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Review

A balanced view of choroid plexus structure and function: Focus on adult humans

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ABSTRACT

Recently tremendous progress has been made in studying choroid plexus (CP) physiology and pathophysiology; and correcting several misconceptions about the CP. Specifically, the details of how CP, a locus of the blood–CSF barrier (BCSFB), secretes and purifies CSF, generates intracranial pressure (ICP), maintains CSF ion homeostasis, and provides micronutrients, proteins and hormones for neuronal and glial development, maintenance and function, are being understood on a molecular level. Unequivocal evidence that the CP secretory epithelium is the predominant supplier of CSF for the ventricles comes from multiple lines: uptake kinetics of tracer ^{22}Na and ^{36}Cl penetration from blood to CSF, autoradiographic mapping of rapid ^{22}Na and ^{36}Cl permeation (high permeability coefficients) into the cerebroventricles, CSF sampling from several different in vivo and in vitro CP preparations, CP hyperplasia that increases CSF formation and ICP; and in vitro analysis of CP ability to transport molecules (with expected directionality) and actively secrete fluid against an hydrostatic fluid column. Furthermore, clinical support for this CP–CSF model comes from neurosurgical procedures to remove lateral ventricle CPs in hydrocephalic children to reduce CSF formation, thereby relieving elevated ICP. In terms of micronutrient transport, ascorbic acid, folate and other essential factors are transported by specific (cloned) carriers across CP into ventricular CSF, from which they penetrate across the ependyma and pia mater deeply into the brain to support its viability and function. Without these choroidal functions, severe neurological disease and even death can occur. In terms of efflux or clearance transport, the active carriers (many of which have been cloned and expressed) in the CP basolateral and apical membranes perform regulatory removal of some metabolites (e.g. choline) and certain drugs (e.g. antibiotics like penicillin) from CSF, thus reducing agents such as penicillin to sub-therapeutic levels. Altogether, these multiple transport and secretory functions in CP support CSF homeostasis and fluid dynamics essential for brain function.

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Abbreviations: AQP, aquaporin; BBB, blood–brain barrier; BCSFB, blood–CSF barrier; CP, choroid plexus; FRα, folate receptor α; GLUT–1, glucose transporter; ICP, intracranial pressure; JJVCPE, JJ vicinal coupling proton exchange (imaging); KO, knockout; OAT, organic acid transporter; PCFT, proton-coupled folate transporter; PEPT2, oligopeptide transporter; VC, ventricular–cisternal; VS, ventricular–subarachnoidal.

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Introduction

The purposes of this review are to summarize newer information about the structure and function of the adult choroid plexus (CP), focusing on issues with clinical relevance, and to correct several misconceptions in the literature. Particularly, we stress the predominant role of the CP in secreting ventricular cerebrospinal fluid (CSF) that maintains ICP and bulk flow down the neuraxis into the subarachnoid space. Our emphasis will be on humans greater than age two since the function of the CP in younger children awaits elucidation (Bateman and Brown, 2012). In this section, we underscore key points expanded upon in the body of the text.

The living anatomy of the CP is very revealing. As aptly remarked by Wei Zheng, "In the human brain at autopsy during which the CSF is usually completely drained, the choroid plexus can be seen to extend along the floor of the lateral ventricles, hang down from the roof of the third ventricle, and overly the roof of the fourth ventricle. The size of the tissue in one ventricle when in a dry, condensed state appears to be nothing more than that of an index finger. These autopsy impressions, which have over the years become the popular perception among many neuropathologists, can be dreadfully misleading and may lead to misjudgments of the function of this tissue. Recent advances in technology have enabled a micro-video probe to be inserted directly into the lateral ventricles. The vivid images illustrate that the live choroid plexus pervades the ventricles, stretching and pulsating in concert with the heart pulse. To better understand this, it may be helpful to make an analogy between the choroid plexus and a fishnet. The fishnet occupies barely one corner of the fishing boat; yet upon spreading in the water, it extends to cover a large area. Likewise, in the life situation where the brain ventricles are full of CSF, the choroid plexus expands to fill nearly all the cerebral ventricles. Unlike the fishnet, however, the plexus tissue possesses well-developed brush-type borders, i.e., microvilli, on the apical epithelial surface. These brush borders further protrude into the CSF and increase the choroidal epithelial surface area, enabling rapid and efficient delivery of the CSF as well as other material included with the CSF secretion" (Zheng and Chodobski, 2005).

Notwithstanding recent definitive data, reference is still made (Tang et al., 2014) to older erroneous histological data claiming that the CP apical surface area is small and therefore not physiologically important for mediating brain-wide molecular distribution (Pardridge, 2011). However, in fact, as discussed below CP surface area is substantial, ~25 to 50% the size of the inner capillary surface area of the brain. This provides an enormous surface area for performing a myriad of choroidal transport functions. Moreover, the large surface area of brain capillaries and CP epithelial cells also allows water to diffuse freely and bidirectionally between blood, brain and CSF. Sweet et al. (1950) first showed this phenomenon in humans. Subsequently Oldendorf demonstrated in rats that greater than 50% of plasma water exchanges with the water of brain and CSF in a single pass of blood through the brain (Oldendorf, 1970). The exact mechanism of this huge bidirectional flux of water through the brain capillaries and CP is unknown since in adults there are no obvious aquaporins in brain capillary endothelium or on the *basal* side of the choroidal epithelium (Speake et al., 2003). We also know that secretion of CSF is volumetrically <1/100 that of CNS water diffusional exchange (Bateman and Brown, 2012; Brinker et al., 2014). The preponderance of CSF is formed by CP and consists of salts, micronutrient vitamins, secreted proteins, hormones and water pulled along passively to maintain osmotic equilibrium, as described below.

One group states that CP does not produce CSF (Oreskovic and Klarica, 2010), a result inconsistent with over 60 years of data obtained for animals and humans. Among the multiple experiments countering this view, we cite three recent examples. First, in accordance with the most powerful of the causality arguments of John Stuart Mill, the method of commitment variation, often termed dose–response causality in pharmacology, one would predict that more CSF would be produced in CP hyperplasia (Smith et al., 2007) if the CP produces CSF. As part of a definitive review of CP hyperplasia cases, Hallaert and colleagues present as an example (Hallaert et al., 2012), a very well-studied case of a 3-year-old child with communicating hydrocephalus in which the lateral CP, but not the third and fourth ventricular CPs, were enlarged on MRI due to a genetic defect; with the external drainage system at the level of the foramen of Monroe, this 10 kg child copiously produced 2 l of CSF per day! On removal of the two enlarged lateral plexuses, the histological appearance of the tissue was normal and the child's CSF overproduction was prevented. There is no doubt that her CP secreted CSF in this case. Similarly, in many other cases of increased ICP (e.g., hydrocephalus) due to relative or absolute overproduction of CSF, as discussed below, removal of the lateral CP tissues is beneficial by substantially lowering the ICP.

Secondly, for decades we have also known that the CP contains multiple transporters capable of transferring Na^+, Cl^-, and HCO_3^- from blood into CSF across the CP — a typical secretory epithelium. Recently, in one example of a sophisticated study in mice (Kao et al., 2011), the investigators knocked out the CP transporter sla4a5 that transports $NaHCO_3$ into CSF. Sla4a5 exists *only* on the apical surface of CP, apparently nowhere else in the CNS. These sla4a5 knockout (KO) mice had a ventricular volume and CSF pressure only ~25% of normal. Moreover, their CSF had a lower HCO_3^- concentration, as expected. This study clearly showed that the CP, with the aid of sla4a5 and other ion transporters, produces HCO_3^--containing CSF. And thirdly, the CP epithelial monolayer in an in vitro trans-well actively transports not only vitamin C (Angelow et al., 2003) but also "CSF" from the basal to the apical (ventricular) side against a considerable hydrostatic pressure gradient (Hakvoort et al., 1998). Such fluid pumping against pressure clearly mimics the in vivo situation of elevated ICP in hydrocephalus.

Another set of concepts needing revision is that drugs and nutrients pass into and out of CSF mainly by passive forces largely dependent on molecular weight, ionic charge and lipid solubility; and do not penetrate deeply into the substance of the brain from CSF (Nagaraja et al., 2005; Pardridge, 2011, 2012). These concepts need qualification in order to promote precise understanding and sound therapeutic regimens, as discussed below.

Anatomy of choroid plexus: structural–functional relationships

Choroid plexus ultrastructure is similar in the lateral, third and fourth ventricles. There is a vascular network surrounded by a single layer of roughly cuboidal epithelial cells that are joined by tight junctions and make up the blood–CSF barrier (Fig. 1) (Smith et al., 2004). The vascular endothelial cells differ from those forming the blood–brain barrier in being fenestrated (Wolburg and Paulus, 2010). Evidence indicates that endothelial fenestrations, in the kidney and CP, facilitate the movement of fluid out of the capillaries (Ballermann and Stan, 2007). Between the endothelium and the epithelium is an area of stroma. The choroidal epithelial cells, linked by tight junctions at the apical, CSF-facing pole of the lateral membrane (thus accounting for the blood–