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Review Article

A balanced view of the cerebrospinal fluid composition and functions: Focus on adult humans

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ABSTRACT

In this review, a companion piece to our recent examination of choroid plexus (CP), the organ that secretes the cerebrospinal fluid (CSF), we focus on recent information in the context of reliable older data concerning the composition and functions of adult human CSF. To accomplish this, we define CSF, examine the methodology employed in studying the CSF focusing on ideal or near ideal experiments and discuss the pros and cons of several widely used analogical descriptions of the CSF including: the CSF as the "third circulation," the CSF as a "nourishing liquor," the similarities of the CSF/choroid plexus to the glomerular filtrate/kidney and finally the CSF circulation as part of the "glymphatic system." We also consider the close interrelationship between the CSF and extracellular space of brain through gap junctions and the paucity of data suggesting that the cerebral capillaries secrete a CSF-like fluid. Recently human CSF has been shown to be in dynamic flux with heart-beat, posture and especially respiration. Functionally, the CSF provides buoyancy, nourishment (e.g., vitamins) and endogenous waste product removal for the brain by bulk flow into the venous (arachnoid villi and nerve roots) and lymphatic (nasal) systems, and by carrier-mediated reabsorptive transport systems in CP. The CSF also presents many exogenous compounds to CP for metabolism or removal, indirectly cleansing the extracellular space of brain (e.g., of xenobiotics like penicillin). The CSF also carries hormones (e.g., leptin) from blood via CP or synthesized in CP (e.g., IGF-2) to the brain. In summary the CP/CSF, the third circulation, performs many functions comparable to the kidney including nourishing the brain and contributing to a stable internal milieu for the brain. These tasks are essential to normal adult brain functioning.

Contents

Abbreviations: AA, ascorbic acid; Aβ, amyloid beta; AE-2, anion exchanger-2; AQP, aquaporin; BBB, blood–brain barrier; BCSFB, blood–CSF barrier; BDNF, brain derived neurotrophic factor; CP, choroid plexus; DPH, diphenhydramine; ECSB, extracellular space of brain; GLUT-1, glucose transporter; 5-HIAA, 5-hydroxyindole acetic acid; HVA, homovanillic acid; IFN-1, interferon-1; IGF, insulin-like growth factor; IsoA, iso-ascorbic acid; K_T, half saturation constant; NBCe1, sodium bicarbonate e1 cotransporter (electrogenic); NBCn1, sodium bicarbonate n1 cotransporter (neuronal expression); NO, nitric oxide; OAT, organic acid transporter; P, permeability constant; PCD, primary ciliary dyskinesia; SVCT, sodium vitamin C transporter.

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1. Introduction

In this review, we focus on recent information in the context of reliable established data concerning the composition and manifold functions of adult human cerebrospinal fluid (CSF). This review is a companion to our recent treatise on the structure and function of the choroid plexus (CP) that secretes the CSF (Spector et al., 2015). We will not discuss children less than two years of age because the functions, flow and reabsorption of CSF in their development are not yet fully studied (Bateman and Brown, 2012; Whish et al., 2015). Also, due to the length consideration of this review, we do not comprehensively treat spinal cord–CSF relationships and associated clinical problems, e.g. syrinx; however, in this regard it is important to acknowledge that Koyanagi and Houkin (2010), and Ushewokunze et al. (2010), respectively, have thoroughly analyzed pathogenetic and surgical aspects of syringomyelia. To understand properly the composition and functions of CSF, we carefully define CSF (Table 1), examine the significant methodologic problems in studying CSF, exemplify and focus on ideal or nearly ideal experiments among hundreds performed, and explicate the differences between CSF formation by CP and the enormous H_2O exchange fluxes in CNS (Davson et al., 1987: Bateman and Brown, 2012; Spector et al., 2015).

As a means of exploring the numerous functions of CSF we employ, in part, a historical approach discussing several widely used analogical descriptions of the CSF as the "third circulation" (Cushing, 1925), the CSF as a "nourishing liquor," similarities between the CSF/CP on the one hand and the renal glomerular filtrate/kidney tubules on the other, and finally the CSF circulation as part of the "glymphatic system" (Iliff et al., 2012, 2013; Xie et al., 2013) (an analogy with the lymphatic system).

In the Introduction section, we briefly introduce these analogical descriptions. In the body of the paper is a discussion of the issues in detail, as well as the possibility of extra-CP CSF formation, and molecular exchange between the CSF and extracellular space of brain [ECSB] (also called interstitial fluid). Finally, throughout the review we address certain misconceptions about the CSF and briefly mention, where appropriate, the clinical implications of recent developments in understanding CSF composition and functions. Noteworthy is the fact that the blood–CSF barrier (BCSFB) consists of the CP epithelial cells and arachnoid membrane cells joined by tight junctions that inhibit the passive flux of H_2O-soluble molecules (Spector et al., 2015). However, there is no appreciable barrier to diffusion between CSF and ECSB because the pial and ependymal linings contain gap junctions in animals and humans (Whish et al., 2015). In humans, the CSF volume is about 150 ml with ~20% residing in the lateral, third and fourth ventricles. The volume of the human ECSB is also ~150 ml (Davson and Segal, 1996). The ECSB, comprising ~15% of brain volume, is a tortuous conduit among cells that slows down simple diffusion by ~50% in part due to large matrix molecules (viscous) in the ECSB (Hladky and Barrand, 2014). Since cortical ECSB decreases progressively as brain size becomes smaller (Greenberg et al., 1965), caution is in order when comparing murine vs. human ISF–CSF dynamics. For a schematic diagram of the relationship between ventricular CSF, ependyma and ECSB, the reader is referred to Fig. 2 in the article by Spector and Johanson, 1989.

For centuries, the CSF has fascinated philosophers, and more recently anatomists, physiologists, biochemists and neurologists who have made progress in defining and understanding the CSF. With the development of anesthesia, neurosurgeons became very interested in CSF. Harvey Cushing synthesized the extant information in 1925 and correctly identified CP as the source of CSF, the bulk flow of CSF through the ventricular system, and the exit of CSF through the foramina of Luschka and Magendie (fourth ventricle) into the subarachnoid space with subsequent absorption into venous blood. He termed this process the "third circulation," the first being that of the blood; and the second, the lymph. Cushing (1925) recognized the important role of the CSF in providing buoyancy for the ~1.2 kg human brain, and so, by the Archimedes principle, operationally only "weighing" ~45 g.

Around the same time, others (Stern and Gautier, 1921, 1922, 1923) proposed the CSF as a "nourishing liquor." This concept now has substantial merit because CSF contains certain essential substances including several micronutrients (e.g., vitamin C, folate) (Spector, 2014; Spector and Johanson, 2014), ions, peptides, proteins and ~90 varieties of small RNA not found in plasma whose function(s) await determination (Gallego et al., 2012). These substances penetrate into the brain from CSF, and are essential for brain health (Table 1). Of course macronutrients (e.g., glucose, amino acids, and lactate) and many micronutrients, hormones, vitamins and minerals are transported from blood directly into the brain by specialized mechanisms in the brain capillaries (Davson and Segal, 1996). Brain capillaries are joined by very tight junctions and are the locus of the blood–brain barrier (BBB) (Whish et al., 2015). Thus, except where there are specialized systems that allow entry (and exit), both the BBB and BCSFB isolate the mammalian brain and CSF from many H_2O-soluble molecules (including drugs) in the blood. Molecular transfer of drugs from blood into ECSB and the CSF, respectively, through the BBB and ECSB depends on several important factors: the size, charge, lipid solubility and plasma protein binding of the molecule; and secondly, the affinity of the molecule, if any, for influx and/or efflux transporters at the BBB and/or BCSF barrier as described below (Spector, 2009, 2010; Spector and Johanson, 2006).

Several pioneering investigators (Pappenheimer et al., 1961, 1962) introduced the technique of ventriculo-cisternal perfusion. They noted the resemblance of the kidney tubules and CP, respectively, in handling many molecules between glomerular filtrate and blood, and between blood and CSF. This led to the so-called "sink" analogy discussed below. The largely protein-free glomerular filtrate and CSF are dissimilar

Table 1
Human CSF composition — selected examples.

1) Ions
a) Na^+, Cl^-, HCO_3^-, K^+, Ca^{++}, Mg^{++}, Mn^{++}
2) Vitamins
a) Vitamin C, folate, thiamine monophosphate, pyridoxal phosphate
b) Paradoxical transport (riboflavin, nucleosides and Cu^+)
3) Peptides and proteins — transported from blood
a) Leptin, prolactin and IGF-1
4) Peptides and proteins synthesized in CP; released into CSF
a) Transthyretin, IGF-2, BDNF
5) Other growth factors and brain maintenance substances
a) Small RNA (90 species not present in plasma)
6) Proteins that diffuse from blood through barriers as a function of size
a) Albumin and immunoglobulins