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Review article

The choroid plexus as a sex hormone target: Functional implications

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ABSTRACT

The choroid plexuses (CPs) are highly vascularized branched structures that protrude into the ventricles of the brain, and form a unique interface between the blood and the cerebrospinal fluid (CSF). In recent years, novel functions have been attributed to this tissue such as in immune and chemical surveillance of the central nervous system, brain development, adult neurogenesis and circadian rhythm regulation. Sex hormones (SH) are widely recognized as modulators in several neurodegenerative diseases, and there is evidence that estrogens and androgens regulate several fundamental biological functions in the CPs. Therefore, SH are likely to affect the composition of the CSF impacting on brain homeostasis. This review will look at implications of the CPs' sex-related specificities.

Contents

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1. Introduction

The choroid plexuses (CPs) are highly vascularized structures, located in the ventricular system of the brain (Fig. 1). In the lateral ventricles of the mammalian brain, CPs form a sheet-like structure, whereas in the third and fourth ventricles these resemble villus-like structures. The CPs are formed by single layers of cuboidal epithelial cells laying on a basement membrane. Bellow the basement membrane, within the connective tissue, lays a network of fenestrated capillaries, fibroblasts and immune cells (e.g., mast cells, macrophages, granulocytes), and a rich extracellular matrix (Redzic and Segal, 2004). The CPs' epithelial cells (CPEC) are connected by tight junctions, adherens junctions and desmosomes, forming a sealed barrier that prevents paracellular movement of substances into and out of the brain.

CPEC also have numerous microvilli and cilia at the ventricle facing (apical) side, and extensive infolding at the blood facing (basolateral) side, thus providing a large surface for contact between the epithelium and the CSF and between the epithelium and the stroma interstitial fluid on the other side (Ghersi-Egea et al., 2009). In addition, the CPEC apical and basolateral membranes contain a wide range of transporters, channels, pumps and receptors that mediate and set the pace for the exchange of compounds between the periphery and the CSF. These are essential to fulfil the CPs' role as a source of nutrients for the brain, and also for the excretion of molecules originating from the brain metabolism.

Several fundamental functions have been attributed to the CPs and have been within the scope of recent reviews. The best known functions of CPs are CSF formation (Damkier et al., 2013), nutrient and hormone supply to the CSF and brain, clearance of deleterious compounds and waste products from brain metabolism (Johanson et al., 2011; Richardson et al., 2015; Spector et al., 2015), immune surveillance (Schwartz and Baruch, 2014), amyloid clearance (Pahnke et al., 2014; Pascale et al., 2011), and neurogenesis (Falcao et al., 2012; Johansson, 2014; Lun et al., 2015). Other emerging functions of the CPs are chemical surveillance as depicted from the presence of the taste and olfactory transduction pathways in CPEC (Gonçalves et al., 2016; Tomás et al., 2016) and the potential function of the CP as an extra-suprachiasmatic nucleus circadian clock (Quintela et al., 2015b).

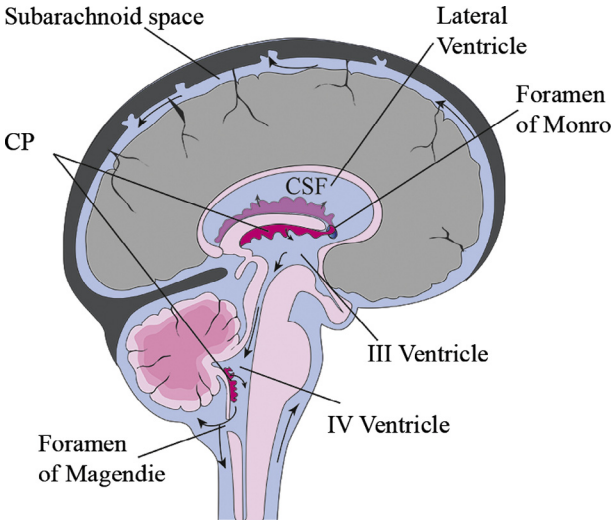

Fig. 1. The cerebrospinal fluid circulation (CP – choroid plexuses; CSF – cerebrospinal fluid).

2. Search strategy, publication selection criteria and data analysis

Research articles were selected from PubMed database from until October 2016 on the basis of the quality of the evidence they provide following the criteria established by the Grading of Recommendations Assessment, Development and Evaluating (GRADE) working group (www.gradeworkinggroup.org). Search terms used were: brain barriers, immune surveillance, chemical surveillance, sex hormones, sex differences, estrogen, androgen, progesterone,

Table 1
Sex hormone receptors expressed in the choroid plexuses.

Gene symbol	Gene name	Female sham	OVX vs Sham	Male sham	OOX vs Sham	Male vs Female
AR	*Androgen receptor*					
Esr1	*Estrogen receptor 1 (ER alpha)*					
Esr2	*Estrogen receptor 2 (ER beta)*					
Gper	*G protein-coupled estrogen receptor 1*					
PR	*Progesterone receptor*					
mPR1	*Progesterone receptor membrane component 1*					
mPR2	*Progesterone receptor membrane component 2*					

OOX – orchidectyomized male rats; OVX – ovariectomized female rats

Basal expression	Fold change up-regulation	Fold change down-regulation
>12	>1,5	>1,5
>8	>2	>2
>4	>3	>3
<3,99		

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