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Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease☆

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ABSTRACT

Cerebrospinal fluid (CSF) circulation and turnover provides a sink for the elimination of solutes from the brain interstitium, serving an important homeostatic role for the function of the central nervous system. Disruption of normal CSF circulation and turnover is believed to contribute to the development of many diseases, including neurodegenerative conditions such as Alzheimer's disease, ischemic and traumatic brain injury, and neuroinflammatory conditions such as multiple sclerosis. Recent insights into CSF biology suggesting that CSF and interstitial fluid exchange along a brain-wide network of perivascular spaces termed the 'glymphatic' system suggest that CSF circulation may interact intimately with glial and vascular function to regulate basic aspects of brain function. Dysfunction within this glial vascular network, which is a feature of the aging and injured brain, is a potentially critical link between brain injury, neuroinflammation and the development of chronic neurodegeneration. Ongoing research within this field may provide a powerful new framework for understanding the common links between neurodegenerative, neurovascular and neuroinflammatory disease, in addition to providing potentially novel therapeutic targets for these conditions. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

1. Introduction

Cerebrospinal fluid (CSF), a clear, secreted fluid filling the cerebral ventricles and surrounding the brain and spinal cord within the subarachnoid space (SAS), serves several functions in the central nervous system (CNS). CSF provides buoyancy to support the weight of the brain and acts as a protective layer to cushion it from injury. CSF also serves regulatory functions, including distribution of neurotrophic factors and stabilization of brain pH and chemical gradients, in addition to supplying an excretory pathway out of CNS for solutes that cannot readily cross the blood brain barrier (BBB). Contributions to CNS development and repair mechanisms have also been noted [1].

Throughout the course of the 20th century, painstaking surgical, physiological and biophysical experiments led to the development of a classical description of CSF secretion, circulation and reabsorption that remains the principal model to this day. Within this model, CSF is secreted actively by the choroid plexuses (CPs), secretory epithelia in the lateral, third and fourth cerebral ventricles [2]. CSF moves by bulk flow, driven by arterial pulsation and respiration, through the ventricular system, exiting into the SAS via the foramina of Luschka and Magendie [3]. From the SAS, CSF is believed to be reabsorbed into the blood stream either through arachnoid villi, valve-like structures within the walls of dural sinuses, or by traveling along cranial or spinal nerve sheaths to reach the peripheral lymphatic drainage. The excretory function of CSF did not come to prominence until the second half of the 20th century with the work of Davson, who suggested that CSF and the brain interstitial fluid (ISF) interacted, and the CSF served as a "sink" for solutes from the brain parenchyma [4].

Recent research, aided by advances in imaging technology, suggests that CSF circulation may not be as linear as the classical model suggests, and that CSF and brain ISF exchange dynamically along organized anatomical pathways. The movement of CSF *through* and the clearance of ISF and its associated solutes *from* the brain parenchyma along perivascular pathways has important implications for current understanding of basic physiological processes such as CNS waste clearance, distribution of trophic factors, nutrients, and neuroactive compounds, and peripheral immune surveillance of the CNS. Derangement of the functions of CSF circulation may play a key role in the development of a wide range of CNS pathologies, including neurodegenerative diseases

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such as Alzheimer's disease (AD), neuroinflammatory conditions such as multiple sclerosis (MS) and neurovascular conditions such as cerebral ischemia, traumatic brain injury (TBI) and subarachnoid hemorrhage [5–10]. Alterations in CSF secretion, circulation and reabsorption are also directly involved in the pathogenesis of different CNS pathologies, including hydrocephalus, pseudotumor cerebri, and neoplasms of the choroid plexus [11–13].

Basic aspects of CSF circulation and CP biology have been the subject of several excellent recent reviews [2, 3,14–16]. Thus in the present review, we will focus on the implications that recent insights into the interactions between CSF circulation and the brain ISF may have for current understanding of AD, MS and neurovascular diseases.

2. Central nervous system fluid dynamics

2.1. Choroid plexus and CSF secretion

CSF is produced primarily by the CPs which are found in the lateral, third and fourth ventricles (Fig. 1) [17]. The CPs were identified as the primary source of CSF by Dandy in 1919, when he observed that hydrocephalus induced by the blockage of the foramina of Monro could be prevented by removal of the CP [18]. Further work has identified extrachoroidal sources, including ependymal cells, limited transcapillary fluid flux, and metabolic water production that contribute to CSF production [19–21]. It is widely agreed, however, that approximately 80% of total CSF is secreted by the CP [3].

In 1960, De Rougemont et al. demonstrated that the electrolyte content of the CSF extracted at the CP was distinct from that of blood plasma, physiologically linking the CPs to CSF production [22]. The secretion and composition of the CSF is tightly regulated by the CPs, which are complex structures comprised of a plexus of fenestrated capillaries surrounded by a layer of cuboidal epithelial cells, with an intervening stromal space between these two components (Fig. 1). The epithelial cells are polarized, with the apical CSF-facing side possessing microvilli and tight junctions that constitute the blood-CSF barrier (BCSFB), which is in many respects analogous in function to the BBB of the cerebrovascular endothelium [23].

Under physiological conditions, CSF is actively secreted, largely independently of choroidal blood flow, through the concerted activity of numerous membrane proteins. These include apical Na^+/K^+ ATPase, the aquaporin-1 (AQP1) water channel, and numerous secondary ion transporters and channels localized specifically to basolateral and/or apical

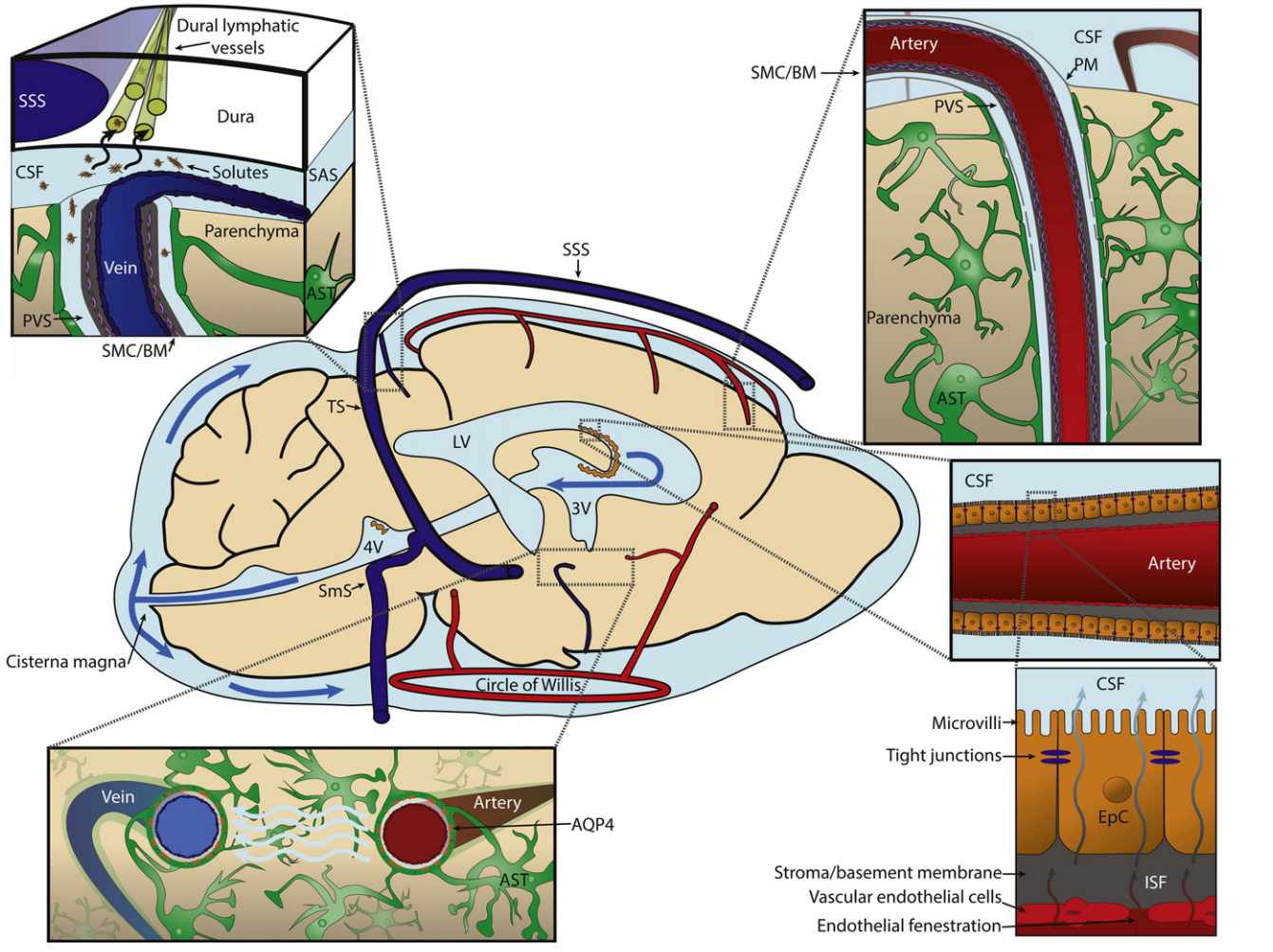

Fig. 1. Schematic of CSF production and circulation in the brain. Cerebrospinal fluid (CSF) is formed in the choroid plexuses in the 3rd (3V), 4th (4V) and lateral ventricles (LV, bottom right), then exits into the subarachnoid space (SAS) at the cisterna magna. Classically, CSF is cleared by bulk reabsorption into the bloodstream via arachnoid villi or by clearance to peripheral lymphatic vessels accessed along cranial nerve sheathes. More recent research suggests that from the SAS, a portion of the CSF circulates into the parenchyma of the brain along perivascular spaces (PVS) surrounding penetrating arteries, exchanging with surrounding brain interstitial fluid (ISF, top right). ISF and its associated solutes and wastes are in turn cleared along PVSs surrounding large caliber draining veins. This processes is supported by astroglial water transport through the aquaporin-4 (AQP4) water channel, which is localized to the perivascular astrocytic endfeet that surround the cerebral vasculature (bottom left). Interstitial solutes are cleared along peri-venous spaces into cisternal CSF spaces, where they have access to sinus-associated lymphatic vessels (top left). Abbreviations: Astrocyte (AST), basement membrane (BM), epithelial cells (EpC), pia mater (PM), vascular smooth muscle cell (VSM), sigmoid sinus (SmS), superior saggital sinus (SSS), transverse sinus (TS). Adapted from [129].