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REVIEW

ROLE OF CHOROID PLEXUS IN CEREBROSPINAL FLUID HYDRODYNAMICS

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Abstract—The classic hypothesis presents the cerebrospinal fluid (CSF) as the ''third circulation,'' which flows from the brain ventricles through the entire CSF system to the cortical subarachnoid space to eventually be passively absorbed into the superior sagittal sinus through arachnoid granulations. The choroid plexus (CP) represents a key organ in the classic CSF physiology and a powerful biological pump, which exclusively secretes CSF. Thereby, the CP is considered to be responsible for CSF pressure regulation and hydrocephalus development. This article thoroughly analyzes the role of the CP in the CSF dynamics, presenting arguments in favor of the thesis that the CPs are neither biological pumps nor the main site of CSF secretion; that they do not participate in regulation of ICP/CSF pressure; are not the reason for the existence of hydrostatic pressure gradient in the CSF system and that this gradient is not permanent (disappeared in the horizontal position); and that they do not generate imagined unidirectional CSF circulation, hydrocephalus development and increased ICP/CSF pressure. The classic hypothesis cannot provide an explanation for these controversies but the recently formulated Bulat-Klarica-Orešković hypothesis can. According to this hypothesis, CSF production and absorption (CSF exchange) are constant and present everywhere in the CSF system, and although the CSF is partially produced by the CP, it is mainly formed as a consequence of water filtration between the capillaries and interstitial fluid.

Key words: cerebrospinal fluid, choroid plexus, classical hypothesis of cerebrospinal fluid physiology, hydrocephalus, Intracranial pressure, Bulat-Klarica-Orešković hypothesis.

Contents

INTRODUCTION

The hydrodynamics of cerebrospinal fluid (CSF) has so far been almost exclusively explained using the classic hypothesis of the CSF. According to this hypothesis, the CSF is actively produced inside the brain ventricles, circulates unidirectionally within the entire CSF space (from formation to absorption site) and is passively absorbed into the venous blood on the brain surface and/or into the lymph via paraneural sheaths of nerves (Fig. 1A; Brierly and Field, 1948; Cserr, 1971; Bradbury, 1981; Davson et al., 1987; Johnston et al., 2005; Koh et al., 2006; Pollay, 2010; Sakka et al., 2011; Brinke et al., 2014; Hladky and Barrand, 2014). The CSF is represented as a river that flows slowly from its source to its mouth. In physiological conditions, the CSF flow is steady, constant, pulsating and without barriers.

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Abbreviations: AQP, aquaporin; BV, brain ventricle; CM, cisterna magna; CNS, central nervous system; CP, choroid plexus; CPC, choroid plexus carcinomas; CPP, choroid plexus papillomas; CSF, cerebrospinal fluid; ICP, intracranial pressure; ISF, interstitial fluid; LV, lateral ventricle; SAS, subarachnoid space.

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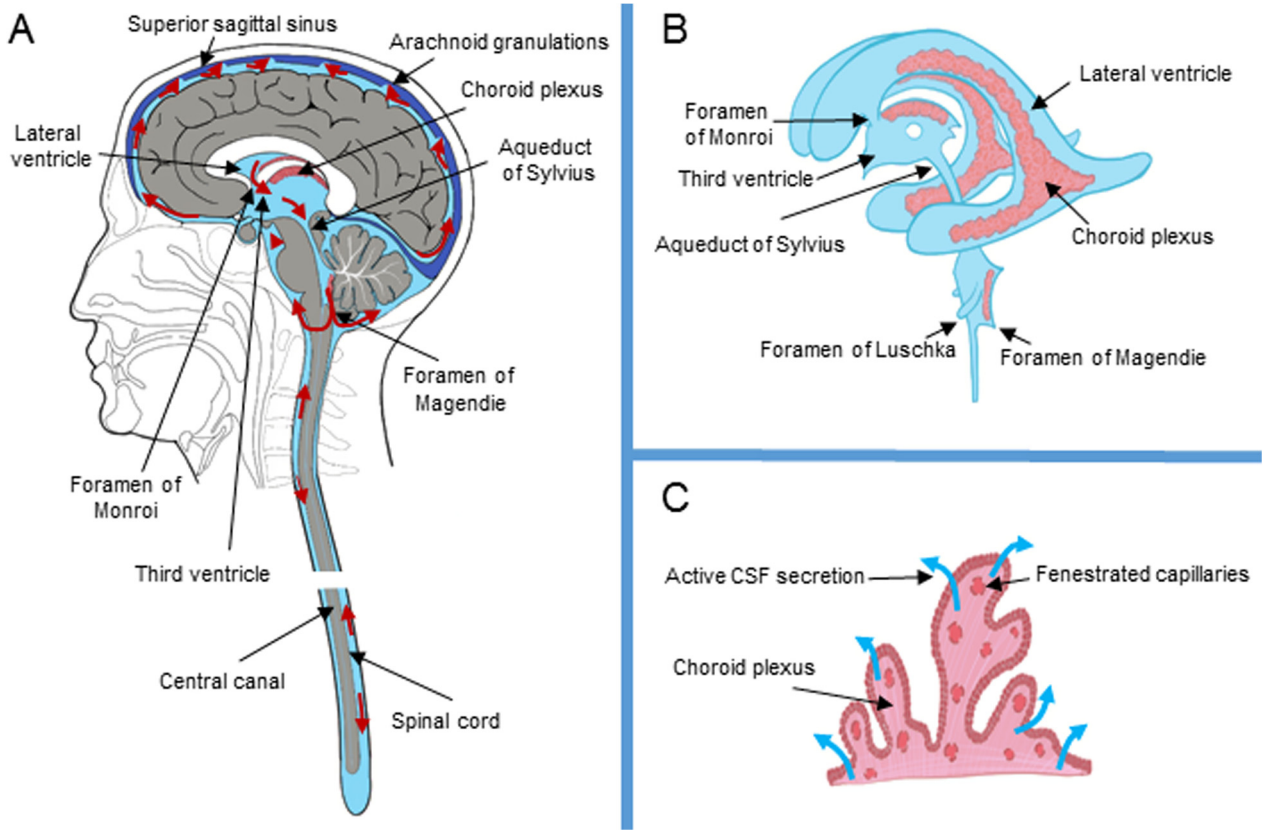

Fig. 1. (A) The scheme of the cerebrospinal fluid system with location of the choroid plexuses, the CSF distribution, and arachnoid granulations. CSF is represented by the light blue area and the direction of CSF circulation and the sites of CSF absorption are represented by red arrows. (B) The scheme of the human brain ventricles with emphasized choroid plexuses in red color and CSF shown as the light blue area. (C) The choroid plexus structure, with emphasized branched choroid plexus structure and the villi projecting into the brain ventricle. The plexus network is presented with fenestrated capillaries and the bold blue arrows indicate the direction and active nature (secretion) of CSF formation.

Consequently, along with blood and lymph, the CSF dynamics in mammals was presented as the ''third circulation" (Cushing, 1914, 1925; Taketomo and Saito, 1965; Milhorat, 1975). According to Cushing's (1925) interpretation (''*that at about the fifth week of embryonic life fluid begins to percolate through the remaining fragment of the roof plate overlying the fourth ventricle; that it finds its way through leptomeningeal channels which are thereby formed in the mesenchyme; and finally, that it escapes by way of persisting leptomeningeal communications, the villi, that project through the dura into its major venous synuses. All of which assuredly indicates the birth of an actual circulation under the pressure of secretion.*"), the site of CSF absorption, the direction of CSF circulation and the energy that stimulates the circulation (pressure of secretion) are strictly defined. If ''the third circulation" or CSF circulation is similar to blood circulation through the body, driven by the pumping action of the heart, it is necessary that an organ similar to the heart (biological pump which constantly pumps blood in the same direction) exists in the CSF system. The working principle of each pump in a circulatory system, including the heart, is the production of constant gradient of hydrostatic pressure between the highest pressure value at the beginning and the lowest pressure value at the end of the circulation. According to the classic hypothesis, this role in the CSF system belongs to the choroid plexuses (CPs). In other words, CPs secrete the CSF in the brain ventricles (Fig. 1; Davson et al., 1987; Brown et al., 2004; Damkier et al., 2013; Lun et al., 2015; Spector et al., 2015). Since the CSF formation is an active process (secretion), moderate changes in intracranial pressure (ICP) should not significantly change the CSF formation rate (Heisey et al., 1962; Rubin et al., 1966; Cutler et al., 1968; Sklar et al., 1980; Pollay et al., 1983).

Consequently the CP is imagined as an organ which represents a biological pump in the CSF system, i.e. as an organ responsible for ''*pressure of secretion*". A hundred years ago Weed (1914) assumed that the intraventricular secretion of the CSF by the CP imparted the energy required for fluid circulation from the ventricles, out over the brain convexities, and back into the blood (Fig. 1). If it is considered that the CSF is passively absorbed from the subarachnoid space into the venous sinuses due to a lower hydrostatic pressure in the sinuses than in the subarachnoid space (Weed, 1935; Brodbelt and Stoodley, 2007; Pollay, 2010), it seems that the conditions for CSF circulation exist. Therefore, the most important role in CSF physiology was given to the CP, and it is necessary to re-elaborate Weed's assumption.

Hence, it could be concluded that the relationship between active CSF formation by the CSF pumps (CPs)