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Nanofluidic Approach to Brain Water Metabolism

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ABSTRACT

The brain interstitial fluid (ISF) in the brain interstitial space (ISS) forms external medium for the neural cells and is involved in various vitally important processes including volume transmission, signal transduction, coordinated response to changes in the external and internal environments of the brain, transport of nutrient and gases, removal of metabolic waste products. It participates in the migration malignant and stem cells, targeted delivery of drugs etc. The ISS presents a nanodimensional structure. This feature of the ISS has been commonly misinterpreted as an indication that it presents a Fickian diffusional barrier to mass-transfer processes there. A new interpretation, based on an interdisciplinary approach, states that the brain interstitial space should be considered the brain nanofluidic domain where fluid flow is governed by the principles of nanofluidics. The nanofluidic approach to the brain water metabolism solves a number of problems inherent to the diffusion barrier theory and opens new perspectives in brain physiology, pathology and in nanomedicine.

Keywords: Brain, Water metabolism, Interstitial system, Diffusion-barrier theory, Nanofluidics, Nanofluidic domain, Nanofluidic mechanism

Abbreviations: ISS: Interstitial Space; ISF: Interstitial Fluid; CSF: Cerebrospinal Fluid; NFD: Nanofluidic Domain; BBB: Blood-Brain Barrier; BCSFB: Blood-CSF Boundary; AQP1: Aquaporin-1; AQP4: Aquaporin-4

INTRODUCTION

The neurons attract the most attention in neurobiology; however, current knowledge of neural circuit scan only partially explains the neurological and pathophysiological conditions of the brain. It is also important to consider the role of brain ISS containing the ISF that bathes the nerve cells and the neurophil [1]. It should be observed that after many decades of research, it came to head that the interstitial space presents a rather neglected area [2]. The ISF forms external medium for the neural cells and is involved in non-synaptic intercellular communication (volume transmission), signal transduction, information processing and integration, coordinated response to changes in the external and internal environments of the brain. It ensures nutrient and gas transport, targeted delivery of drugs and metabolites, formation and resolution of the brain β-amyloid deposits and other metabolic waste products. The ISF is involved in maintaining ionic homeostasis, participates in the migration of cells (malignant cells, stem cells), transfer of heat generated by neuro-activity [1,3,4]. Dynamic and complex ISS connects the vascular system and neural networks and plays crucial roles in brain physiology. Investigation of the ISS can provide new perspectives for understanding brain function and exploring new strategies to treat brain disorders. In our era of interdisciplinary research new groundbreaking ideas may emerge from apparently far removed non-biological disciplines. The issue of fluid movement and mass-transfer events in the ISS seems to come to a stall in view of its nanodimensionality [5]. However, from an interdisciplinary approach, it is the nanodimensionality that might servea clue to solving its puzzle: the ISS characteristic width of 20-60 nm [6] puts this water system into the realm of nanofluidics. Nanofluidics, a rapidly developing over last two decades branch of science, deals with the phenomena and fluid behavior in compartments of various geometry where at least one characteristic geometrical dimension is the range of 1-100 nm [7]. Due to domination of the surface effects, water in

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nanoconfinement demonstrates physical properties and rheology dramatically different from those of the bulk water in larger compartments [8]. At the centre of this paper are current views on the brain fluids along with the problems arising from misinterpretations of fluid behavior in nanoconfined spaces. Due attention is given to presenting interdisciplinary nanofluidic approach to brain water metabolism and related issues to demonstrate how those problems might be overcome.

BRAIN FLUIDS AND COMPARTMENTS

The extracellular fluids of the human brain are contained in compartments varying in size from nano- to macro-dimentional ones. Containing nanoconfined water, the ISS occupies up to 20% of the total brain volume and falls into the category of nanodimentional structures [2,5,6,9]. By definition, the ISS is a NFD.

The CSF, of about 11% of the brain volume, fills the ventricular and the subarachnoid macro-compartments and contains bulk water [10]. The parenchymal blood microvessels, occupying 1.5%-5.5% of the brain volume, present another bulk-water compartment [11]. The nanoconfined ISF bridges the bulk water moieties of the blood and the SCF. The exchange of water between blood and the ISF is controlled by the BBB [12]. The CSF is in a constant to-and-fro motion driven by the oscillations of the brain intracranial pressure [13]. The integral CSF flow might proceed in either inward or outward direction. The CSF and the ISF present one functional moiety of freely communicating fluid. The BBB controls water transition between the blood bulk water and the nanoconfined water of the ISS. The BCSFB regulates water flow between two bulk water volumes: the blood and the CSF. The transition from the nanoconfined water of the ISS to the CSF bulk water also takes place with water moving on over larger the extended-nano compartments (the characteristic width from 100 nm to 1 μm), micro-compartments and macro-compartments [14,15].

Figure 1 demonstrates the distribution of bulk and nanoconfined water in the brain.

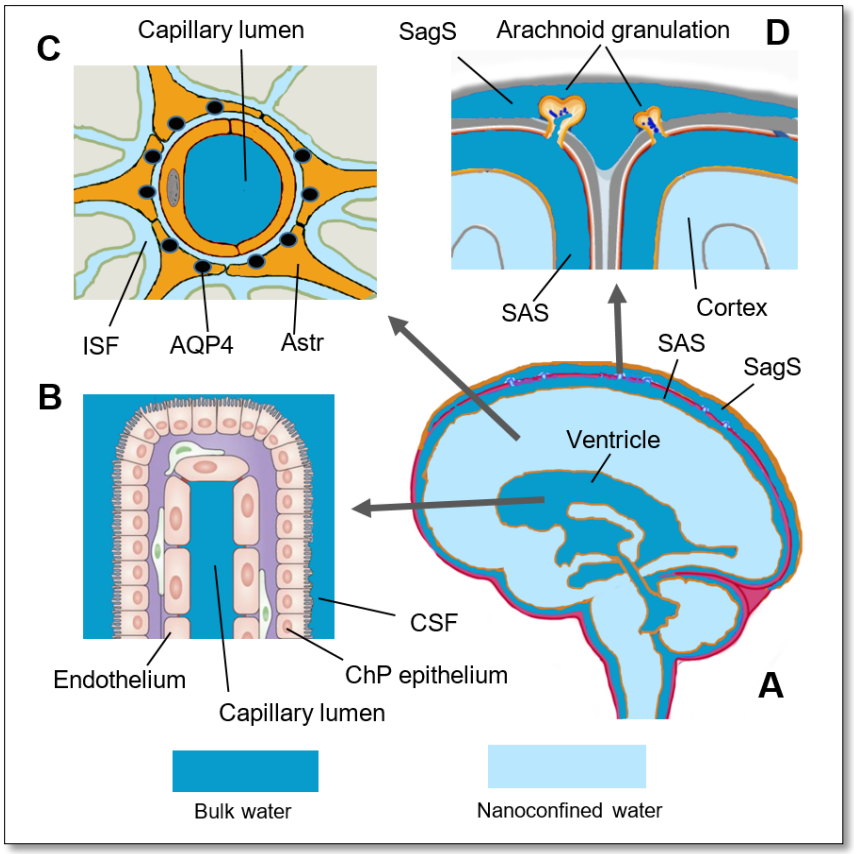

Figure 1. Topography of bulk and nanoconfined water in the brain.
A. Bulk and nanoconfined water distribution presented on the sagittal view of the brain.
B. The choroid plexus and the BCSFB.
C. BBB at capillary level.
SAS: Subarachnoid Space Filled with the CSF; SagS: Sagittal Sinus; Ventricle: Ventricular Space Filled with Bulk CSF
Astr: Astrocyte Endfeet Enveloping the Capillary. The black filled circles present AQP4 in the astrocyte endfeet membrane
D. The BCSFB at the arachnoid granulation level.

There are at least two distribution patterns as far as the proximity of the bulk and the nanoconfined water moieties is concerned. One of those is the bulk/bulk water pattern observed at the BCSFB of the choroidal plexus **(Figure 1B)** and at the BCSFB of the arachnoid granulations **(Figure 1D)**. Another pattern is presented by the bulk/nanoconfined water divide of the BBB **(Figure 1C)**. **Figure 1A** shows that two basins of bulk water (e.g. the subarachnoid CSF and the ventricular CSF) might be short-circuited with the nanoconfined water of the brain nanofluidic domain.

BULK WATER FLOW ROUTES

According to the classical views, the choroid plexus inside the brain ventricles is the main source of CSF formation. The secreted CSF flows as a bulk fluid along the cerebral macrospaces to get absorbed mostly into the venous sinuses through arachnoid granulations [16-18]. Apart from that CSF is absorbed into lymph flowing along the perineural spaces to reach the lymph nodes [19,20] and via the glymphatic pathway [21-24].

A hypothesis opposing the orthodox theory states that exchange of water occurs everywhere in the brain parenchyma between brain capillaries, the ISF and CSF Water is constantly formed and reabsorbed at the microvascular level and does not flow in a unidirectional way along CSF spaces [25-27]. Contrary to the predictions of classical theory, CSF circulation is pulsatile with the to and fro movement throughout the entire brain. Key controlling elements in brain water and CSF homeostasis are astrocytes and aquaporins [20].

A stumbling block of the theories of brain water metabolism is the mechanism of fluid passage through the nanodimensional ISS. A dominating opinion in the medical community is that the ISS, an irregular, tortuous and narrow space among neural cells, capillaries and neurophil, is too narrow to permit any bulk flow [9,28]. Fickian diffusion has been considered a dominant governing mechanism there with the ISS presenting a diffusion barrier to fluid movement [5,28,29]. Mass transfer events in the ISS are described in terms of diffusion coefficients, gradients and ISS tortuosity [5,30,31]. ISF drainage through the ISS is deemed to be a diffusion-driven process [5,29].

The diffusion-barrier theory conflicts with the experimental evidence demonstrating convection and bulk flow in the confined fluid compartments of the brain [32-37]. There is observed very fast water movement from artery to brain parenchyma and ventricular CSF [38]. The small and large molecules may move with the same rate in the ISS while, according to the diffusion theory, they should have individual effective diffusion coefficients [23,39-41]. The orthodox views on the ISS find their reflection in simulations of mass transfer events taking place there. These models are built on either Darcy's laws for fluid flow through porous media [42-44] or Fick' laws of diffusion [29,45,46].

Animal experiments with the use of two-photon imaging of small fluorescent tracers demonstrate that CSF enters the parenchyma along paravascular spaces surrounding penetrating arteries and were cleared along paravenous drainage pathways. The bulk fluid flow between these anatomical influx and efflux routes is controlled by water channel AQP4 expressed in the astroglia end feet at the border dividing the periarterial compartment and the ISS [22,33,47]. This route of CSF exchange presents the glymphatic mechanism based on fluid convection and bulk flow [48]. According to glymphatic mechanism, the CSF bulk flow is driven by the cerebral arterial pulsations [36]. Much prominence is given to its role in removal β-amyloid that is believed to be involved in pathogenesis of Alzheimer disease [49-51].

The fluid flow route after glymphatic mechanism, as well as other convectional mechanisms, includes a stage when water enters into and passes through the ISS. At this step convection clashes with the diffusion-barrier theory. The adherents of convection chose to sidestep this theoretical nuisance and not to go any deeper into the controversy. It is not that this fact did not receive due attention from other researchers. Thus, the Verkman's group, on modeling the glymphatic mechanism found that unrealistically high hydrostatic pressure gradient is needed to energize local parenchymal convective flow and fluid passage through the ISS [43]. The results of this research might be extended to include other cases of convection in the ISS. Incidentally, the Verkman's group used the no-slip Navier-Stokes equation to model water passage through the nanodimensional ISS. The significance of this misconception is discussed further in the text.

At present, the experimental results on water movement in the ISS facts speak against diffusion as the only mechanism of fluid movement and mass transfer in the brain. At the same time, the nanodimensionality of the ISS is used as an argument for the diffusion-barrier theory. The controversy stays unresolved still pending its solution.

NANOFLUIDIC APPROACH TO THE BRAIN INTERSTITIAL SPACE

A striking feature of the nanoconfined water is significant enhancement of its flow rate due to the hydrodynamic surface slip [52,53]. From the conventional point of view, it seems counterintuitive and even unsupported as has been demonstrated in simulations based on Darcy's or the no-slip Hagen-Poiseuille's equations [54,55]. An interesting example of such unexpected behavior presents aquaporins, the water-conducting nanopores. They exhibit water permeability typically three orders of magnitude higher than follows from the classical no-slip framework for the same pore size [56]. On the whole the flow capacity of confined

water might be up to ~10^7 times of that calculated with the no-slip Hagen-Poiseuille's equation for nanopores with various contact angles and dimensions [57,58]. Much valuable information on water rheology in nanoconfinement, relevant to biological systems, has been obtained using carbon nanotubes and nanotubes manufactured from other materials [59-64]. They present non-biological systems of nanoconfined water making it possible to get a deeper insight into water rheology with biological implications. Water flow rates through carbon nanotubes were comparable to the flow rates for AQP1 and were practically independent of the length of the nanotube, in contrast to predictions of macroscopic hydrodynamics [65]. Initially aquaporins held the first place as far as the high water-transfer rate was concerned being an object of professional envy and a target to achieve for nanoengineers. Finally, this record was beaten with the use of the thin-walled carbon nanotubes [61]. We introduced the nanofluidic slip-flow approach to fluid movement in the ISS as early as 2018 to model brain water metabolism [66]. Theoretical and experiment-based assumptions of the model were as follows: (a) the brain nanodimensional interstitial space presents NFD with the fluid movement there governed by the slip-flow mechanism [18,25]; (b) aquaporin AQP4 ensures kinetic control over water movement between the blood and the ISS [26,29,34,39]; (c) the pulsatory intracranial pressure presents a driving force behind the isosmotic fluid exchange between the capillaries and the interstitial space [26,35,36,38,40]. Introducing the nanofluidic approach makes redundant the diffusion-barrier theory with its intrinsic problems. The model demonstrated good predictability in respect to physiology of brain water metabolism and relevance in explaining some clinical conditions [66]. The nanofluidic approach was used to model convective mass-transfer events in the ISS. Computer simulation of convective transfer of glucose, oxygen and carbon dioxide, taking place within the NFD of the brain neurovascular unit, demonstrated that this mechanism is physiologically realistic [67]. Other volume transmission events in the brain ISS might also find their solutions within the nanofluidic model. The model may find its use in neurobiological research, development of the AQP4-targeted drug therapy, optimization of the intrathecal drug delivery to the brain tumors, in a research on a broad spectrum of water-metabolic-disorder-related conditions. The nanofluidic mechanism of brain water metabolism makes it possible to see in a new light the events taking place in the ISS. It solves a number of issues inherent to the diffusion-barrier theory that has been unaccounted for so far. A criticism coming from Verkman's group concerning fluid flow in the nanodimensional ISS demonstrates unlikeliness of this event due to high energy demands [43]. Unfortunately, the authors routinely used the no-slip Navier-Stokes approach to model water flow through the nanodimensional ISS. This basic approach needs to be reconsidered within the slip-flow paradigm as the nanodimensionality of the ISS demands. A controversy about the role of AQP4 in water moment across the BBB presents another problem of the diffusion-barrier theory. Abundantly expressed in the astrocyte end-feet membranes enveloping the capillaries, the nanochannel AQP4 controls, according to various experimental data, water exchange across the BBB and, hence, water movement in the brain [26-34]. But the role of AQP4 as a kinetically limiting step, on one hand, and the diffusion-barrier function of the ISS, on the other, present two incompatible views. The ISS diffusion-barrier, as the slowest step of the two, should have assumed a kinetically limiting role in the overall water moment thus making AQP4 redundant. The nanofluidic approach solves this controversy asserting the kinetically limiting role of AQP4.

MORE ON THE DIFFERENCES BETWEEN BULK AND NANOCONFINED WATER

Dimensionality of compartments changes the properties of the contained fluids. Following this dictum, the ISF, presenting the nanoconfined water and the bulk water of the CSF are not identical systems. Physical properties of nanoconfined liquids strikingly differ from those in bulk phase. This dramatically affects biophysical and biochemical events taking place in respective medium. Taking into account those differences becomes highly relevant to brain physiology and pathology. It is not surprising that the nanoconfined systems have attracted keen interest in recent years [1-4]. Apart from the enhanced fluid flow phenomenon, there are a number of other surprising parameters peculiar to the nanoconfined water. Of those, the dielectric permittivity is probably one of the most important parameters for the events taking place in the brain interstitial space and for studying and modeling molecular action mechanisms in nanomedicine. Dielectric properties of water in nanoconfinement are significantly different from those of the bulk-state water. The dielectric constant of nanoconfined water captured between too plane surfaces is anisotropic. Molecular dynamics simulations demonstrate that it is surprisingly low in the perpendicular direction ($\varepsilon_\perp \approx 10$) and very high in the axial direction ($\varepsilon_\parallel \approx 700$) with the isotropic dielectric constant for bulk water ≈ 80 [68,69]. The microscopic structure of water changes depending on the distance from the pore wall and temperature [70]. The nanoconfined water may not be considered a homogeneous fluid but is rather a heterogeneous system with ε value depending on the direction and hydrophobicity of the bounding surfaces. Enzyme catalysis, chemical reactions and other physico-chemical processes taking place in nanoconfined spaces are receiving increasing attention due to their importance to biology [71,72]. An important fact is that the thermodynamic activity of nanoconfined water is different from that of the bulk water [73]. Nanoconfined water affects profoundly catalytic reactions, the energetic and the reaction mechanisms, the properties of biomolecules, DNA conformation, protein folding, to list a few, while its properties play critical roles in a wide range of biological

processes [73-76]. Kinetics of enzymatic reactions in nanoconfinement may significantly deviate from the Michelis-Menten behavior observed in bulk water solutions. This deviation is reversible and disappears when confinement is released by return to the bulk state [73]. The effects of nanoconfinement on enzyme catalysis depend on the size of the confinement where the reaction occurs. The effects of spatial confinement, which is especially relevant to living systems, might be viewed as a new mechanism of metabolism control [77,78]. A research on solubility of gases in nanoconfined fluids has demonstrated that bulk-water Henry constants are no longer applicable at nanoscale. There is observed, instead, a striking increase in solubility defined by the term "oversolubility". This may result in large uptakes of gases as high as a few hundred times over expected from bulk solubility [79]. The molecular dynamic simulations and experimental evidence demonstrated an increase of oxygen solubility in water under confinement by a factor of 5-10 [80-82]. Solubility increase by factor 15 was found for CO_2 [80].

CONCLUSION

Paradigm shift from the diffusion-barrier concept in the brain water metabolism to the slip-flow nanofluidic approach asks for awareness of the fluid behavior principles in nanoconfined spaces, the new fluid properties and their effects on the solvents. Overwhelming share of biochemical and biophysical knowledge has been obtained so far using bulk water. Usually it would be diluted solutions where thermodynamic activity coefficients for respective solutes, as well as for water, would be assigned unity. Already from rather limited information given in this review one can see how dramatically different the properties of the nanoconfined water are from those of the bulk water. All that should be taken into account while considering brain water metabolism and other events taking place in the brain NFD. At present an urgent problem is development technologies and instrumentation to boost further research in the nanoconfined ISS *in vivo*. The proverbial Genie, called Nanofluidics, is now out of the bottle. Implementation of new interdisciplinary knowledge and its translation into basic and clinical research would open wide perspectives in our understanding of brain physiology, pathology and therapy. It holds in store a promise of fascinating research along with new challenges.

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CONFLICT OF INTEREST DECLARATION

The author declares no competing financial interests.

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