the brain to the lymphatic system.

The flow of cerebrospinal fluid through perivascular spaces seems to be driven, at least in part, by the pulsing of arteries and larger changes in the diameter of blood vessels initiated by sensory stimulation or the slow contraction and relaxation of smooth muscle in the blood-vessel wall (vasomotion)[11–14]. The exact signals that trigger changes in blood-vessel diameter and vasomotion, and therefore increase glymphatic clearance, have not been identified.

Murdock and colleagues bring a new aspect of glymphatic regulation into play: the control of vasomotion by neuropeptide molecules. By monitoring the release of a neuropeptide by active neurons in real time, the authors find that gamma stimulation upregulates neuropeptide signalling in the interstitial fluid. Neuropeptides can act on the vasculature and astrocytes, both of which are crucial components of the perivascular space. The main question now is: how does synchronized neuronal activity trigger neuropeptide signalling and, ultimately, upregulate fluid flow?

Both papers raise several further questions. For example, how might burst firing of neurons — fast, sequential pulses of electrical activity (action potentials), rather than sparse firing of a single action potential at a time — affect interstitial fluid flow and clearance? Are neurons the main cell responsible for the changes to glymphatic flow? Additional signalling pathways might exist: the signalling molecule adenosine is a potent dilator of blood vessels and is released by neurons after visual stimulation at 40 Hz (ref. 15). Also, astrocytes buffer large potassium-ion gradients at the synapse, wrap the perivascular space, can sense neuropeptides and are connected by intercellular 'gap junctions'[16]. Yet, the way in which astrocytes might buffer ionic gradients in the interstitial fluid, potentially driving 'rivers' of flow around neurons, has yet to be investigated.

Furthermore, does the cellular shape (morphology) of neurons and astrocytes matter? How might interstitial flow in highly organized spaces such as the cortex and hippocampus differ from that in regions of the hypothalamus, which are less organized but have enriched neuropeptide signalling? Currently, there are no good ways to answer these questions, but they should be the focus of the next stages of glymphatics research.

Jiang-Xie and colleagues suggest that, as long as neurons fire in synchrony, the frequency of firing is not that important. At first glance, this contrasts with Murdock and colleagues' findings, which suggest that neuronal oscillations at 40 Hz are required for clearance. But both studies could be correct if a provocative alternative hypothesis is true: each brain region might have a 'tuning frequency', in which a defined pattern of neuronal firing drives efficient clearance. If that is the case, perhaps it is possible to harness this knowledge for the treatment of brain disorders in which the loss of cell populations is a contributing factor, such as Parkinson's disease, in which dopamine-releasing neurons are lost. Understanding the physiology and drivers of localized waste clearance in the brain could be the key that unlocks the therapeutic potential of the glymphatic system.

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Condensed-matter physics

Quantum sensor settles debate about hydrides

Kin On Ho & Sen Yang

By adapting a device designed to create extremely high pressures into one that can sense magnetic fields, researchers have obtained evidence that a hydrogen-rich material is a superconductor, eliminating long-standing doubts. **See p.73**

Superconductors are materials with no electrical resistance below a critical temperature — a tantalizing prospect for efficient power transmission. The lack of resistance is usually the first clue that a material can superconduct, but its candidacy must be supported by other properties, including a tendency to expel magnetic fields through a phenomenon known as the Meissner effect. On page 73, Bhattacharyya *et al.*[1] report evidence of the Meissner effect in cerium superhydride, a material belonging to a series of hydrogen-rich materials having a maximum critical temperature close to room temperature. The authors' feat was made possible by the clever use of a quantum device that can apply the pressure required to make cerium superhydride superconducting, and that can simultaneously sense magnetic fields.

Superconductivity was first discovered in 1911 in mercury, a material that superconducts at temperatures around 4.2 kelvin, which can be achieved only with cryogenic cooling[2]. A milestone was reached in the late 1980s, when a series of copper oxides was shown to display superconductivity up to 93 kelvin, a temperature that is higher than the boiling point of liquid nitrogen[3,4]. But the quest continues for a material that superconducts at close to room temperature, which would broaden the technological potential of this extraordinary state.

Theory predicts that, below the critical temperature, electrons start to form pairs (called Cooper pairs) with the help of crystal-lattice vibrations known as phonons[5]. The condensation of these pairs leads to superconductivity, so inducing Cooper pair formation can increase the critical temperature at which superconductivity appears. Metallic hydrogen is expected to superconduct close to room temperature because its low atomic mass