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Neuroscience Reviews: The Physiology of the Choroid Plexus

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Introduction

Maturation of the human brain relies in part on experience-driven development of neural circuits. Thus, homeostatic mechanisms have evolved that provide neuronal signaling with a highly controlled and stable microenvironment. The physiology of the choroid plexus is one such mechanism, as this secretory and highly permeable tissue is responsible for producing cerebrospinal fluid and establishing a barrier that controls the brain's internal environment. This brief review focuses on the choroid plexus in the context of ion and water transport, and then attempts to integrate the physiology of this secretory tissue to aspects of human health and pathology.

Microanatomy of the Choroid Plexus

The choroid plexus (CP; from the Latin: *delicate knot*) is an ependymal-derived structure lining the four ventricles of the human brain (two lateral CPs, CPIII and CPIV; **Fig. 1**). The constitutive cells of the choroid plexus are primarily cuboidal epithelial surrounding a core of fenestrated capillaries with microvilli of variable frequency and size (Wolburg and Paulus, 2010; Lun et al., 2015). The CP is a highly vascularized tissue that floats within the ventricular system and depending on the location, receives its blood supply from the anterior and posterior choroidal arterial network (Lun et al., 2015). Interestingly, the CP anatomy is conserved in vertebrate species and its function also seems to be conserved, as the CP secretes analogous chemical signals across different nervous systems (Bill and Korzh, 2014). This clearly illustrates the evolutionary importance of the CP for the integrity and function of the vertebrate brain.

Physiology of the Choroid Plexus

CP cells are frequently exposed to mechanical and biochemical signals, which can be generated within or from adjacent structures of the developing and mature brain. As of result of this, the turnover rate of endothelial cells is fast and must be tightly linked to apoptotic cell death to preserve two of the main functions of the CP: the formation of an anatomical barrier, the blood-cerebrospinal fluid barrier (BCSFB), and the synthesis and secretion of cerebrospinal fluid (CSF). This biological barrier actively separates CSF from the brain interstitial fluid and circulating blood, thus preventing the diffusion of water-soluble molecules across the BCSFB (Brinker et al., 2014; Abbott, 2015; Balusu et al., 2016). There are, however, numerous transport mechanisms that allow for the direct transport of ions, nutrients and growth factors into the CSF and the clearing of unwanted and po-

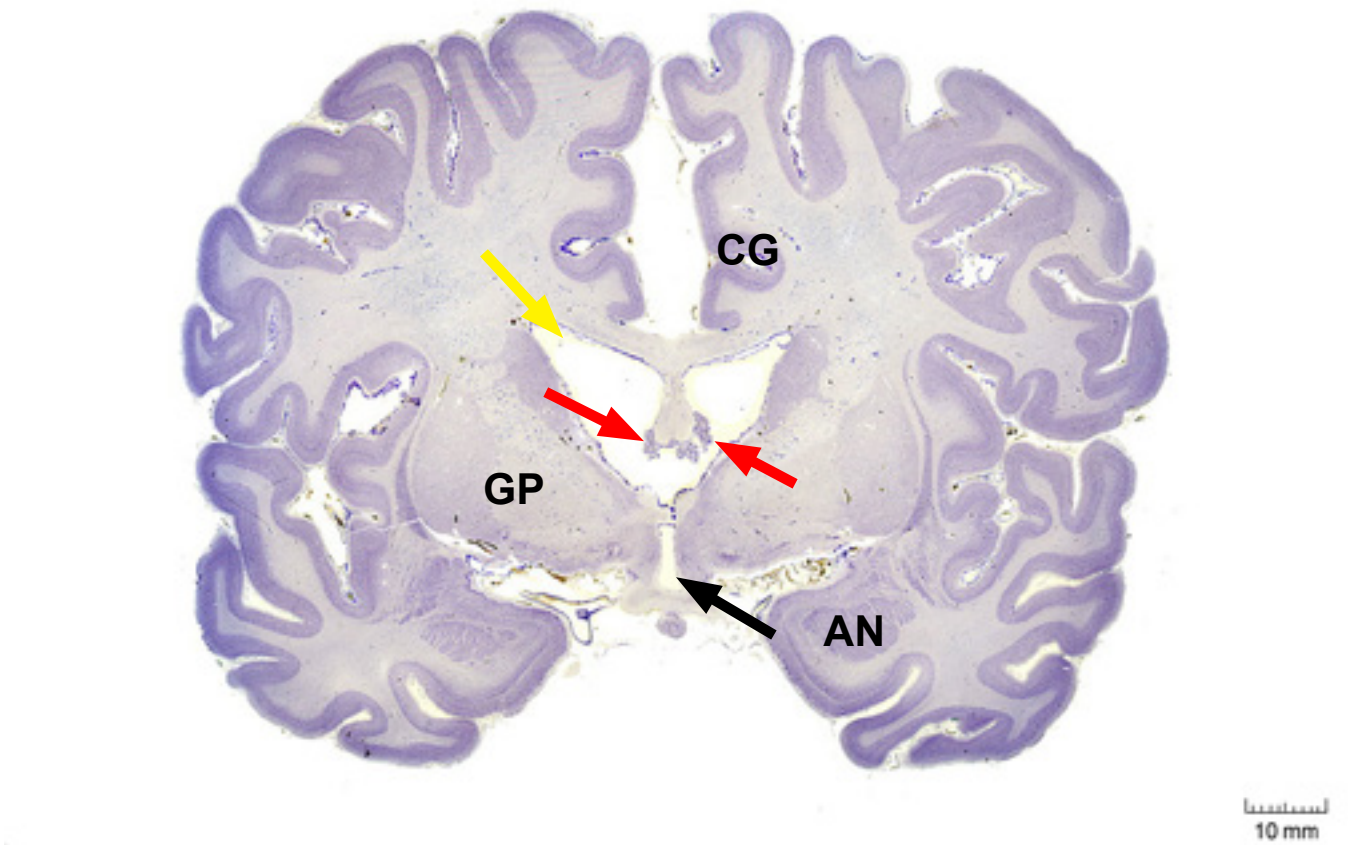


Fig. 1. A coronal (Nissl-stained) section of the adult human brain depicts the topographical location of the CP within the lateral ventricles (yellow arrow). Note that the CP hangs inside the ventricular system (red arrows). The CP is a complex secretory structure whose epithelial-cell layers are essential for their protective and regulatory function of brain development and ion water homeostasis. Although rare, pathologies of the CP include cysts, hemorrhages, diffuse villous hyperplasia and tumors (Lun et al., 2015). In most cases, CP neoplasms are diagnosed in the pediatric population with dismal clinical outcomes (Gopal et al., 2008). The third ventricle (CP III; black arrow) differentiates much earlier in brain development than the other ventricular cavities. The fourth ventricle (CPIV) extends over the surface of the medulla to eventually open into the medulla-cerebellum junction (Haines, 2002). For orientation purposes, the globus pallidus (GP), cingulate gyrus (CG) and amygdala nucleus (AN) are illustrated. Images from the Yakovlev-Haleem collection are used courtesy of the National Museum of Health and Medicine, Armed Forces Institute of Pathology. Michigan State University Brain Biodiversity Bank.

tentially infectious proteins (e.g., β-amyloids) from the CSF (Damkier et al., 2013; Lun et al., 2015). Thus, the CP epithelium produces the CSF and in doing so influences the chemical composition of the interstitial fluid of the brain (**Fig. 2**). This represents an important evolutionary advantage for the brain, as neuronal activity and ion water (e.g., K+, Na+, HCO3- and Cl-) homeostasis are inextricably coupled (Abbott, 2015).

Although CSF is mostly produced in the CP, this assumption has been challenged by evidence that CSF is formed throughout the brain parenchyma, involving water channels and peri-capillary fluid filled spaces. For example, the Virchow-Robin space, a continuous canal surrounding blood vessels, represents an additional site where CSF circulation not only depends on the CP but also on integral membrane proteins that facilitate the movement of water across biological barriers (Brinker et al., 2014; Nakada, 2014). These integral proteins, known as aquaporins (AQP; water channels), are responsible for maintaining proper water flux between plasma membranes, with the AQP-1 isomer uniquely found in the CP epithelium (Nakada, 2014).

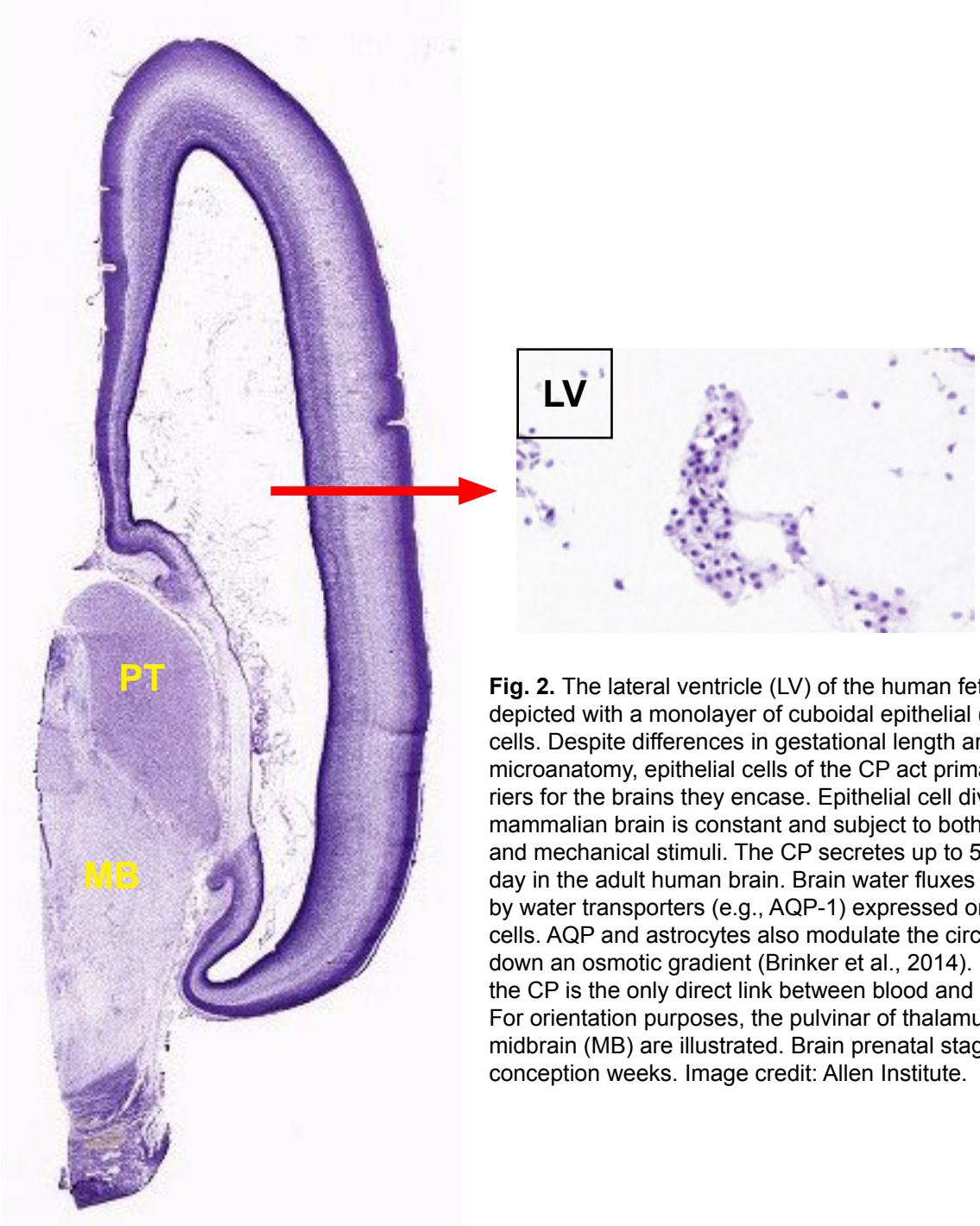


Fig. 2. The lateral ventricle (LV) of the human fetal brain is depicted with a monolayer of cuboidal epithelial (Nissl-stained) cells. Despite differences in gestational length and fetal brain microanatomy, epithelial cells of the CP act primarily as barriers for the brains they encase. Epithelial cell division in the mammalian brain is constant and subject to both biochemical and mechanical stimuli. The CP secretes up to 500 ml of CSF/day in the adult human brain. Brain water fluxes are regulated by water transporters (e.g., AQP-1) expressed on CP epithelial cells. AQP and astrocytes also modulate the circulation of CSF down an osmotic gradient (Brinker et al., 2014). In general, the CP is the only direct link between blood and CSF circuits. For orientation purposes, the pulvinar of thalamus (PT) and midbrain (MB) are illustrated. Brain prenatal stage: 15 post-conception weeks. Image credit: Allen Institute.

In this regard, it is thought that failure of AQP function is a major contributing factor for the onset of cerebral edema, including water intoxication, cerebral ischemia and bacterial meningitis (Badaut et al., 2002; Boassa and Yool, 2005). Consequently, the secretory role of CP appears to be responsible for the regulation of fluid and electrolyte balance, as specific aspects of CSF circulation (and absorption) are evident in key aspects of neuronal development (**Fig. 3**).

The Choroid Plexus and Immune Cells

As discussed earlier, the CP is a highly permeable structure due in part to the expression of AQP-1 on epithelial cells. This perme-

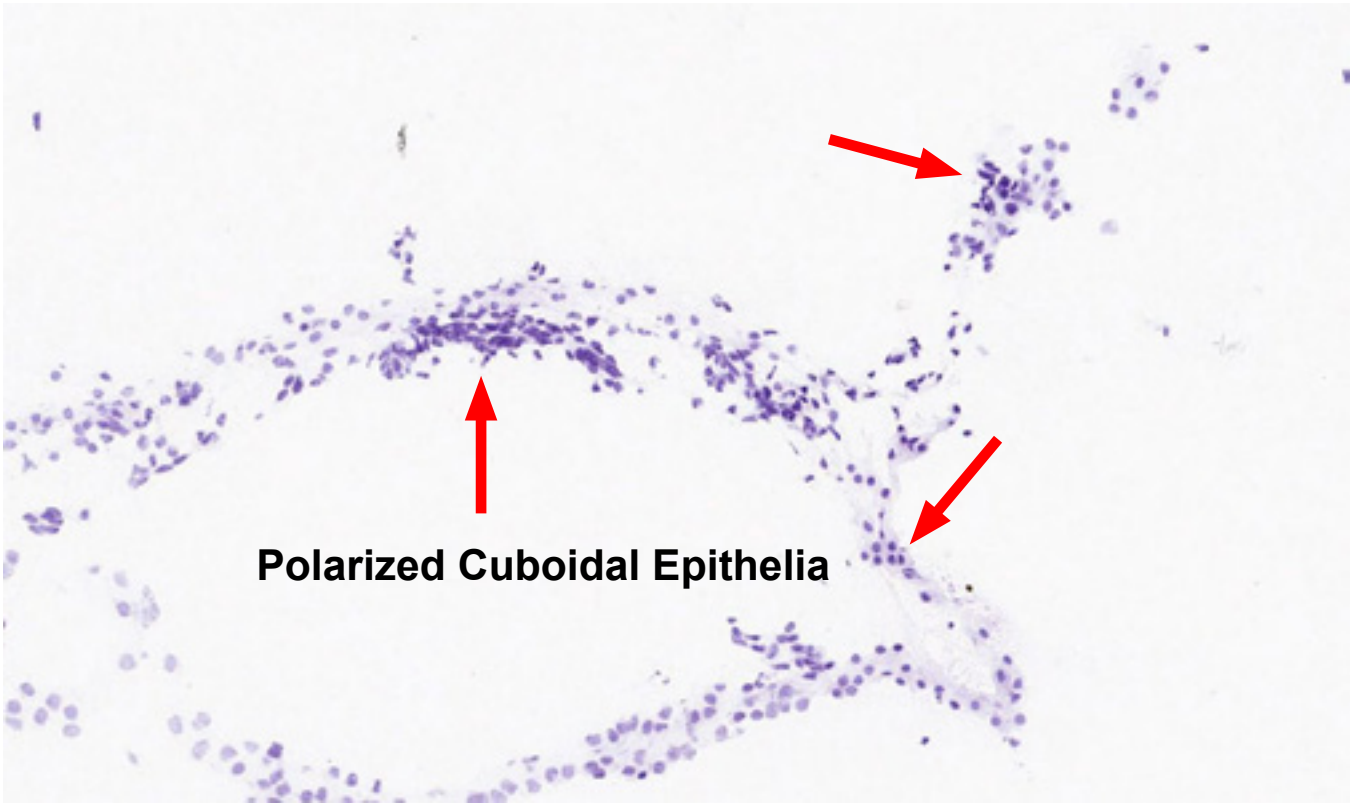
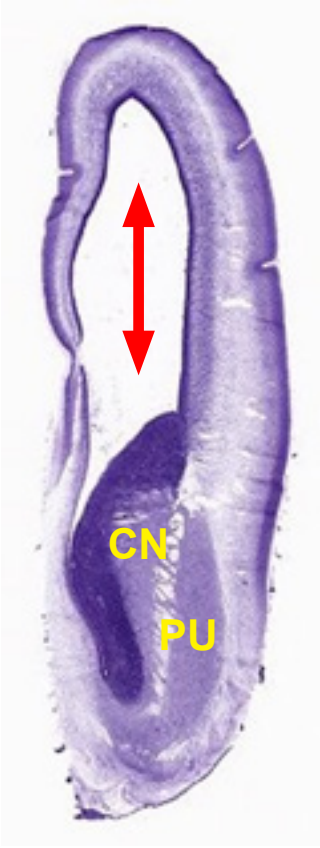


Fig. 3. Layers of fetal human cuboidal epithelial cells from the CP are depicted in this particular photomicrograph (red arrows). These (Nissl-stained) cells represent an active interface between blood and CSF. CP epithelial cells are joined together by tight and adherens junctions to form the BCSFB. CP epithelial cells are polarized: tight junctions and AQP are expressed at the apical pole, whereas nuclei are located at the basolateral pole (facing the blood compartment). It should be noted that CP epithelial cells also secrete hundreds of molecules and microRNAs (19-22 nucleotide-long non-coding RNA) into the CSF, including transthyretin, a thyroid hormone carrier (Lun et al., 2015). CP-based signaling events have, therefore, broad effects on the human brain beyond those related to CSF pulsatile secretion. Brain prenatal stage: 15 post-conception weeks. Image credit: Allen Institute.

ability allows the infiltration of immune cells (e.g., CD4+ T cells, macrophages, dendritic cells) into the CP to modulate adaptive immunity responses within the central nervous system (CNS). In this regard, we now know that immune cells are found in CSF where they survey the brain landscape for potentially noxious antigens (Baruch and Schwartz, 2013). Thus, the CP is now recognized as an important immunological site in maintaining immune competence following acute and chronic inflammation (**Fig. 4**). Along the same lines, it is thought that damage to the CP may allow the unbridled passage of antigens into the CNS to trigger chronic immune-pathological conditions such as multiple sclerosis (Lun et al., 2015; Balusu et al., 2016). New insights into the physiology of the CP have important clinical relevance for understating immunological diseases of the brain.

Conclusion

The CP has profound effects on brain physiology. It not only influences ion water fluxes across biological membranes, but it also guides critical periods of immunity in the developing and mature brain. Further mechanistic dissection of the CP will improve our understanding of neuronal maintenance, and will also provide insights into removal mechanisms of toxic proteins that contribute to early circuit dysfunction as seen in Alzheimer's disease.



Ionic Homeostasis
Aquaporins (AQP-1)
Clearance of Toxic Proteins
CSF
Entry Gate for Leukocytes
Blood-CSF Fluid Barrier
CNS-Specific CD4⁺ T Cells

Fig. 4. A Nissl-stained photomicrograph of the fetal human CP (long red arrow) is depicted above. The functions of the CP range from CSF secretion to adaptive immunity responses. The clearance of β-amyloid proteins by CSF raises the possibility that therapies for Alzheimer's disease involving the accelerating removal of toxic proteins could be rational approaches to treatment. Indeed, the discovery of a glymphatic system associated with CSF flow, the Virchow-Robin space and AQP-gating supports the possibility of designing therapeutic strategies in relation to CP physiology (Hitscherich et al., 2016). For orientation purposes, the caudate nucleus (CN) and putamen (PU) are illustrated. Brain prenatal stage: 15 post-conception weeks. Image credit: Allen Institute.

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Editor's Column

An Open Invitation

The David Kopf Instrument Company is inviting readers of the Kopf *Carrier* and company customers to submit articles for publication in the *Carrier*. This newsletter has been published continuously since 1973. It is intended to bring interesting and informative information to the neuroscience community. Various types of articles have been published in the 90 *Carrier* issues that can all be viewed and downloaded at the Kopf website (kopfinstruments.com). We have published articles on techniques, interesting data, views and reviews.

We are interested in soliciting articles from the neuroscience community that present novel or unusual techniques and viewpoints. For example, if you are working with neonatal animals, an article on the unique aspects of this type of work and aspects of stereotaxic methods involved would be valuable. Perhaps you have developed unique ways to deal with methods involved in working with animal species not usually used. Let your colleagues know what this involves. You may have published unusual findings and want to get these out to a larger audience. We do not copyright our articles and will publish previously published findings with appropriate permissions. You may be working with the Model 1900 ultraprecise stereotaxic system and wish to share you experience with its use through an article. You may have experience with one of the Neurostar motorized small animal stereotaxic systems that would be of help to your colleagues; such an article would be very useful.

If you are interested in writing an article for the *Carrier*, you can review previous articles for format and length (www.Kopfinstruments.com). There is a $500 honorarium for each published article. Articles can be directed to either Dawn Gelsinger at David Kopf Instruments (dawng@kopfinstruments.net) or to Michael M. Patterson, Ph.D., (drmikep1@me.com). We would like to hear from you.

This issue of the *Carrier* is another in the Neuroscience Reviews series by German Torres, Ph.D. In it, Torres gives an overview of the Choroid Plexus and how it operates to maintain brain function and stability. As always, the review is both interesting and timely.

As I write this column here in Florida, several parts of the country are still experiencing winter-like weather, despite the fact that spring has sprung. We here will soon enter our own dangerous weather period, the hurricane season. This season runs June 1 through November 30. We have been lucky for several years in the no severe hurricanes have hit southern Florida for a number of years. Hopefully this will continue this year. The tree trimmers are currently trimming the hardwood trees in our association community in hopes that a windstorm will blow through rather than take down our big trees. Hopefully, it will work.

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