

Rethink the classical view of cerebrospinal fluid production

Margaux Roques¹, Amaury De Barros and Fabrice Bonneville

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