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### Mass-Transfer Events in the Nanofluidic Domain of the Brain Interstitial Space: Paradigm Shift

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#### ABSTRACT

Brain water metabolism ensures mass transfer of various substrates and signaling molecules, participates in the clearance of pathogenic metabolites. At present, there are two theories, diffusion and convection, employed to consider the mass-transfer events taking place within the brain interstitial system. A new nanofluidic approach, that takes into account the nanodimensionality of the brain interstitial space, makes it possible to outline a novel nanofluidic mechanism of brain water metabolism with its important practical ramifications. An overview of the conventional approaches and the nanofluidic one is presented to find a possible solution of the current debate on the mass-transfer events in the brain interstitial space.

Keywords: Brain water metabolism, Interstitial mass-transfer, Diffusion and convection, Nanofluidic domain, Nanofluidic mechanism

Abbreviations: ISF: Interstitial Fluid; ISS: Interstitial Space; AQP4: Aquaporin-4; NVU: Neurovascular Unit

#### INTRODUCTION

The ISF is involved in transport of nutrients and gases, neuroactive substances, non-synaptic intercellular communication (volume transmission), signal transduction, maintaining ionic homeostasis, formation and resolution of the brain edema, targeted delivery of drugs, removal waste products, transfer of heat generated by neuroactivity, migration of cells (malignant cells, stem cells) [1-3].

The ISF serves an external environment for the brain cells. It envelopes the cells by the sheets of fluid 10-40 nm width connected by the tubular tunnels of 40-80 nm diameter into an intricate nanodimensional network [4-6].

A commonly accepted opinion in the medical community asserts that the ISS is too narrow for any significant bulk flow and rather presents a diffusion barrier to fluid movement. The laws of diffusion are deemed sufficient to account for the events taking place there [4,7-12]. The researchers dissatisfied with the diffusion barrier theory put forward fluid convection instead [8,13-22].

# BRAIN INTERSTITIAL SPACE AND NANOFLUIDICS

An interdisciplinary nanofluidic approach makes it possible to view the issue in a new light. Nanofluidics deals with the behavior of fluids confined to nanoslits, nanochannels, nanopores, etc., where at least one characteristic dimension is in the range of 1-100 nm [23]. A significant enhancement of fluid flux there due to the surface hydrodynamic slip is a special rheological feature of the nanoconfined fluids [24,25]. It is rather counterintuitive and disagrees with the orthodox views. The characteristic properties of nanoconfined fluid in the ISF were revealed in the first groundbreaking research on the live brain, carried out with the use of the injected single-walled carbon nanotubes [26].

Two recent publications pioneer a nanofluidic approach to model brain water metabolism and the mass transfer events related to fluid movement in the ISS [27,28]. According to this research, the nanodimensional compartment of the ISS is considered a nanofluidic domain with fluid flow there governed by the slip-flow principles of nanofluidics. AQP4 ensures overall kinetic control over fluid movement across the blood-brain barrier (BBB) and in the nanofluidic domain [16,29-31]. The pulsatory intracranial hydrostatic pressure presents a driving force behind fluid movement [32-35]. A modified phenomenological equation, based on the Kedem-

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Katchalsky formalism of irreversible thermodynamics [36] has been used to describe fluid movement between the capillary blood and the ISS.

#### DISCUSSION

The nanofluidic model describes brain water metabolism and realistically accounts for some relevant clinical cases. It demonstrates a possibility of a convective mode of mass transfer of glucose, oxygen and carbon dioxide within the NVU. The suggested principle could also be applied to volume transmission and other mass-transfer events in the brain.

The mechanism of fluid movement and mass transfer in the ISS is a hotly debated issue. Computer simulations of the ISF flow based on either Darcy or Navier-Stockes formalism demonstrate that unrealistically high hydrostatic pressure gradients are required for any significant convection there [10,37]. Unfortunately, in both works a non-slip approach for fluid flow has been used. For obvious reasons it is not applicable to the nanoconfined fluids thus rendering the simulation results inconclusive.

#### CONCLUSION

The nanofluidic mechanism presents an important missing piece in the mosaic of the brain water metabolism and mass transfer. It opens a new still unexplored venue of research with many promises and challenges on the way. It strongly suggests necessity of paradigm shift from the orthodox diffusional concept to the nanofluidic one.

#### REFERENCES

- 1. Veening JG, Barendregt HP (2010) The regulation of brain states by neuroactive substances distributed via the cerebrospinal fluid: A review. Cerebrospinal Fluid Res 7: 1.
- 2. Lei Y, Han H, Yuan F, Javeed A, Zhao Y (2017) The brain interstitial system: Anatomy, modeling, *in vivo* measurement and applications. Prog Neurobiol 157: 230-246.
- 3. Simon MJ, Iliff JJ (2016) Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease. Biochim Biophys Acta 1862: 442-451.
- 4. Abbott NJ, Pizzo ME, Preston JE, Janigro D, Thorne RG (2018) The role of brain barriers in fluid movement in the CNS: Is there a 'glymphatic' system? Acta Neuropathol 135: 387-407.
- Kinney JP, Spacek J, Bartol TM, Bajaj CL, Harris KM, et al. (2013) Extracellular sheets and tunnels modulate glutamate diffusion in hippocampal neuropil. J Comp Neurol 521: 448-464.

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- 6. Nicholson C (2007) Modeling brain extracellular space from diffusion data. Diffusion Fundamentals 6: 75.71-75.15.
- 7. Thorne R, Nicholson C (2006) In vivo diffusion analysis with quantum dots and dextrans predicts the width of brain extracellular space. PNAS 103: 5567-5572.
- 8. Abbott NJ (2004) Evidence for bulk flow of brain interstitial fluid: Significance for physiology and pathology. Neurochem Int 45: 545-552.
- Kamali-Zare P, Nicholson C (2013) Brain extracellular space: Geometry, matrix and physiological importance. Basic Clin Neurosci 4: 282-286.
- Jin BJ, Smith AJ, Verkman AS (2016) Spatial model of convective solute transport in brain extracellular space does not support a "glymphatic" mechanism. J Gen Physiol 148: 489-501.
- 11. Sykova E, Nicholson C (2008) Diffusion in brain extracellular space. Physiol Rev 88: 1277-1340.
- Nicholson C, Kamali-Zare P, Tao L (2011) Brain extracellular space as a diffusion barrier. Comput Vis Sci 14: 309-325.
- 13. Buishas J, Gould IG, Linninger AA (2014) A computational model of cerebrospinal fluid production and reabsorption driven by Starling forces. Croat Med J 55: 481-497.
- Miyajima M, Arai H (2015) Evaluation of the production and absorption of cerebrospinal fluid. Neurol Med Chir (Tokyo) 55: 647-656.
- 15. Orešković D, Radoš M, Klarica M (2017) New concepts of cerebrospinal fluid physiology and development of hydrocephalus. Pediatr Neurosurg 52: 417-425.
- Igarashi H, Tsujita M, Kwee IL, Nakada T (2014) Water influx into cerebrospinal fluid is primarily controlled by aquaporin-4, not by aquaporin-1: 17O JJVCPE MRI study in knockout mice. Neuroreport 25: 39-43.
- 17. Titovets E (2007) Aquaporins of man and animals. Basic and clinical aspects [in Russian]. (Minsk., Belarus: Izdatelski Dom "Belaruskaya Nauka").
- Bobo R, Laske D, Akbasak A, Morrison PF, Dedrick R, et al. (1994). Convection-enhanced delivery of macromolecules in the brain. Proc Nat Acad Sci 91: 2076-2080.
- 19. Jessen N, Munk A, Lundgaard I, Nedergaard M (2015) The glymphatic system: A beginner's guide. Neurochem Res 40: 2583-2599.
- 20. Titovets E, Nechipurenko N, Griboedova T, Vlasyuk P (2000) Experimental study on brain oxygenation in

#### J Genet Cell Biol, 2(3): 112-114

relation to tissue water redistribution and brain edema. Acta Neurochir Suppl 76: 279-281.

- 21. Titovets E, Stepanova T (2004) Conceptual mathematical model for convective mechanism of brain cortex oxygenation News Biomed Sci 2: 127-134.
- 22. Nakada T, Kwee IL (2019) Fluid dynamics inside the brain barrier: Current concept of interstitial flow, glymphatic flow and cerebrospinal fluid circulation in the brain. Neuroscientist 25: 155-166.
- 23. Abgrall P, Nguyen NT (2009) Nanofluidics. Boston, London: Artech House.
- 24. Eijkel J, van den Berg A (2005) Nanofluidics: What is it and what can we expect from it? Microfluidics and Nanofluidics 1: 249-267.
- 25. Sparreboom W, van den Berg A, Eijkel JCT (2010) Transport in nanofluidic systems: A review of theory and applications. N J Phys 12: 1-23.
- 26. Godin AG, Varela JA, Gao Z, Danne N, Dupuis JP, et al. (2017) Single-nanotube tracking reveals the nanoscale organization of the extracellular space in the live brain. Nat Nanotechnol 12: 238-243.
- 27. Titovets E (2018) Novel computational model of the brain water metabolism: Introducing an interdisciplinary approach. J Comp Biol Sys 2: 103.
- 28. Titovets E (2019) Computer modeling of convective mass transfer of glucose, oxygen and carbon dioxide in the neurovascular unit. J Comp Biol Sys 4: 1-8.
- 29. Nagelhus EA, Ottersen OP (2013) Physiological roles of aquaporin-4 in brain. Physiol Rev 93: 1543-1562.
- Desai B, Hsu Y, Schneller B, Hobbs JG, Mehta AI, et al. (2016) Hydrocephalus: The role of cerebral aquaporin-4 channels and computational modeling considerations of cerebrospinal fluid. Neurosurg Focus 41: E8.
- Brinker T, Stopa E, Morrison J, Klinge P (2014) A new look at cerebrospinal fluid circulation. Fluids Barriers CNS 11: 10.
- 32. Mestre H, Tithof J, Du T, Song W, Peng W, et al. (2018) Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat Commun 9: 4878.
- 33. Kao YH, Guo WY, Liou AJ, Chen TY, Huang CC, et al. (2013) Transfer function analysis of respiratory and cardiac pulsations in human brain observed on dynamic magnetic resonance images. Comput Math Methods Med 157040.
- 34. Wagshul M, Chen J, Egnor M, McCormack E, Roche P (2006) Amplitude and phase of cerebrospinal fluid

pulsations: Experimental studies and review of the literature. J Neurosurg 104: 810-819.

- 35. Wagshul M, Eide P, Madsen J (2011) The pulsating brain: A review of experimental and clinical studies of intracranial pulsatility. Fluids Barriers CNS 8: 1-23.
- 36. Friedman M (1986) Principles and models of biological transport. Springer: Verlag Berlin Heiderberg GmbH.
- 37. Soltani M, Chen P (2013) Numerical modeling of interstitial fluid flow coupled with blood flow through a remodeled solid tumor microvascular network. PLoS One 8: 1-18.