AUCTORES
Globalize your Research

Journal of Pharmaceutics and Pharmacology Research
Titovets E.*

Open Access

Review Article

Nanofluidic Mechanism of Brain Water Metabolism and Its Pharmacological Control

Titovets E.

Department of Neurosurgery of Republican Research and Clinical Center of Neurology and Neurosurgery, Minsk, Belarus.

***Corresponding Author:** Department of Neurosurgery of Republican Research and Clinical Center of Neurology and Neurosurgery, Minsk, Belarus.

Received Date: August 08, 2022; Accepted Date: September 29, 2022; Published Date: October 10, 2022

Citation: Titovets E, (2022). Nanofluidic Mechanism of Brain Water Metabolism and Its Pharmacological Control. *J Pharmaceutics and Pharmacology Research.* 5(9), DOI: 10.31579/2693-7247/094

Abstract

Brain water metabolism is involved in realization of a broad spectrum of vitally important physiological functions of the brain. Its disorders in various pathologies often lead to serious complications and death. Finding ways of pharmacological control of brain water metabolism is important to therapy of many conditions in neurology and neurosurgery. At present, there are the two mutually excluding basic views on brain water metabolism making it a center of theoretical controversy. A conventional approach affirms that the brain nanodimentional extracellular space presents a diffusion barrier to water movement. An interdisciplinary approach suggests that a slip-flow mechanism governs water movement there in the extracellular space that presents an integral part of the brain nanofluidic domain. This review centers on the nanofluidic mechanism of brain water metabolism and the AQP4-targeted drug control of brain water metabolism. The information presented here might be used in a neurobiological research, development of the AQP4-targeted drug therapy, optimization of intrathecal drug delivery, in a research on the therapy of the brain water metabolism disorders.

Keywords: brain water metabolism; diffusion barrier theory; nanofluidic mechanism of brain water metabolism; AQP4-targeted drug therapy.

Abbreviations: ISS – the interstitial space; ISF –the interstitial fluid; BBB - the blood-brain barrier; AQP1- aquaporin-1; AQP4- aquaporin-4.

Introduction:

The red arrow indicates the direction of the blood flow in the capillary. The dotted blue line with AQP4 present this aquaporin in the astrocyte endfeet membrane enveloping the capillary. The functionally different parts of the capillary are designated as FS (the Filtration Section), OS (the Oscillatory Section), and RS (the Reabsorption Section). The blue arrows, with the rate symbols "J_v", "$\pm J_v$", and "$-J_v$", indicate the direction of the water flows in the respective sections. The oncotic pressure in the capillary and the interstitial fluid is π_C and π_{ISF}, respectively. Hydrostatic pressure is p_a at the arterial end of the capillary and p_v at the venule end. The intracranial pulsatory pressure is $f(t)$. The square brackets indicate the nanofluidic domain. Note that the schematic is not drawn to scale and does not represent the true ratio between capillary diameter and the capillary length [8] .

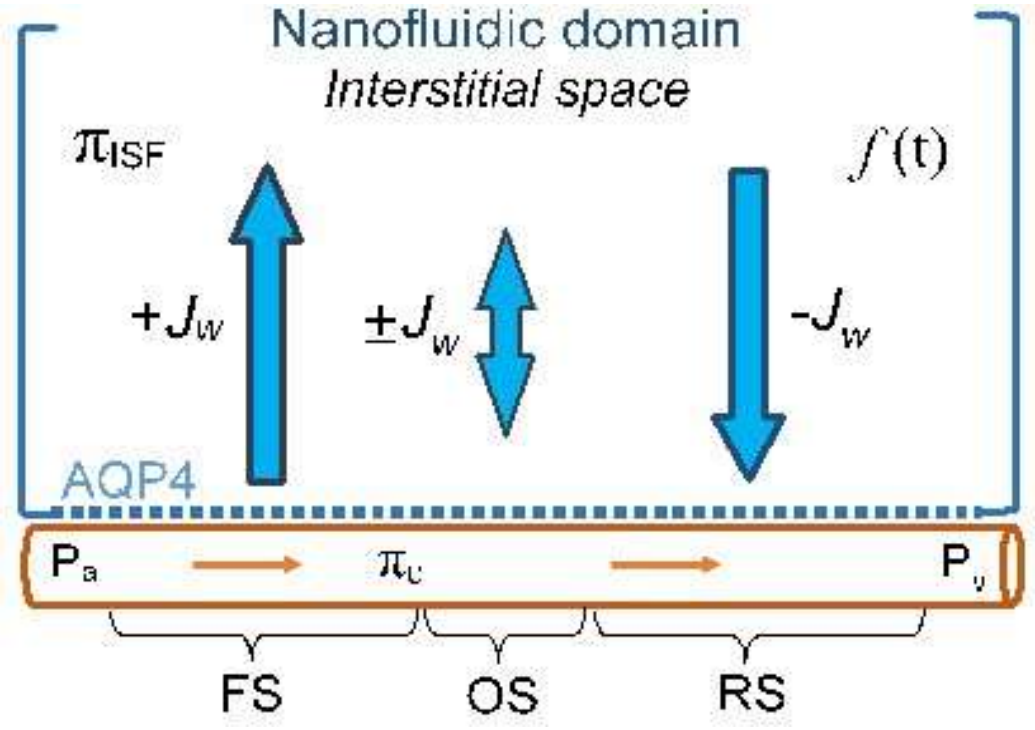

Figure 1: *Nanofluidic mechanism of brain water metabolism*

This interdisciplinary approach opens new fascinating perspectives in elucidating the so far concealed features of the brain water metabolism with important physiological implications.

Having adopted the nanofluidic approach and employed computer simulation technique, we have studded, in some detail, the brain water metabolism and related issues [8],[9],[10], [11],[12],[13],[14],[15].

The nanofluidic model of brain water metabolism is built on the following assumptions:

the brain nondimensional extracellular space presents a nanofluidic domain where water movement there governed by the slip-flow mechanism; aquaporin AQP4 ensures kinetic control over water movement between the blood and the brain extracellular space;the overall fluid transfer between the capillary blood and the interstitial fluid is isosmotic;the pulsatory intracranial pressure presents a driving force behind the isosmotic fluid exchange between the capillaries and the interstitial space [8].

A study of brain water metabolism, using a new approach, makes it possible to observe its many features relevant to brain physiology and pathological situations. It has been demonstrated the way AQP4 polarization in the astrocyte endfeet membrane affects the radial water fluxes. The model made it possible to assess quantitatively the influence of elevated intracranial hydrostatic pressure and elevated venous hydrostatic pressure on the transcapillary water exchange. An interesting feature of the model is that it makes possible to study mass-transfer events in the brain tissue. Thus it has been employed to study tissue oxygenation, transfer of carbon dioxide and glucose. The model might be used to study the effects of pharmacological modulators of AQP4 activity (the BBB permeability). The model demonstrates an intimate connection between brain water metabolisms and heart activity.

Brain edema brings about an increased intracranial pressure, effects cerebral circulation, causes brain hypoxia and a number of pathophysiological changes leading to severe neurological disorders and death. Cerebral edema occurs in a wide range of pathologies like traumatic brain injury, the stroke, hemorrhages, hydrocephalus, brain tumors, etc. The brain edema may also arise from the causes originated outside the brain: postoperative trauma, hemodynamic and hormonal-electrolyte disorders; cardiac, hepatic, renal, respiratory insufficiency; decompensated endocrine pathology, etc. Clinical practice demonstrates that there are still remain unresolved problems about the correction of the water metabolism disorders [16] , [17]. There are also remain some controversies abbot understanding, at the basic level, the mechanism of the brain water metabolism `

This metabolism has been a subject of close attention of researchers and of hot debates. To date, there is remain controversy about the issue. It stands in the way of the development of the effective means of the treatment of the brain water metabolism disorders.

The role of the choroidal plexus in the brain water metabolism has been scrutinized and subjected to criticism as untenable in the light of the latest basic and clinical research evidence [18] [19]. Acceding to an alternative theory, the main participants in the cerebral water exchange are the capillaries of the whole brain parenchyma, and not the choroidal plexus [20].

Water metabolism is associated with the activity of the quantitatively predominant and functionally most important aquaporin AQP4. This aquaporin is expressed in large quantities, as the two-dimensional orthogonal structures, in the plasma membrane of the astrocyte endfeet enveloping the capillaries [21], [22]. AQP4 controls the transfer of water across the BBB. Controlling the water movement between the blood and the interstitial space, it plays an important role in brain physiology, as well as in the development of pathological reactions leading to edema [23] [24].

AQP4 is viewed a molecular target for drug action directed at correction the disorders of brain water metabolism. Figure 2 demonstrates the results of AQP4 inhibition on water flow into brain parenchyma.

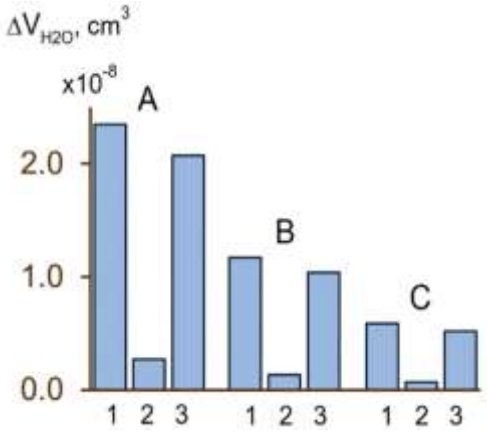

Figure 2. *Aquaporin AQP4 inhibition and water transfer across the BBB into brain parenchyma.*

A. No AQP4 inhibition. B. 50% inhibition of AQP4 activity C. 75% inhibition of AQP4 activity

1. The total racial water volume transferred over a cardiac cycle. 2. The racial water volume transferred over the systolic phase of the cardiac cycle. 3. The racial water volume transferred over the diastolic phase of the cardiac cycle.

New knowledge makes it possible to outline promising approaches in the treatment of the brain water metabolism disorders [3], [9],[12],[25]. The pharmacological arsenal of medicines currently used to correct disorders of cerebral water metabolism and combat brain edema represents a complex, which includes means of osmotherapy (mannitol, hypertonic sodium chloride solution), diuretics (furosemide, bumetanide) and other drugs with different mechanisms of action (corticosteroids, testosterone, dexamethasone, propofol, piroxicam, acetazolamide, etc.).

The osmotherapy is used to provide an osmotic pressure gradient between blood and the brain fluids and to ensure directed water flow from the brain tissues into the systemic circulation. Diuretics serve the same purpose.

The success of osmotherapy depends on water permeability of the BBB controlled by AQP4. Numerous studies have shown that the level of expression and the degree of polarization of AQP4 in the BBB structures are labile and depend on many physiological factors. Significant changes in the activity of AQP4 are observed in pathologies [26].

The concept according to which aquaporins present molecular targets for drugs is very attractive and practically important [27], [28], [29], [30] . In view of this, much research has been carried out to study the action of drugs on aquaporin activity.

The Table shows the effects of some drugs, used in the treatment brain edema and water metabolism disorders, on the activity of aquaporins AQP1 and AQP4.

Pharmacological preparation	Effect on AQP1	Effect on AQP4	References
Testosterone	Increases the level of expression	Increases the level of expression	[31]
Propofol	Vector inhibitor	Lowers the level of expression	[32] [33] [34]
Dexamethasone	Increases the level of expression	The expression level is different in different parts of the GM	[35]
Piroxicam	-	Inhibitor	[36]
Acetazolamide (diacarb)	Inhibitor	Inhibitor	[37], [38]
Bumetanide	Inhibitor	Inhibitor	[39]
AqB013, a derivative of bumetanide	Inhibitor	Inhibitor	[40]
Furosemide (lasix, furon)	Inhibitor	Inhibitor upon penetration into the cell	[41]
Corticosteroids	Increase the expression of AQP1 in capillaries	-	[42]

Table. *Pharmacological modulators of AQP1 and AQP4 activity*

Chemical modulators of aquaporins penetrating into the cell produce either an inhibitory or an activating effect on a specific aquaporin. The same aquaporin in different tissues may be involved in implementation of different physiological functions and thus be involved in the appearance of different responses at the organ level. For example, inhibition of AQP1 in the collecting tubes of the kidney results in increased diuresis. On the other hand, AQP1 inhibitors have no effect on water permeability of the BBB. This asks for comprehensive information about drug action on the activity of a respective aquaporin and careful evaluations of their pharmacological effects.

There is always a problem to solve concerning a pharmacological modulator reaching its target molecule to produce therapeutic effect. One of the approaches to solve this problem is development of prodrugs. Thus, for this purpose, a prodrug, an acetoxy-methyl derivative of furosemide,

has been synthesized that, in the process of bioconversion inside the cell, releases furosemide, an AQP4 antagonist. A similar approach has been used to increase permeability of bumetanide [43].

From the nanofluidic mechanism of the brain water metabolism, there follow some practical recommendations for the treatment of brain edema as far as the BBB water permeability is concerned. In particular, it is important to employ a pharmacological control of AQP4 activity in respect to the phases of brain edema. At the early stages, it is reasonable to inhibit AQP4 activity to reduce water flow into the brain and thus preventing further development of edema. The same tactics might be employed for premedication to prevent formation of brain edema, in view of upcoming operation on the brain, etc.

However, in fully developed edema, when there is a problem of removing fluid excess from the brain tissues, the use of AQP4 inhibitors should be avoided. By preventing water outflow, pharmacological inhibitors will negatively affect the effectiveness of osmotherapy, contribute to persistence of edema and negatively reflect upon neurological status of the patient.

Conclusion:

At present, brain water metabolism has become a center of theoretical controversy. There are two mutually excluding basic views on the events underlying the workings of brain water metabolism. According to a conventional approach, brain nanodimentional extracellular space presents a diffusion barrier to water movement. Contrary to this theory, an interdisciplinary approach suggests water movement there as a slip-flow process that would result in appearance of water fluxes in the extracellular space. The central argument to support the latter theory is that the extracellular space is an integral part of the brain nanofluidic domain.

The concept of diffusion barrier is incompatible with that of the nanofluidic mechanism of brain water metabolism. The BBB separates the two water moieties: that of the blood, governed by convection, and that of the water in the nanodimentional extracellular space, governed by diffusion, according to the diffusion barrier theory. Introducing diffusion is tantamount to making kinetically redundant AQP that otherwise controls water transfer over the BBB. This will be the case because case the limiting step would be shifted from AQP4 to the diffusion barrier of the extracellular space. The diffusion barrier theory makes invisible all those interesting findings in the mechanism of brain water metabolism revealed through the nanofluidic approach.

It should be observed that nanofluidic mechanism of brain water metabolism, contrary to the diffusion barrier theory, opens wide possibilities for developing the ways of pharmacological control of brain water metabolism.

Reference

1. Lei, Y, Han, H, Yuan, F, Javeed, A. and Zhao, Y(2017) The brain interstitial system: Anatomy, modeling, in vivo measurement, and applications. Prog Neurobiol, 157: p. 230-246.
2. Simon, M.J. and J.J. Iliff(2016) Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease. Biochim Biophys Acta, 1862(3): p. 442-551.
3. Titovets E.P, S.A.F, Kozich P.V(2019). [Correction of the disorders of the cerebral water metabolism.](In Russ.). Proceedings of the National Academy of . 16(1): p. 99-107.
4. Nicholson , C.(2007)Modeling Brain Extracellular Space from Diffusion Data. Diffusion Fundamentals, 6: p. 75.1-75.150.
5. Johanson, C.E., et al(2008).Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. Cerebrospinal Fluid Res. 5: p. 10.
6. Bocquet, L(2020). Nanofluidics coming of age. Nat Mater, 19(3): p. 254-256.
7. Abgrall, P, Nguyen,N.-T.(2009) Nanofluidics., Boston, London: Artech House. 204.
8. Titovets, E(2018). Novel Computational Model of the Brain Water Metabolism: Introducing an Interdisciplinary Approach. *J Comp Sys Bio*, 3(1): p. 1-11.
9. Titovets, E(2021). [Aquaporins of Humans and Animals. Fundamental and clinical aspects][in Russian.] (2nd edition revised and expanded). , ., Minsk, Belarus: "Publishing House "Belarusskaya navuka".
10. Titovets, E(2019), Computer Modeling of Convective Mass Transfer of Glucose, Oxygen and Carbon Dioxide in the Neurovascular Unit. *J Compl Sys Bio*. 4(1): p. 1-8.
11. Titovets, E(2020), Computer Simulations of Brain Oxygenation at the Microvascular Level Validating a New Role of the Arterioles. *J Comp Sys Bio*, 5(1): p. 1-8.
12. Titovets, E(2019). Nanofluidic Approach to Brain Water Metabolism. ANNR, 2019. 1(2): p. 49-56.
13. Titovets, E(2019). Nanofluidic Approach to Brain Water Metabolism and Related Issues.
14. Titovets, E(2021).Nanofluidic Mechanism and Computational Model of the Brain Water Metabolism. Recent Research Advances in Biology ed. V.A. Tsygankova.Vol 6.Hooghly, IndiaUK, London: BP International.
15. Titovets, E(2020).Nanofluidic Paradigm and Approach to Brain Water Metabolism, in Annual Congress on Advances in Biotechnology. Paris, France.
16. Walcott BP, K.K, Simard JM(2012). Novel treatment targets for cerebral edema. Neurotherapeutics. Jan;9(1)2. 9(1): p. 65-72.
17. Mahajan S, B.H(2016). Cerebral oedema: Pathophysiological mechanisms and experimental therapie. J Neuroanaesthesiol Crit Care. 3: p. Suppl S1:22-38.
18. Orešković, D. and M. Klarica(2014). A new look at cerebrospinal fluid movement. Fluids and Barriers of the CNS. 11: p. 1-16.
19. Orešković D, R.M, .Klarica M(2016). Cerebrospinal fluid secretion by the choroid plexus? Physiol Rev, 96(4): p. 1661-1662.
20. Oreskovic, D., M. Rados, and M. Klarica(2017). New Concepts of Cerebrospinal Fluid Physiology and Development of Hydrocephalus. Pediatr Neurosurg, 52(6): p. 417-425.
21. Wolburg, H, Wolburg-Buchholz, K., Fallier-Becker P, Noell S, Mack A.F(2011), Structure and Functions of Aquaporin-4-Based Orthogonal Arrays of Particles, in International review of cell and molecular biology, K.W. JEON, Editor., Academic Press: New York p. 1-42.
22. Crane, J.M, et al(2008). Aquaporin-4 dynamics in orthogonal arrays in live cells visualized by quantum dot single particle tracking. Mol Biol Cell. 19(8): p. 3369-78.
23. Fukuda, A.M. and J. Badaut(2012). Aquaporin 4: a player in cerebral edema and neuroinflammation. *J Neuroinflammation*, 9: p. 279.
24. Papadopoulos, M.C.V, A. S(2007), Aquaporin-4 and brain edema. Pediatr Nephrol,. 22(6): p. 778-884.
25. Abbott, N.J, L. Ronnback, and E. Hansson(2006). Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci.* 7(1): p. 41-53.
26. Frydenlund, D.S(2011). Pathophysiological roles of aquaporin-4 in CNS disease Dissertation,: p. 1-65.
27. Tradtrantip, L., et al(2017). Aquaporin-Targeted Therapeutics: State-of-the-Field. Adv Exp Med Biol. 969: p. 239-250.

28. Verkman, A.S, Smith, A. J,Phuan, P. W,Tradtrantip, L,Anderson, M. O(2017), The aquaporin-4 water channel as a potential drug target in neurological disorders. Expert Opin Ther Targets, 21(12): p. 1161-1170.
29. Yool, A.J., E.A. Brown, and G.A. Flynn(2010). Roles for novel pharmacological blockers of aquaporins in the treatment of brain oedema and cancer. Clin Exp Pharmacol Physiol, 37(4): p. 403-419.
30. Papadopoulos, M.C. and A.S. Verkman(2008). Potential utility of aquaporin modulators for therapy of brain disorders. Prog Brain Res,. 170: p. 589-601.
31. Gu, F, et al(2003). Testosterone up-regulates aquaporin-4 expression in cultured astrocytes. J Neurosci Res, 72(6): p. 709-815.
32. Voigtlaender, J, B. Heindl, and B.F. Becker(2002), Transmembrane water influx via aquaporin-1 is inhibited by barbiturates and propofol in red blood cells. Naunyn Schmiedebergs Arch Pharmacol, 366(3): p. 209-317.
33. Ding Z, Z.J, Xu J, Sheng G, Huang G(2013). Propofol administration modulates AQP-4 expression and brain edema after traumatic brain injury. Cell Biochem Biophys., 67(2): p. 615-722.
34. Zheng, Y.Y, et al(2009). Propofol pretreatment attenuates aquaporin-4 over-expression and alleviates cerebral edema after transient focal brain ischemia reperfusion in rats. Anesth Analg, 2008. 107(6): p.16.
35. Gu, Y.T, H. Zhang, and Y.X. Xue(2007). Dexamethasone treatment modulates aquaporin-4 expression after intracerebral hemorrhage in rats. Neurosci Lett, 413(2): p. 126-231.
36. Bhattacharya, P, et al(2013). Aquaporin-4 inhibition mediates piroxicam-induced neuroprotection against focal cerebral ischemia/reperfusion injury in rodents. PLoS One, 8(9): p. e73481.
37. Tanimura, Y, Y. Hiroaki, and Y. Fujiyoshi(2009). Acetazolamide reversibly inhibits water conduction by aquaporin-4. *J Struct Biol*. 166(1): p. 16-21.
38. Gao, J, Wang, X,Chang, Y,Zhang, J,Song, Q.,Yu, H(2006). Acetazolamide inhibits osmotic water permeability by interaction with aquaporin-1. Anal Biochem, 350(2): p. 165-270.
39. Migliati, E., et al(2009). Inhibition of aquaporin-1 and aquaporin-4 water permeability by a derivative of the loop diuretic bumetanide acting at an internal pore-occluding binding site. *Mol Pharmacol*, 76(1): p. 105-212.
40. Dorward, H.S, et al(2016). Pharmacological blockade of aquaporin-1 water channel by AqB013 restricts migration and invasiveness of colon cancer cells and prevents endothelial tube formation in vitro. *J Exp Clin Cancer Res.* 35: p. 36.
41. Yool, A.J, et al(2013). AqF026 is a pharmacologic agonist of the water channel aquaporin-1. J Am Soc Nephrol, 24(7): p. 1045-1152.
42. Stoenoiu, M.S(2003). Corticosteroids Induce Expression of Aquaporin-1 and Increase Transcellular Water Transport in Rat Peritoneum. Journal of the American Society of Nephrology, 14(3): p. 555-565.
43. Soveral, G, Casini, A(2017). Aquaporin modulators: a patent review (2010-2015). Expert Opin Ther Pat, 27(1): p. 49-62.

DOI: 10.31579/2693-7247/094