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Full-Length Review

Therapeutic implications of the choroid plexus–cerebrospinal fluid interface in neuropsychiatric disorders

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ABSTRACT

The choroid plexus (CP) comprises an epithelial monolayer that forms an important physical, enzymatic and immunologic barrier, called the blood–cerebrospinal fluid barrier (BCSFB). It is a highly vascularized organ located in the brain ventricles that is key in maintaining brain homeostasis as it produces cerebrospinal fluid (CSF) and has other important secretory functions. Furthermore, the CP–CSF interface plays a putative role in neurogenesis and has been implicated in neuropsychiatric diseases such as the neurodevelopmental disorders schizophrenia and autism. A role for this CNS border was also implicated in sleep disturbances and chronic and/or severe stress, which are risk factors for the development of neuropsychiatric conditions. Understanding the mechanisms by which disturbance of the homeostasis at the CP–CSF interface is involved in these different chronic low-grade inflammatory diseases can give new insights into therapeutic strategies. Hence, this review discusses the different roles that have been suggested so far for the CP in these neuropsychiatric disorders, with special attention to potential therapeutic applications.

1. Introduction

The brain is immune-privileged due to the presence of three different barriers: (1) the blood brain barrier (BBB), (2) the blood–cerebrospinal fluid barrier (BCSFB) and (3) the arachnoid barrier. The BBB consists of the tight junction (TJ)-containing endothelial cells of the brain capillaries, while the BCSFB is formed by the epithelial cell monolayer of the choroid plexus (CP), which is located in the brain ventricles. Besides the epithelium, the CP consists of a stromal compartment containing immune cells and fenestrated endothelial cells. The CP plays a pivotal role in neural function by maintaining brain homeostasis, surveying the immunological status of the brain, and participating in inflammatory processes and repair following trauma (Aube et al., 2014; Szmydynger-Chodobska et al., 2009, 2012; Shechter et al., 2013; Shrestha et al., 2014; Simard et al., 2011). Even modest structural and/or functional changes of the CP can have significant effects and have been linked to several central nervous system (CNS) diseases and trauma (Aube et al., 2014; Szmydynger-Chodobska et al., 2009, 2012; Shechter et al., 2013; Shrestha et al., 2014; Simard et al., 2011). The BCSFB responds basolaterally to the blood side and apically to the cerebrospinal fluid (CSF) side, hence, it forms a well-positioned interface between periphery and CNS. Certain inflammatory stimuli lead to changes in the secretome of the CP and consequently, to changes in CSF composition (Thouvenot et al., 2006). Therefore, alterations in the CSF are often a reflection of a specific disease state, so measuring CSF biomarkers has diagnostic potential. In addition, the CSF-producing CP is in close contact with the subventricular zone (SVZ) of the hippocampus, which is important in neurogenesis, implying a possible key role for the CP–CSF interface in neurodevelopmental disorders (e.g. autism and schizophrenia) (Falcao et al., 2012). Changes at the CP–CSF interface during neurodevelopment are considered risk, causative and/or participating factors for the development of neuropsychiatric disorders (Palha et al., 2012). These alterations include for example the disturbed production of neurogenesis-related molecules by the CP, such as retinoic acid (Yamamoto et al., 1996, 1998), insulin growth factor II (IGF II) (Lehtinen and Walsh, 2011) and Slit1 (Sawamoto et al., 2006), or inflammatory -induced proteins that modulate neurogenesis, such as Slit2 (Marques et al., 2009), and disturbances in CSF formation, circulation and/or homeostasis (Palha et al., 2012). Therefore, this gives a window of opportunity for therapeutic targeting of neural maturation and brain plasticity in the early years of life, in people at risk,

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to prevent the exacerbation of social, emotional and cognitive deficits into a full-blown neuropsychiatric disorder (Misra, 2014).

Acute mental stress is accompanied by an accumulation of lymphocytes at the CP, which is thought to be important in maintaining and restoring brain homeostasis, for example by restoring the levels of brain-derived neurotrophic factor (BDNF) in the hippocampus (Schwartz and Baruch, 2012; Lewitus et al., 2008). However, severe and/or chronic stress can lead to a sustained inflammatory state that can cause post-traumatic stress disorder (PTSD), depression or other neuropsychiatric illnesses in genetically predisposed individuals. Sleep disorders, such as narcolepsy and insomnia, are also associated with changes at the CP and are considered a risk factor for the development of other neuropsychiatric diseases. Clearly, the CP is gaining increasing interest as an important secretory, immunological and sensory organ in neuropsychiatric diseases. However, more research is needed to unravel its mechanistic role in order to identify new, more specific, therapeutic targets. This review gives an overview of the current knowledge on the effect of the CP in these different diseases and their therapeutic implications.

2. The choroid plexus: anatomy and functions

The choroid plexuses (CP) are located in the lateral, third and fourth brain ventricle where they produce cerebrospinal fluid (CSF). The CP consists of an epithelial cell monolayer, forming a physical barrier called the blood–CSF barrier (BCSFB), and a stromal compartment containing permeable fenestrated blood vessels, fibroblasts and immune cells, such as dendritic cells and macrophages. In between adjacent CP epithelial cells, tight junctions (TJs) and gap junctions (GJs) are present limiting the paracellular passage and allowing intercellular communication, respectively (Falcao et al., 2012; De Bock et al., 2014) (Fig. 1A, left panel). Molecules such as amino acids, ions and proteins are too big, hydrophilic and/or highly polarized to freely cross the BCSFB via paracellular diffusion due to the presence of these TJs (Saunders et al., 2013, 2012). Moreover, transport across the BCSFB is highly controlled and occurs in a directional way. It includes different classes of transporters involved in movement into the cell (influx) and out of it (efflux) (Saunders et al., 2013) (Fig. 1, right panel). Additionally, there are both active and passive transporters: active mechanisms move solutes up their concentration gradients and require energy (adenosine triphosphate, ATP), while passive mechanisms move solutes down their concentration gradients and are energy-independent processes (Saunders et al., 2013). This passive transport includes diffusion and facilitated diffusion that is carrier-mediated. Building up concentration gradients of different solutes is not only important for the functioning of the mature brain, but also for cell division, migration, differentiation and synaptogenesis during early brain development (Saunders et al., 2013). The BCSFB is, besides a physical barrier, also an enzymatic barrier as it contains enzymes that conjugate drugs in order to eliminate them and since it expresses enzymes that protect the brain against free-radical oxidative stress (Mortazavi et al., 2013). Moreover, since the CP contains resident immune cells, has the ability to produce pro-inflammatory cytokines, expresses MHC molecules and molecules for leukocyte adhesion, thereby providing a route for activated immune cells to pass, the BCSFB is also an immunological barrier (Mortazavi et al., 2013).

The production of CSF by the CP occurs by passive filtration of fluid across the highly permeable capillary endothelium and regulated secretion across the CPE (Brinker et al., 2014). The movement of ions via carriers and ion channels creates an osmotic gradient which drives the secretion of H_2O via aquaporins (AQP) (Brown et al., 2004). Strong expression of AQP1 is observed at the apical membrane of the CP, which leads to a high water permeability (Nielsen et al., 1993; Speake et al., 2003; Wu et al., 1998). In contrast, no significant AQP1 expression was detected basolaterally (Brown et al., 2004; Nielsen et al., 1993; Speake et al., 2003; Wu et al., 1998). Some studies suggest that the CP–CSF system could constitute an important pathway for neuroendocrine signaling in the brain, but there is no clear-cut direct evidence for this yet (Skipor and Thiery, 2008; Nilsson et al., 1992). Indirect evidence is provided by the presence of many different neuroendocrine substances in the CSF and/or their corresponding receptors on the CPE cells (Nilsson et al., 1992; Redzic and Segal, 2004). Some of the endocrine substances in the CSF, e.g. serotonin, atrial natriuretic peptide (ANP), vasopressin and insulin-like growth factor (IGF), have a high receptor concentration at the CP and have been shown to influence CP function (Nilsson et al., 1992). The adult CP produces IGF-II and a number of transport proteins, of which the most important is transthyretin (TTR) (Nilsson et al., 1992). TTR is a thyroid hormone-binding protein, produced by the liver and CP, that regulates the transport of the hormone from blood to brain (Nilsson et al., 1992). Clearly, the CP is an important physical, enzymatic and immunological barrier with key secretory and regulatory functions.

2.1. Immune surveillance

In health, the interplay between CP and CSF is important for immune surveillance, and in disease, it participates in immune-skewing (Demeestere et al., 2015). In general, leukocytes enter the CSF via the fenestrated endothelium where they migrate through the CP stroma, followed by transmigration across the CPE (Fig. 1, right panel). In the steady state, they do not invade the parenchyma (Engelhardt and Ransohoff, 2012; Shechter et al., 2013). Findings by Nataf et al. (2006) suggest that the CP contains myeloid progenitors, distinct from the circulating monocytes, that can differentiate into macrophages or DCs. A lot of DCs positive for major histocompatibility complex II (MHCII+) were observed on the CSF-facing surface of the CP, thereby providing easy access to antigens present in the CSF (McMenamin et al., 2003). Interestingly, the intra-epithelial DCs at the CP express IL10, suggesting an immunosuppressive role (Serot et al., 2000). In humans, DCs were identified in the CSF, stroma and in between the CPE cells (McMenamin et al., 2003). A large majority of macrophages was found to be less evident at CSF-exposed sites since they were mainly located within the connective tissue of the CP stroma (McMenamin et al., 2003). It remains unclear whether these resident APCs at the apical side of the CPE, also called epiplexus or Kolmer cells, are considered to be DCs and/or macrophages, but they contribute to the immune component of the BCSFB (McMenamin et al., 2003; Lu et al., 1993; Maslieieva et al., 2014). They are thought to play a role in immune tolerance to CP-processed brain-derived molecules in the CSF leading to immunological silencing of the brain (McMenamin et al., 2003; Serot et al., 1997).

The tissue-resident antigen presenting cells (APCs) are thought to present antigens to the T cells that are present in the normal, healthy stroma of the CP (Anandasabapathy et al., 2011; Kivisakk et al., 2009, 2003; Hanly and Petito, 1998). Considering the strategic location of the CP, which receives signal from both the periphery and CNS, and the enrichment of CD4+ T cells specific for brain self-antigens under normal conditions, the CP is suggested to play an important role in the maintenance of brain function and activity (Baruch and Schwartz, 2013). Cognitive functions, such as spatial learning and memory, are supported by these CD4+ T cells as they play a role in hippocampal neurogenesis (Ziv et al., 2006; Wolf et al., 2009; Ron-Harel et al., 2008; Derecki et al., 2010). Furthermore, T cells accumulate at the CP during mental stress

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