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CEREBROSPINAL FLUID SECRETION BY THE CHOROID PLEXUS?

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TO THE EDITOR: In their review, "Cerebrospinal fluid secretion by the choroid plexus," Damkier, Brown, and Praetorius (3) aimed to present recent advances in understanding the regulation of cerebrospinal fluid (CSF) secretion and limitations of current understanding of CSF formation and choroid plexus (CP) physiology. However, this review seems rather incomplete because an important part of CSF physiology, which disagrees with the classic view (2, 11, 13), had not been discussed. In this letter, we want to draw attention to only few of the many argumentations against the classic hypothesis. Due to the space limitation, the presented materials of CP here is very simplified.

In the light of classic hypothesis, CSF is presented as the so-called "third circulation" where CSF circulates as a slow river from the brain ventricles through entire CSF system to the cortical subarachnoid space to eventually be passively absorbed into superior sagittal sinus through arachnoid granulations. The CP represents a key organ in classic CSF physiology and is presented as a powerful biological pump responsible for CSF secretion (3, 14). Thereby, CP is considered to be responsible also for CSF pressure regulation (9) as well as for the development of hydrocephalus (as reviewed in Ref. 11).

CP IN CSF Secretion

According to the classic hypothesis, there is no doubt that CP is the main place of CSF formation and a biological pump by which CSF is exclusively secreted (14). By definition, CSF formation is production of CSF volume rate per unit of time. Since the volume of CSF represents the volume of water (becauce 99% of CSF is water), the CP should be the main place of water entry into CSF system. But both experimental (4, 5, 12) and clinical data (1, 10) have clearly shown that there is no significant contribution of CPs to water influx into the CSF system. Consequently, if the CP does not behave as a biological water pump (99% of CSF volume), it cannot be regarded as a CSF pump.

CP in CSF Circulation

According to the classic hypothesis, there is no doubt that CSF circulates. By law of fluid mechanics, the constant circulation is possible only if permanent hydrostatic pressure gradient between the beginning (the highest pressure) and the end (the lowest pressure) of circulation exists. In blood circulation, the heart is the pump producing those conditions, thus enabling permanent blood circulation. In the CSF system, the analogous role is attributed to CP, considering it a biological pump responsible for CSF circulation. But the fact is that, in the CSF system, such gradient required for CSF circulation does not exist (7). In the horizontal body position, there is no pressure gradient, and, in the vertical body position, values (gradients) are opposite to the direction needed for (hypothetical) CSF circulation, i.e., the lowest hydrostatic pressure exists in ventricles (-10 cmH_2O), it is higher in cistern magna (0 cmH_2O), and the highest in the lumbar sac ($+70$ cmH_2O). Obviously, existing hydrostatic gradient in the CSF system has nothing to do with the CPs. In ventricles where CPs should act as biological pump and secrete CSF, the hydrostatic pressure is low, and, oppositely, in lumbar space where there is no CP, hydrostatic pressure is the highest. Consequently, inside the CSF system, there is no hydrostatic pressure gradient enabling the circulation of CSF.

CP in Development of Hydrocephalus

According to the classic hypothesis, there is no doubt that hydrocephalus would develop in a situation where the CSF system is blocked between the site of secretion and the site of absorption. Due to continuous CSF secretion by CP (biological pump) and the inability of CSF absorption, hydrocephalus would occur in front of the blockade. But the facts are that, even with CSF pathways completely blocked, hydrocephalus would not develop every time (6, 11, 12). Furthermore, when CPs where removed in hydrocephalic patients, hydrocephalus still persisted, and shunt should have been reinstalled (11, 12). On the other hand, hydrocephalus might develop although blockade between the site of CSF secretion and absorption does not exist (8). Consequently, blockade of CSF circulation as well as CP functioning does not represent a key factor in hydrocephalus development.

All of these facts cannot be explained by the classic hypothesis but are easily explicable and fit very well in a new hypothesis of CSF physiology (2, 7, 11, 13) stating that CSF formation and absorption (CSF exchange) are constant and omnipresent processes in the CSF system, mainly as a consequence of water filtration between the capillaries and interstitial fluid of the central nervous system, and only partially in the CPs. There-

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fore, when elaborating the CP functions, it would be necessary to discuss the new approach to the CSF physiology, even if authors disagree with this new hypothesis. It is the only way to elucidate the true role of CP in the nervous system.

DISCLOSURES

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REFERENCES

1. Bering EAJr. Water exchange of central nervous system and cerebrospinal fluid. *J Neurosurg* 9: 275–287, 1952.
2. Bulat M, Klarica M. Recent insights into a new hydrodynamics of the cerebrospinal fluid. *Brain Res Rev* 65: 99–112, 2011.
3. Damkier HH, Brown PD, Praetorius J. Cerebrospinal fluid secretion by the choroid plexus. *Physiol Rev* 93: 1847–1892, 2013.
4. Igarashi H, Tsujita M, Huber VJ, Kwee IL, Nakada T. Inhibition of aquaporin-4 significantly increases regional cerebral blood flow. *Neuro Rep* 24: 324–328, 2013.
5. Klarica M, Miše B, Vladić A, Radoš M, Orešković D. "Compensated hyperosmolarity" of cerebrospinal fluid and the development of hydrocephalus. *Neuroscience* 248: 278–289, 2013.
6. Klarica M, Orešković D, Božić B, Vukić M, Butković V, Bulat M. New experimental model of acute aqueductal blockade in cats: effects on cerebrospinal fluid pressure and the size of brain ventricles. *Neuroscience* 158: 1397–1405, 2009.
7. Klarica M, Radoš M, Erceg G, Petošić A, Jurjević I, Orešković D. The influence of body position on cerebrospinal fluid pressure gradient and movement in cats with normal and impaired craniospinal communication. *PLoS One* 9: e95229, 2014.
8. Klarica M, Jukić T, Miše B, Kudelić N, Radoš M, Orešković D. Experimental spinal stenosis in cats: new insight in mechanisms of hydrocephalus development. *Brain Pathol*. In press.
9. Marmarou A, Shulman K, Rosende RM. A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. *J Neurosurg* 48: 332–344, 1978.
10. Mehemed TM, Fuchimi Y, Okada T, Yamamot A, Kanagask M, Kido A, Fujimoto K, Sakashita N, Togashi K. Dynamic oxygen-enhanced MRI of cerebrospinal fluid. *PLoS One* 9: e100723, 2014.
11. Orešković D, Klarica M. Development of hydrocephalus and classical hypothesis of cerebrospinal fluid hydrodynamics: facts and illusions. *Progr Neurobiol* 94: 238–258, 2011.
12. Orešković D, Klarica M. The controversy on choroid plexus function in cerebrospinal fluid production in humans: How long different views could be neglected? *Croat Med J* 56: 306–310, 2015.
13. Orešković D, Klarica M. The formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations. *Brain Res Rev* 64: 241–262, 2010.
14. Spector R, Keep RF, Snodgrass RS, Smith QR, Johanson CE. A balanced view of choroid plexus structure and function: focus on adult humans. *Exp Neurol* 267: 78–86, 2015.