Review Article

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Cerebrospinal fluid circulation: What do we know and how do we know it?

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Abstract:

The central nervous system's (CNS) complicated design is a double-edged sword. On the one hand, the complexity is what gives rise to higher order thinking; but on the other hand, damage to the CNS evokes its unforgiving nature. The cerebrospinal fluid (CSF) circulation system is an intricate system embedded in and around the CNS that has been the topic of debate since it was first described in the 18th century. It is underscored by the choroid plexus's distinct vascular network which has conventionally been seen as the most prominent structure in CSF production through a variety of active transporters and channels. Despite the ubiquity of this circulation system in vertebrates, some aspects remain understudied. Recent advances in scientific methodology and experimentation have proven to be effective tools for elucidating the mechanisms of the CSF circulation system and the pathological conditions associated with its malfunction. In this review, we capitulate the classical understanding of CSF physiology as well as a new, emerging theory on CSF production.

Keywords:

Absorption, circulation, CSF flow, production

Introduction

Cerebrospinal fluid (CSF) is a clear, proteinaceous fluid that exists in the surrounding spaces of mammalian central nervous systems (CNS). It is a multifaceted marvel, able to continuously support the nervous system through the lifespan of the organism. In the average adult human, there is roughly 150 mL of CSF circulating at any given moment. The ventricular portion amounts to roughly 17% of the total fluid volume, the rest of which lies in the cisterns and subarachnoid space. CSF forms at a rate of about 0.3–0.4 mL/min; translating to 18-25 mL/hour and 430–530 mL/day.[1] The classic thought is that CSF flows due to the forces generated by cardiac pulsations and pulmonary respiration. In this review, we will outline the physiology of CSF in the typical adult, as well as the pathologies associated with CSF circulation, malabsorption, and production.

The existence of CSF has been known for centuries. Hippocrates was among the first to describe the fluid as water that surrounded the brain.[2] The constant production of fluid was hypothesized, but anatomists could not describe, nor pinpoint, the means of production. It was not until Cushing published his paper "Studies on the Cerebro-Spinal Fluid" in 1914 that a source for CSF, the choroid plexus, had come to be acknowledged.[3] Dandy, soon after, conducted an experiment in which he ablated the choroid plexus of one lateral ventricle in a dog, then obstructed the foramen leading into the third ventricle; he discovered that the ventricle that was ablated and evacuated of CSF would collapse, while the ventricle that was not manipulated would expand.[4] This led to the belief that the choroid plexus is the main generator of CSF. Since then, this theory has been taken as fact, and many studies conducted on the choroid plexus and CSF secretion have revolved around this concept. The original theory of CSF production views 75% of all CSF being produced by the choroid plexus

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epithelium, while the remaining quarter being produced by other CNS structures such as the ependymal wall, cerebral parenchyma, and interstitial fluid (ISF).[5] Recently, however, there has been criticism regarding the design of experiments conducted by Cushing and Dandy on the choroid plexuses– calling into question the veracity of what we know about CSF.

Cerebrospinal Fluid Production

The secretion of CSF from any of the four choroid plexuses occurs as a two-stage process.[6] In the first stage, plasma is passively filtered across the fenestrated capillary endothelium into the choroidal interstitial space due to the osmotic pressure gradient between the two surfaces. The ultrafiltrate then undergoes active transport across the choroidal epithelium into the ventricular spaces.

An alternative hypothesis on the production of CSF brought about by Orešković and Klarica sheds light on new developments regarding the choroid plexus as the main site of CSF formation. They call into question nearly 100 years of research which elucidated the role of the plexuses in the CSF system, citing faulty methodologies that are highly subject to error and misinterpretation as well as experimental settings (*ex vivo* and *in vitro*) that do not represent the true physiology of the system. The authors assert that no experiment has undoubtedly confirmed the capacity of the choroid plexus to completely generate the predicted volume of CSF. The main criticism asserted is that Dandy's previously mentioned experiment was not reproducible and conducted on only a single canine subject, yet served as a foundation for the classical theory. The new working theory they posit sees CSF formation as an active process that is not affected by intracranial pressure. In balanced physiological conditions, the rate of CSF formation must be equal to the rate of absorption. They postulate that this could extend to flow rate, given that formation and absorption occur in different compartments of the system. To them, it is, therefore, logical to say that secretion of CSF is the driving force of flow and circulation if there is going to be a steady volume of CSF.[7]

Orešković and Klarica examine the implications of choroid plexectomies on CSF physiology. According to the classical theory, a choroid plexectomy should significantly reduce the overall secretion of CSF, therefore providing some pressure relief in patients who have hydrocephalus. However, this is not always the outcome of the procedure; in fact, research shows that two-thirds of patients who receive the treatment should be shunted due to the recurrence of hydrocephalus.[8] In addition, Orešković and Klarica cite a study conducted by Hammock and Millhorat on rhesus monkeys in which a choroid plexectomy was performed, yet the biochemical composition of the fluid remained normal; this suggests a lesser role for the choroid plexus in molecular transport.[9] Bearing in mind nearly a century of a century of CSF research, a critical, new theory emerged in an attempt to reconcile the apparent inconsistencies of the classical theory. The new theory takes a more systematic approach, it shifts attention to the Virchow–Robin spaces (also known as perivascular spaces), which exist between where the cerebral vasculature descends from the subarachnoid space into the CNS, perforating the pia mater.[10] It is at this junction that the formation and absorption of both interstitial and CSFs occur, driven by both hydrostatic and osmotic pressure differences between the CSF circulation system and surrounding tissue. This would indicate that CSF is continually produced throughout the circulatory route and not in localized secretory organs, and any changes in the volume of CSF are influenced by the CSF osmolarity.[9] Interestingly, however, osmolarity changes can be particularly acute, where CSF volume flow can return to normal despite hypotonic serum (sink action).[11]

While there is evidence to support these claims of CSF mixing and production, there is also a wealth of literature describing the ebbs and flows of CSF, and net flow.[12] The proposed active secretion and absorption of CSF by the entire CSF circulation system, according to Spector, ignores the mixing of CSF which is substantiated by the motile cilia present on the ependymal wall as well as the shuttling of growth factors to certain regions of the brain.[12]

The Composition of Cerebrospinal Fluid

CSF is mainly composed of water (99%), with the remaining 1% accounted for by proteins, ions, neurotransmitters, and glucose.[13] The concentration of each of these proteins, the total viscosity, and the CSF surface tension varies with pathology.[14,15] On the apical side, epithelial cells are anchored together by tight junctions which restrict the movement of these molecules; this and intercellular gap junctions give rise to the blood–CSF barrier. The composition of CSF varies from that of serum due to the differential expression of membrane-associated channels and transport proteins, ultimately resulting in the unidirectional nature of the choroidal epithelium.[1] The apical side of the epithelium is covered in microvilli that beat with the motion of the CSF, while the basolateral side is packed with folds and creases which increase the cells' surface area, making it more suited for absorption. Compared to plasma, CSF generally contains a higher concentration of sodium, chloride, and magnesium and lower concentrations of potassium and calcium.[16] This difference is conferred by active transport from the interstitial compartment that is propagated by cytoplasmic carbonic anhydrases which produce the H^+ and HCO_3^- ions that are exchanged

for Na^+ and Cl^- by basolateral transport proteins.[1] On the apical side, active transport pumps release the ions into the ventricular spaces. Movement of water across the apical membrane has been shown to be due to the presence of aquaporin-1 (AQ-1); in fact, a study conducted by Mobasheri and Marples revealed that choroid plexus was among the tissues with the highest expression of AQ-1 in the body.[17] The method for water transport across the basolateral membrane remains to be inconclusive; many studies have seen diverging results pertaining to AQ-4, which was believed to be the prime candidate for the mechanism.

The function of CSF has been one focus of mechanistic study, and the study of disease states which influence production, absorption, or CSF composition. Other than its mechanical role, CSF plays a significant role in biochemical homeostasis throughout the CNS. It has playfully been called a "nourishing liquor," among, others for its filtering functions.[12] New techniques to analyze proteins, lipids, hormones, and microRNAs suggest the robust diversity of CSF constituents, their diffusion, and their active transport across patient cohorts, within a patient over development or time, or dependent on a disease state.[18] Some CSF biomolecules, such as secreted growth factors, neurotransmitters, morphogens, cytokines, extracellular matrix proteins, proteins involved in permeability, binding proteins, and adhesion molecules can influence production, absorption, and periventricular tissue and CSF homeostasis. Similarly, the microenvironment composition surrounding periventricular cells, and their activity, are manipulated by changes in solute transporters and CSF pathologies.[18]

Movement and Absorption of Cerebrospinal Fluid

After production, CSF movement generally occurs through the ventricular system, assisted, in part, by ciliated ependyma which beat in synchrony.[19] CSF net flow is still generally believed to flow through the ventricular system, initiated at the lateral ventricles.[5] From the lateral ventricles, CSF flows through the left and right foramen of Monro to the third ventricle. Next, it flows through the aqueduct of Sylvius into the fourth ventricle. From the fourth ventricle, the CSF may exit through the foramen of Lushka laterally, or the foramen of Magendie medially to the subarachnoid space. Passing through the foramen of Magendie results in filling of the spinal subarachnoid space. CSF egressing through the foramen of Lushka travels into the subarachnoid space of the cisterns and subarachnoid space overlying the cerebral cortex. The CSF from the subarachnoid space is eventually reabsorbed through outpouchings into the superior sagittal sinus (SSS) known as the arachnoid granulations. Arachnoid granulations act as an avenue for CSF reabsorption into the blood circulation through a pressure-dependent gradient.[6,20] The arachnoid granulations appear as outpouchings into the SSS due to the pressure in the subarachnoid space being greater than the venous sinus pressure (NB: direct visualization of arachnoid granulations intraoperatively would reveal the inverse).

Similar to new theories on CSF production are theories of absorption. Studies in rabbit and ovine models have revealed that CSF may also be significantly absorbed by way of cervical lymphatics.[6] CSF not reabsorbed through arachnoid granulations may reach the cervical lymphatics through two potential pathways. The first is along the subarachnoid space of exiting cranial nerves.[6,21] This provides a direct route in which CSF may be transferred from the cisterns to the to the extracranial lymphatics. The second pathway by which CSF may reach lymphatics is along the Virchow–Robin space of arteries and veins penetrating brain parenchyma.[22] The Virchow–Robin space is the potential space surrounding penetrating arteries and veins of the brain parenchyma that may vary in size depending on pathology. When CSF is not absorbed through the classical pathway, it may enter the Virchow–Robin space or be shunted to the ISF. The ISF is a compartment with the bidirectional flow to the Virchow–Robin and subarachnoid space that is believed to be mediated by AQs; but this is the topic of ongoing research. If CSF enters the ISF, it will ultimately be reabsorbed into the bloodstream, enter the Virchow–Robin space, or reenter the subarachnoid space. From the Virchow–Robin space, CSF can reenter the subarachnoid space or be reabsorbed by cervical lymphatics dependent on the forces exerted by cardiac pulsations and pulmonary respiration.

In addition to the circulation of CSF into cervical lymphatics, there have been studies describing CSF reabsorption into the dural venous plexus. At birth, arachnoid granulations are not fully developed, and CSF absorption relies on the venous plexus of the inner surface of dura that is more robust in infants.[23,24] Although not as extensive in adults, the dural venous plexus is still believed to play a role in absorption. Adult and fetal cadaver dissections and animal models with intradural injections have all been shown to demonstrate filling of the parasagittal dural venous plexus.[25-27] The exact mechanism of CSF uptake still has not been elucidated.[24]

The Pathophysiology of Cerebrospinal Fluid

Disruption of CSF homeostasis can result in overproduction or decreased absorption of CSF, both of which may result in pathologies; one of interest is

hydrocephalus. Obstruction anywhere in the ventricular system may result in increased intracranial pressure, which can create cascades of brain abnormalities, including cell death, inflammatory cell response, and cell shedding from the ventricular wall, or manipulation of the biochemical response of the cells.[28] Common the result of obstructive hydrocephalus include tumors, intraventricular hemorrhages, and congenital webs.[29] Blockage of the ventricular system proximally at the third ventricle, aqueduct of Sylvius, or fourth ventricle prevents absorption of CSF through the classical pathway and alternative pathways such as extracranial lymphatics. Alternatively, hydrocephalus caused by decreased absorption of CSF is commonly the result of infection, meningitis, subarachnoid hemorrhage, and trauma.[29] Infection, meningitis, and subarachnoid hemorrhage lead to an inflammatory response that causes scarring and obstruction of arachnoid granulations with a resultant decrease in CSF absorption and dysregulation of CSF homeostasis. Posttraumatic hydrocephalus is a little more complex and may be multifactorial. In the event of a patient with traumatic brain injury (TBI), ventriculomegaly may result from neuronal loss, ischemic events, or increased brain compliance after a craniectomy.[30,31] In the case of craniectomy, the dura is not closed and the bone flap may be left off for weeks to months before cranioplasty which leads to decreased resistance to CSF flow and a resultant increase in brain compliance.[20,32] Cranioplasty may result in the resolution of these changes or the alterations in brain compliance may not be readily reversed leading to the need for ventricular shunting of the excess CSF.[31,33] It is the increased intracranial pressure from the hydrocephalus not the ventriculomegaly that is the problem. Ex vacuo hydrocephalus, or enlarged ventricles due to loss of brain matter, is commonly seen secondary to brain atrophy. Common causes in addition to the neuronal loss seen from traumatic brain injury are any pathologies resulting in a significant neuronal loss such as dementia, alcoholism, and advanced age. In ex vacuo hydrocephalus, the ventricles are enlarged, but the brain compliance and CSF outflow resistance are not increased.

Certainly, the study of the mechanisms by which CSF circulation is produced, absorbed, and regulated is an area of ongoing research, of which can be influenced by age and pathology. Future work is needed to understand the intricacies of each.

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Conflicts of interest

There are no conflicts of interest.

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