Rethink the classical view of cerebrospinal fluid production

Margaux Roques¹, Amaury De Barros² and Fabrice Bonneville¹

In their brilliant review, Joanna Wardlaw and colleagues describe those well-known but poorly understood CNS features, the perivascular spaces (Wardlaw, J. M. et al. Perivascular spaces in the brain: anatomy, physiology, and pathology. *Nat. Rev. Neurol.* **16**, 137–153 (2020)¹). Questions persist on the role of these spaces in interstitial fluid–cerebrospinal fluid (ISF–CSF) metabolite clearance, such as drainage pathways, the role of aquaporin 4 in water transport, and the effects of sleep on their function. In their discussion, the authors accurately indicate that the occurrence of CSF drainage via arachnoid granulations in humans has been questioned. We believe that their statement that CSF is “produced continuously in the choroid plexus” should be examined too.

The traditional ‘bulk flow’ theory of active production of CSF in the choroid plexus and its passive absorption via arachnoid granulations — historically presented as the ‘third circulation’ — mostly originates from a single experiment by Dandy published in 1919 that has not been reproduced since. He performed a unilateral choroid plexectomy and obstruction of the foramen of Monro on one dog, which led to the collapse of the plexectomized ventricle and dilation of the ventricle containing a choroid plexus². By contrast, in 1969, Milhorat et al.³ obstructed the ventricular system of 76 monkeys, which caused hydrocephalus independently of choroid plexectomy, suggesting a role for extra-choroidal sites in CSF production.

The function of the choroid plexus has frequently been investigated in *in vitro* and *ex vivo* experiments, the conditions of which could differ from physiological conditions. However, MRI can be used to explore CSF dynamics *in vivo*. Use of dynamic oxygen-enhanced MRI has demonstrated that inhaled oxygen predominantly diffuses into the sulcal CSF rather than the ventricular CSF⁴. This observation could be explained by the abundance of pial arterioles relative to intraventricular vessels and the direct crossing of intra-arterial molecules through the blood–CSF barrier to form CSF. In addition, use of several imaging techniques in which CSF motion is directly visualized has demonstrated no motion around the choroid plexus, which contradicts the notion that choroid plexus arterial pulsation is the driving

force for CSF pulsatile motion⁵. These *in vivo* findings support a new model, in which CSF is produced by water filtration across capillary walls throughout the CNS and is subjected to a combination of multidirectional motions, where hydrodynamic and osmotic changes play a crucial role⁶.

Another line of evidence that suggests that the choroid plexus is not the only site of CSF production is the failure of plexectomy to treat paediatric hydrocephalus. This approach, which was used for decades, has largely been replaced by shunt or endoscopic ventriculostomy owing to its lack of efficacy in all but exceptional cases of CP hyperplasia⁷. In addition, the combination of choroid plexus cauterization with ventriculostomy does not improve outcomes for children with post-infectious hydrocephalus⁸. Inflammation has recently been proved to play a prominent role in acquired hydrocephalus, but further experiments are required for greater clarity⁹.

In summary, the oversimplified bulk flow theory is commonly presented as fact in textbooks and medical schools but should be presented as one of several models, along with its limitations and flaws. Examination of the entire ISF–CSF pathway from production to clearance is essential for improving treatment of conditions that involve altered CSF dynamics, such as obstructive hydrocephalus, normal pressure hydrocephalus and even

intracranial hypotension, by taking into consideration not only the symptoms but, above all, the responsible mechanisms.

There is a reply to this letter by Wardlaw et al. *Nat. Rev. Neurol.* <https://doi.org/10.1038/s41582-021-00539-z> (2021).

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Competing interests

The authors declare no competing interests.

Reply to: Rethink the classical view of cerebrospinal fluid production

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We thank Roques and colleagues for their comments on our Review (Wardlaw, J. M. et al. Perivascular spaces in the brain: anatomy, physiology, and pathology. *Nat. Rev. Neurol.* **16**, 137–153 (2020)¹), in which they correctly point out some textbook dogma that needs to be re-evaluated (Roques, M., De Barros, A. & Bonneville, F. Rethink the classical view of cerebrospinal fluid production. *Nat. Rev. Neurol.* <https://doi.org/10.1038/s41582-021-00538-0> (2021)²). We agree that the questions of how much cerebrospinal fluid (CSF) is produced and from which structures remain unanswered. In our Review, we noted that there are several potential sources of CSF, including the choroid plexus, but information about the relative contributions of each source is unfortunately limited.

In our Review¹, we focused on perivascular spaces as seen *in vivo* on human brain

imaging, how these relate to perivascular spaces as described histologically, and their role in brain fluid management. Perivascular spaces themselves have been a controversial topic since the 1800s, and clarification of their role, along with a full understanding of brain fluid management, would be of great value.

Some evidence supports the existence of several sources of interstitial fluid and CSF and several sites of their drainage from the cranial cavity, including a return to the venous circulation via arachnoid granulations and intradural channels³, and drainage via meningeal lymphatics^{1,4}, including via skull base lymphatics to nasal lymphatics⁵. However, the major remaining questions concern how much fluid is produced and removed by each route, and whether the function of these pathways differs by age, sex, brain and physical activity (including sleep and wakefulness) and disease states.

The choroid plexus is generally agreed to be a key site of CSF production⁴, although the relative contributions of choroid plexus in the lateral ventricle versus that in the fourth ventricle are uncertain and may differ between species. There are also longstanding arguments that interstitial fluid contributes to the CSF and ultimately to lymphatic drainage^{4,6,7}. Water is a byproduct of metabolic reactions in the brain, so excess needs to be removed. Filtration at the level of capillaries via the blood–brain barrier also allows fluid to enter the brain interstitial space, a process that might subtly increase in many disease states, including Alzheimer disease and small vessel disease. Fluid can enter the interstitial space directly from the ventricles, as in ventricular obstruction, although this route is unlikely to be a major contributor to physiological interstitial fluid. Fluid also enters the brain from CSF via the perivascular spaces as part of the glymphatic flushing system, as explained in our Review¹. Therefore, it is possible that some fluid has passed through several intracranial compartments before

exiting via one of the several exit routes (the arachnoid granulations to venous sinuses, the meningeal lymphatics along the dural sinuses, or the nasal lymphatics⁵), which compounds the difficulties of measuring the source of fluid.

Measurement of intracranial fluid production is difficult. In humans, opening of the cranial cavity, even with small burr holes, disturbs the usual pressure balance between intravascular and extravascular compartments⁸, so might also perturb blood and fluid transit through the various compartments. Cranial windows in rodents affect brain temperature, thus altering blood flow and cellular activity⁹, so might also affect fluid production and movement. The temperature effects persist after re-closure of the cranial cavity with a glass window that is sealed with dental cement or by substituting the window by thinning the cranium⁹, and these processes could also affect pressures, as the properties of these materials differ from those of the intact skull. Improvements in non-invasive medical imaging techniques, such as recent non-invasive approaches to the measurement of fluid crossing the blood–brain barrier and blood–CSF barrier¹⁰, the use of multi-pronged approaches, and awareness of the limitations of each approach, will clarify the importance of each intracranial fluid production and drainage route in the near future.

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