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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.

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