JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

Шолу Мақала / Обзорная Статья / Review Article *DOI: 10.23950/1812-2892-JCMK-00721*

The role of aquaporins in the regulation of body fluids homeostasis

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Received: 2019-12-22
Accepted: 2020-01-03
UDC: 616.1

J Clin Med Kaz 2019; 4(54):15-20

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Abstract

The rapid transfer of the water across the cells occurs via specialized channels called aquaporins (AQPs). The structure of AQPs comprises of homotetramers with each of the four units functioning as an independent channel. The distribution of total body water is into intracellular (40% of total body weight) and extracellular compartments (20% of total body weight). While there is some degree of physical separation of the compartments, water freely moved between them with the intent of achieving homeostasis. The typical role of AQP is to act as an effector in the regulation of water at cellular, tissue and organ levels, although recent evidence suggested it can also act as a sensor-effector system. The regulatory roles include cell volume regulation (CVR), which comprises of regulatory volume decrease and regulatory volume increase. The AQPs are also involved in the total body water homeostasis via short- and long-term regulatory mechanisms. The short-term water regulation takes place within minutes, and it typified by insertion of AQP2 into the apical cell membrane of collecting duct following activation of V2 receptor by vasopressin. The long-term regulation by the AQPs involves increased expression of AQPs. Hence, this narrative reviewed the importance of AQPs in the ability to facilitate highly efficient, yet strictly selective permeation of small molecules including water, solutes, and ions, transport across the plasma membrane as it relates to body fluid homeostasis.

Key words: aquaporins, total body fluids, regulations

АҒЗАНЫҢ БИОЛОГИЯЛЫҚ СҰЙЫҚТЫҚТАРЫНЫҢ ГОМЕОСТАЗЫН РЕТТЕУДЕГІ АКВАПОРИНДЕРДІҢ РӨЛІ

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ТҰЖЫРЫМДАМА

Судың жасушалар арқылы жылдам қозғалуы аквапориндер деп аталатын арнайы арналар арқылы жүреді. Аквапориндердің құрылымы гомотетрамерлерден тұрады, олардың әрқайсысы тәуелсіз канал болып табылады. Денедегі барлық су жасуша ішілік (дене салмағының 40%) және жасушадан тыс бөліктер (дене салмағының 20%) арқылы бөлінеді. Бөлімдердің белгілі бір физикалық бөлінуіне қарамастан, су гомеостаз мақсатында олардың арасында еркін қозғалады.

Аквапориндердің типтік рөлі жасушалық, тіндік және ағзалық деңгейлердегі суды реттеуде эффектор рөлін атқарады, дегенмен, соңғы деректер олардың сенсорлық-эффекторлық жүйе ретінде де әрекет ете алатындығын көрсетеді. Реттеуші функциялар жасуша көлемін реттеуден тұрады және реттеуші көлемнің төмендеуі мен жоғарылауынан тұрады. Аквапориндер сонымен қатар қысқа мерзімді және ұзақ мерзімді реттеу тетіктері арқылы организмдегі судың жалпы гомеостазына қатысады.

Судың қысқа мерзімді реттелуі бірнеше минут ішінде жүреді және рецепторды V2 вазопрессин арқылы жандандырғаннан кейін аквапорин 2-ні жинау түтігінің апикальды жасуша мембранасына шығару арқылы көрінеді. Аквапориндермен ұзақ мерзімді реттелу аквапориндердің жоғары экспрессиясын қамтиды. Осылайша, осы зерттеуде аквапориндердің дене сұйықтықтарының гомеостазына қатысты плазмалық мембрана арқылы кішкене молекулалардың, соның ішінде судың, еріген заттар мен иондардың жоғары тиімді, бірақ қатаң таңдамалы енуіне ықпал ету қабілеттілігінің маңызы қарастырылады.

Негізгі сөздер: аквапориндер, ағзадағы сұйықтықтың жалпы көлемі, реттеу

РОЛЬ АКВАПОРИНОВ В РЕГУЛЯЦИИ ГОМЕОСТАЗА БИОЛОГИЧЕСКИХ ЖИДКОСТЕЙ ОРГАНИЗМА
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РЕЗЮМЕ

Быстрое перемещение воды по клеткам происходит через специальные каналы, называемые аквапоринами. Структура аквапоринов состоит из гомотетрамеров, каждый из которых является независимым каналом. Распределение всей воды в организме происходит по внутриклеточным (40% от общей массы тела) и внеклеточным компартментам (20% от общей массы тела). Несмотря на некоторую степень физического разделения компартментов, вода свободно перемещается между ними с целью гомеостаза. Типичная роль аквапоринов заключается в том, чтобы действовать в качестве эффектора в регуляции воды на клеточном, тканевом и органном уровнях, хотя последние данные свидетельствуют о том, что они также могут действовать как сенсорно-эффекторная система. Регуляторные функции состоят в регуляции объема клеток и включают в себя уменьшение и увеличение регуляторного объема. Аквапорины также участвуют в общем гомеостазе воды в организме посредством краткосрочных и долгосрочных регуляторных механизмов. Кратковременная регуляция воды происходит в течение нескольких минут, и выражается путем введения аквапорина 2 в апикальную клеточную мембрану собирающего протока после активации рецептора V2 вазопрессином. Долгосрочная регуляция аквапоринами включает повышенную экспрессию аквапоринов. Таким образом, в данном исследовании рассматривается важное значение аквапоринов в способности содействовать высокоэффективному, но строго избирательному проникновению малых молекул, включая воду, растворенные вещества и ионы, через плазматическую мембрану применительно к гомеостазу биологических жидкостей организма.

Ключевые слова: аквапорины, общий объем жидкости в организме, регуляция

Introduction

The most abundant molecules in all living creatures, including human, is water. Water constitutes about 55-65% of total body weight in an adult and is found predominantly inside the cells. Through movement in and out of the cells, water plays critical roles in the cells, tissue and whole body homeostasis [1]. While the movement of the water across the cell membrane can occur slowly by simple diffusion, fast movement occurs via specialized channels in some specific cells [2–4]. The specialized cells are known as aquaporins (AQPs), a word coined from two Latin words: aqua (water) and porus (passage) [5]. The AQPs are transmembrane proteins that have a specific three-dimensional structure with a pore that provides a pathway for water permeation across biological membranes and can increase water permeability by 10-100 folds [5–7]. There are several homologous that have been identified (over 450 in all kingdoms of life), however, only 13 AQPs have been found in the humans, which are involved in cellular regulatory processes through movements of solutes, water, and ions [8,9].

Hence, this narrative reviewed the importance of AQPs in the ability to facilitate highly efficient selective permeation of water across the plasma membrane as it relates to body fluid homeostasis.

Aquaporins: structure

The AQPs belong to the membrane intrinsic proteins (MIPs) superfamily with molecular masses between 28 and 30 kDa [7,10]. The hydropathy analysis of amino acids sequence of AQPs revealed residues that range from 270 to 290 [11]. The typical structure of AQP is depicted with an “hour-glass model” with AQP1 as a prototype. The AQP1 is made up of a single chain polypeptide chain with about 270 amino acids that have terminal amino and carboxyl groups located in the cell cytoplasm [12]. The proteins form six transmembrane domains (TMDs) that are highly hydrophobic and have an α-helix structure with five connecting loops (Figure 1) [13]. The α-helices are named from the N-end successively H1, H2, H3, H4, H5, and H6, and the loops are named A, B, C, D, and E (Figure 1). The TMDs and the loops form a core (embedded in the membrane lipid bilayer), to which two ‘‘legs’’ (represented by the cytosolic N- and C-ends) are attached. Present within the loops is two highly conserved sequence motifs-asparagine-proline-alanine (NPA) with short helix (B and E) located on opposite sides of the monomer [12]. The loops are folded into the lipid bilayer

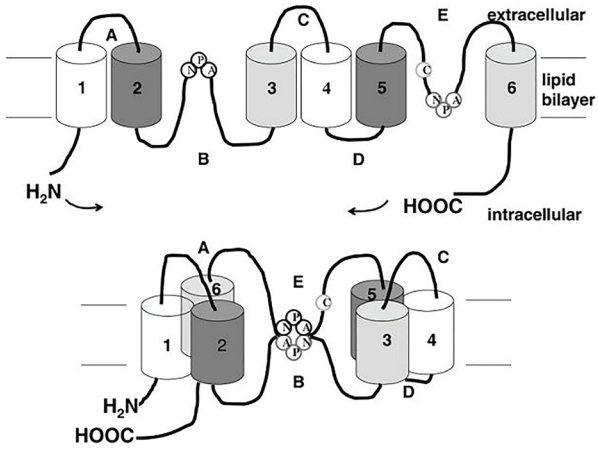

Figure 1. Structure of Aquaporin-[13]

and surrounded by transmembrane domains where they form a hydrophilic path for the water transfer through the lipid bilayer [14,15].

Aquaporins: mechanism of action

The mechanism of vasopressin mediated increase water reabsorption of AQP2 remained one of the best studied. This mechanism is activated when vasopressin binds to its receptor located on the basolateral membrane of collecting duct principal cells, which initiates a cascade of events that results in the insertion of aquaporin-2 (AQP2) into the apical plasma membrane [16]. The steps involved stimulation of adenylate cyclase (AC) by the heterotrimeric G protein (Gs) and an increase in intracellular cAMP. AQP2 located on intracellular vesicles is phosphorylated at serine-256 by protein kinase A (PKA), and the vesicles move toward the plasma membrane, with which they ultimately fuse by exocytosis, thus inserting AQP2 into the membrane [17]. The AQPs allow faster flow of water along its concentration gradient at a rate of approximately $3x10^9$ water molecules per subunit per second, which is considerably faster than that any other channels [18]. Besides, the AQPs also transport the water molecule via facilitated diffusion at low activation energy (Ea<5 Kcal/mol) compared to conventional diffusion that is slow and used activation energy that ranged between 10-20 Kcal/mol [19].

Body fluid compartments

The human beings are mostly water, ranging from about 75 to 80 percent of body mass in infants to about 50 to 60 percent in adult males and females, and 45 percent in the elderly [20]. The total body water occupies three main locations within the body, referred to as fluid compartments [21]. The fluid compartments are separated by a semi-permeable plasma membrane that provides physical barriers but still allows movements of fluids between the compartments. The physical barriers allow the fluids to be in constant motion from one compartment to another, although the volume of fluid in each compartment remains relatively stable.

About two-thirds of body fluid is located in within the cells referred to as intracellular fluid (ICF) compartment while the remainder fluids are located outside the cells [extracellular fluid (ECF) compartment] [22]. The third compartment is a small compartment of fluids referred to as transcellular fluid compartment [22].

Role of aquaporins in body water homeostasis

The survival of each cell in the human system depends on the provision of optimal environments through homeostasis [23,24]. The role AQPs in body fluid homeostasis depends on the location and type of AQPs. While AQP1, AQP2, AQP3, AQP4, AQP5, and AQP8 are involved in water regulations in various parts of the body, AQP7 and AQP9 are involved primarily in glycerol metabolism with little or no role in the body fluid homeostasis [25,26]. The details functions of both AQP11 and AQP12 are yet to be fully known although recent evidence suggested that AQP11 may play a role in water homeostasis in the kidney tubules and adipocytes [27,28]. AQPs functions more as an effector in the water homeostasis at the cellular level and as part of the regulation of total body fluids [6,23,26]. The recent studies suggested that besides the AQPs being primarily effectors, they can also act as sensor-effector to changes in the external environment [26].

The mechanisms of AQPs acting as a sensor depends on change in ionic or receptor potential or tonicity around the AQPs [26]. Kitchen and colleagues found that hypotonicity induced rapid translocation of AQP5 to membrane (HEK293) that was not dependent on phosphorylation of Ser156 of loop or activation of Protein Kinase A [29].

The roles of AQPs in the body fluid homeostasis ranges from cell volume regulation to total body fluid regulations. The regulation of cell volume involves regulatory volume decrease (RVD), usually in response to hypotonicity-induced cell swelling, and regulatory volume increase (RVI), usually in response to hypertonicity induced cell shrinkage [26,30,31]. The exact details molecular mechanism underlying RVD in response to hypotonicity is yet to be fully elucidated, but it revolves around K+ channels activation.

The activator of the K+ channels also varies among different cell types. For examples, the K+ channels are activated by intracellular Ca2+ in the human cervical cancer, while in the trigeminal ganglion neurons, it is activated by cytochalasin D (an actin polymerization inhibitor) [32,33]. The activation of K+ channels allows K+ efflux from the cell, which is followed by water loss [32]. The water loss occurs either through AQPs or directly through the lipid bilayer [32,34]. The evidence in support of the role of the AQP in RVD was the observation that AQP5 knockout cells subjected to hypotonicity do not induce calcium-mediated K+ efflux and no RVD [35].

The molecular mechanisms that underlying regulatory volume increase (RVI) are also not fully elucidated but activation of Na+-H+ exchangers and Na+-K+-2Cl− co-transporters (NKCCs) causes a cellular influx of Na+ and subsequent volume increase by an osmotic movement of water. The Na+-H+ exchange pump is known to be activated by cell shrinkage [36]. The co-transporter, NKCC1, is known to be activated by cell shrinkage, potentially through lysine-deficient protein kinase 1 (WNK1) and a proline/alanine-rich protein kinase (SPAK) signaling [36]. Although, almost all human cells can internally regulate cell volume via RVD and RVI when exposed to osmolar stress, continue fluctuation in the internal environments poses challenges to the adaptive mechanisms [36].

Besides the CVR, aquaporins roles in homeostasis of total body water involves the short-term and long-term regulation mechanisms [37]. The short term regulation takes place in minutes and is exemplified by the acute effect of vasopressin causing water reabsorption by changing the osmotic permeability of the kidney collecting duct with the intent of restoring the body fluid volume [37]. On the other hand, the long-term regulation refers to the adaptational changes that occur over periods of hours to days, changes which are also dependent to some extent on aquaporins [37].

In the kidney, AQP1 expressed in the thin descending limb allows a rapid osmotically driven exit of water from the lumen, hence, concentrating the luminal fluid, which is vital in the countercurrent mechanism [23]. Also, AQP2 stored in the intracellular vesicular compartment of principal cells of the collecting duct upon ADH stimulation moves rapidly to the apical membrane, where it acts as channels for increase reabsorption of water [23,38]. Study also revealed that AQP2 could be regulated independent of vasopressin, usually in response to hypertonic conditions [39]. Hypertonic exposure (600 mOsM/kg) was shown to significantly increase the activity of the AQP2 promoter, independent of vasopressin, in Madin-Darby canine kidney (MDCK) cells expressing murine AQP2 [39].

The AQP3, constitutively localized to the basolateral plasma membrane of collecting duct principal cells, tubule cells, and inner medullary collecting duct cells, and it provides an exit route for the water that enters across the apical plasma membrane through AQP2 [16]. Like AQP2, its abundance is regulated in hours to days by vasopressin through changes in its messenger RNA (mRNA) levels. The AQP4 also localized at the basolateral membrane (BLM) of the principal cells of CDs serves as a channel for the exit of water from BLM for the concentration of urine [40]. AQP3/APQ4 double knockout mice show more significant impairment of urine-concentrating ability than AQP3 single knockout mice [41].

The long-term adaptational changes in body water balance occur in part by regulated changes in AQP2 and AQP3 expression levels within the cell [38]. The changes in expression occur over hours to days. The increase in AQP2 and AQP3 expression levels are induced by ADH that triggers increase gene transcriptions of the two AQPs, leading to more being synthesized [23].

The human AQPs also play roles in the water regulation of the various systems in the body and abnormality in several members of the AQPs have been implicated in the pathophysiology of water-related disorders [29]. As the main AQP of the central nervous system, AQP4 plays a major role in the regulation of water flow in the brain, spinal cord and interstitial fluid surrounding neurons [42]. In support of this role, when AQP4 was silenced in astrocytes by RNA interference, the apparent diffusion coefficient decreased by 50% in rat brain [42].

Low AQP4 expression levels found in some epileptic seizures linked with AQP4 mediated regulation of extracellular K+ [43–45]. AQP4 has also been associated with the pathophysiology of brain oedema [45]. Movement of water from the blood across endothelia into astrocytes is mediated by AQP4 channels as reduced cytotoxic oedema occurred in AQP4 −/−mice [46]. Besides its localisation in the astrocytes, AQP4 are present in the retina, the olfactory epithelium and within Claudius' and Henson's cells of the inner ear [47]. AQP4 null mice are completely deaf with no alterations to the morphology of the inner ear [47]. AQP1 is found in the microvascular endothelia and reactive astrocytes of brain tumours and thought to play a role in the development of vasogenic oedema [48,49].

In the renal system, AQP2 dysfunction exemplifies the critical role of this mechanism in the control of water reabsorption in nephrogenic diabetes insipidus [16]. In this disease, mutations in the vasopressin 2 receptor or in AQP2 itself lead to impair water reabsorption. Besides, study demonstrated that the diuretic effect of acetazolamide involves triggered AQP1 translocation [50].

The main AQP of the cardiovascular system is AQP1 which probably regulates water permeability of the heart's capillary networks by mediating the flow of water through the endothelial layer into the blood. AQP1 is believed to be responsible for absorption of excess water from the interstitial space into the capillaries [51]. AQP4 recently detected at the protein level within human cardiac myocytes and required further research regarding its roles in the heart [52].

The AQP5 and AQP1 are the main routes for transcellular water flow in the airway [53]. The primary role of AQP5 being water transport across the apical plasma membrane of type I alveolar epithelial cells while AQP1 mediate water flow in the endothelia of the airways [54]. This movement of water between the capillary and alveolar airspace is essential for airway hydration, effective airways defences and reabsorption of excess alveolar fluid [26].

The AQPs also play role in the reproductive system as demonstrated by McConnell and colleagues that water movement into the antrum of isolated rat follicles was 3.5-fold higher than that of C-inulin [55]. When the follicles were pre-treated with HgCl2 (an AQP inhibitor), the movement of water reduced to that of inulin. This study suggested a role for AQPs in mediating water movement during folliculogenesis, and recently AQP7, AQP8 and AQP9 have been detected in the granulosa cells [56]. There is increasing evidence that shows AQPs play an essential role in sperm cell RVD, which ensures the maintenance of the structure and function of sperm [57]. AQP3 is present at the plasma membrane of the sperm flagellum. AQP3 mutant cells showed reduce motility, swelling and tail bending after entering the hypotonic uterus; therefore hindering the sperm's chances of reaching the oviduct and mediating a fertilisation event [56].

The digestive system is an important site of fluid movement and has an extensive AQP expression profile within its organ network [58]. In the digestive tract, AQP3 is expressed abundantly from stratified epithelia of the oral cavity up to the stomach. AQP3 is present in the basal and intermediate cell membrane becoming less abundant towards the epithelial surface and is thought to supply of water from the sub-epithelial side of these cells which face harsh environment, such as the low pH of the stomach, and prevent them from dehydration [58]. AQP3 is also present in the distal colon and rectum (basolateral membrane of the epithelial cells lining the lumen). Inhibition of AQP3 by HgCl2 in rats causes severe diarrhoea, suggesting a role for AQP3 in regulating faecal water content [59].

AQP1 and AQP4 are present in skeletal muscle and study showed that cell volume changes that occur during muscle contraction rely on rapid water influx [60,61]. The localisation of AQP1 and AQP4 within the muscle tissue suggests a pathway for transcellular water flow through the endothelial cell membrane and the sarcolemma and the two AQPs may function together as transporters for water between the blood and myofibrils during mechanical muscle activity [26].

The skin plays an integral part in water homeostasis by providing barrier function against excessive water loss [24]. Its water and glycerol content is essential for a healthy skin function which is mainly under the control of AQP3 [62]. The AQP3 is expressed mainly in the plasma membranes of the stratum basale of the epidermis, with decreasing expression towards the stratum granulosum and none in the stratum corneum. AQP5 is also found in the plasma membrane of the stratum granulosum and may play a role in transcellular water homeostasis in the skin [63].

The specialised secretory tissues rely on AQP-dependent transcellular water flow to facilitate their fluid homeostasis. In the salivary gland, AQP5 facilitates transcellular water flow in both acinar and parotid salivary cells [64]. The salivary cells isolated from AQP5 −/− mice had dramatically reduced membrane water permeability following exposure to hypertonic or hypotonic conditions [63]. AQP5 is involved in regulating transcellular water flow in the luminal regions of eccrine sweat glands where it facilitates the formation of secretions at the necessary concentrations and viscosities required to maintain water homeostasis [26].

Conclusion

The discovery of aquaporins has solved the myriad surrounding the transcellular transfer of water. The aquaporins provide pores for the rapid transfer of water, and other uncharged solutes across diverse cell membranes that are critical components of water homeostasis at cellular levels (cell volume regulation), tissues/organs and body as a whole.

The aquaporins carried out these roles predominantly as the effector but at times as effector-sensor part of the body homeostasis. The understanding of some of the physiological roles of aquaporins in body fluid homeostasis has provided insights into pathophysiology that ensure from various diseases processes in the body where there is associated abnormality in water homeostasis. Thus, aquaporins are potential therapeutic target that may address various clinical conditions.

Acknowledgement

The authors appreciate the kind permission of Prof. Peter Agre to use the Figure in this manuscript.

Disclosures: There is no conflict of interest for all authors.

References

1. Verbalis J. Disorders of body water homeostasis. *Best Pract Res Clin Endocrinol Metab.* 2003; 17(4):471-503. https://doi.org/10.1016/S1521-690X(03)00049-6
2. Pohl P. Combined transport of water and ions through membrane channels. *Biol Chem*. 2004; 385(10):921-926. https://doi.org/10.1515/BC.2004.120
3. Fanning AS, Mitic LL, Anderson JM. Transmembrane proteins in the tight junction barrier. *J Am Soc Nephrol.* 1999; 10(6):1337-1345.
4. Goodman BE. Transport of small molecules across cell membranes: water channels and urea transporters. *Adv Physiol Educ.* 2002; 26(3):146-157. https://doi.org/10.1152/advan.00027.2002
5. Benga G. Water channel proteins (later called aquaporins) and relatives: Past, present, and future. *IUBMB Life.* 2009; 61(2):112-133. https://doi.org/10.1002/iub.156
6. Agre P, King LS, Yasui M, Guggino WB, Ottersen OP, Fujiyoshi Y, et al. Aquaporin water channels – from atomic structure to clinical medicine. *J Physiol.* 2002; 542:3-16. https://doi.org/10.1113/jphysiol.2002.020818
7. Benga G. On the definition, nomenclature and classification of water channel proteins (aquaporins and relatives). *Mol Aspects Med.* 2012; 33(5-6):514-517. https://doi.org/10.1016/j.mam.2012.04.003
8. Tanghe A, Van Dijck P, Thevelein JM. Why do microorganisms have aquaporins? *Trends Microbiol.* 2006; 14(2):78-85. https://doi.org/10.1016/j.tim.2005.12.001
9. Benga G. Aquaporinology. *Acta Endocrinol.* 2014; 1(1):1-8. https://doi.org/10.4183/aeb.2014.1
10. Nordén K. From Sequence to Structure: Characterizing Human and Plant Aquaporins. Department of Chemistry, Lund University; 2012.
11. King LS, Kozono D, Agre P. From structure to disease: the evolving tale of aquaporin biology. *Nat Rev Mol Cell Biol.* 2004; 5(9):687-698. https://doi.org/10.1038/nrm1469
12. Walz T, Hirai T, Murata K, Heymann JB, Mitsuoka K, Fujiyoshi Y, et al. The three-dimensional structure of aquaporin-1. *Nature.* 1997; 387(6633):624-627. https://doi.org/10.1038/42512
13. Borgnia M, Nielsen S, Engel A, Agre P. Cellular and molecular biology of the aquaporin water channesls. *Annu Rev Biochem.* 1999; 68:425-458. https://doi.org/10.1146/annurev.biochem.68.1.425
14. Gonen T, Walz T. The structure of aquaporins. Quartely Rev Biophys. 2006; 39(4):361-396. https://doi.org/10.1017/S0033583506004458
15. Ho JD, Yeh R, Sandstrom A, Chorny I, Harries WEC, Robbins RA, et al. Crystal structure of human aquaporin 4 at 1 . 8 Å and its mechanism of conductance. *PNAS*. 2009; 106(18):7437-7442. https://doi.org/10.1073/pnas.0902725106
16. Agarwal SK, Gupta A. Aquaporins : The renal water channels. *Indian J Nephrol.* 2010; 18(3):95-100. https://doi.org/10.4103/0971-4065.43687
17. Brown D, Katsura T, Gustafson CE. Cellular mechanisms of aquaporin trafficking. *Am J Physiol.* 1998; 275(3 Pt 2):F328-31. https://doi.org/10.1152/ajprenal.1998.275.3.F328
18. Gravelle S, Joly L, Detcheverry F, Ybert C, Cottin-Bizonne C, Bocquet L. Optimizing water permeability through the hourglass shape of aquaporins. Proc Natl Acad Sci U S A. 2013; 110(41):16367-1672. https://doi.org/10.1073/pnas.1306447110
19. De Groot BL, Hub JS, Grubmüller H. Dynamics and energetics of permeation through aquaporins. What Do we learn from molecular dynamics simulations? Handb Exp Pharmacol. 2009; 190:57-76. https://doi.org/10.1007/978-3-540-79885-9_3
20. Linda S C. *BRS Physiology.* 5th ed. Philadelphia,: Lippincott Williams & Wilkins; 2011.
21. Bianchetti MG, Simonetti GD, Bettinelli A. Body fluids and salt metabolism - Part I. *Ital J Pediatr.* 2009; 35(1):36. https://doi.org/10.1186/1824-7288-35-36
22. Sembulingam K, Sembuligan P. *Essential of Medical Physiology*. 6th ed. India: Jaypee Brothers Medical Publishers (P) Ltd; 2012.
23. Knepper MA, Kwon T, Nielsen S, Knepper, Mark A; Kwon, Tae-Hwan; Nielsen S. Molecular Physiology of Water Balance. N Engl J Med. 2015; 372(14):1349-1358. https://doi.org/10.1056/NEJMra1404726
24. Modell H, Cliff W, Michael J, McFarland J, Wenderoth MP, Wright A. A physiologist's view of homeostasis. *Adv Physiol Educ.* 2015; 39(4):259-266. https://doi.org/10.1152/advan.00107.2015
25. Lebeck J. Metabolic impact of the glycerol channels AQP7 and AQP9 in adipose tissue and liver. *J Mol Endocrinol.* 2014; 52(2). https://doi.org/10.1530/JME-13-0268
26. Day RE, Kitchen P, Owen DS, Bland C, Marshall L, Conner AC, et al. Biochimica et Biophysica Acta Human aquaporins : Regulators of transcellular water flow. *Biochim Biophys Acta.* 2014; 1840(5):1492-1506. https://doi.org/10.1016/j.bbagen.2013.09.033
27. Okada S, Misaka T, Tanaka Y, Matsumoto I, Ishibashi K, Sasaki S, et al. Aquaporin-11 knockout mice and polycystic kidney disease animals share a common mechanism of cyst formation. *FASEB J.* 2008; 22(10):3672-3684. https://doi.org/10.1096/fj.08-111872
28. Madeira A, Fernández-Veledo S, Camps M, Zorzano A, Moura TF, Ceperuelo-Mallafré V, et al. Human Aquaporin-11 is a water and glycerol channel and localizes in the vicinity of lipid droplets in human adipocytes. *Obesity.* 2014; 22(9):2010-2017. https://doi.org/10.1002/oby.20792
29. Kitchen P, Öberg F, Sjöhamn J, Hedfalk K, Bill RM, Conner C, et al. Plasma membrane abundance of human aquaporin 5 is dynamically regulated by multiple pathways. PLoS One. 2015; 10(11):1-17. https://doi.org/10.1371/journal.pone.0143027
30. Ishibashi K, Kondo S, Hara S, Morishita Y. The evolutionary aspects of aquaporin family. *Am J Physiol Regul Integr Comp Physiol.* 2011; 300(3):R566-R576. https://doi.org/10.1152/ajpregu.90464.2008
31. Danziger J, Zeidel ML. Osmotic homeostasis. *Clin J Am Soc Nephrol.* 2015; 10(5):852-862. https://doi.org/10.2215/CJN.10741013
32. Shen MR, Chou CY, Browning JA, Wilkins RJ, Ellory JC. Human cervical cancer cells use Ca2+ signalling, protein tyrosine phosphorylation and MAP kinase in regulatory volume decrease. *J Physiol.* 2001; 537(Pt 2):347-362. https://doi.org/10.1111/j.1469-7793.2001.00347.x
33. Piao L, Li HY, Park C. Mechanosensitivity of voltage-gated K+ currents in rat trigeminal ganglion neurons. *J Neurosci Res.* 2006; 1380:1373-1380. https://doi.org/10.1002/jnr
34. Heo J, Meng F, Hua SZ. Contribution of aquaporins to cellular water transport observed by a microfluidic cell volume sensor. *Anal Chem.* 2008; 80(18):6974-6980. https://doi.org/10.1021/ac8008498
35. Liu X, Bandyopadhyay B, Nakamoto T, Singh B, Liedtke W, Melvin JE, et al. A role for AQP5 in activation of TRPV4 by hypotonicity:

Concerted involvement of AQP5 and TRPV4 in regulation of cell volume recovery. *J Biol Chem*. 2006; 281(22):15485-15495. https://doi.org/10.1074/jbc.M600549200
36. Jentsch TJ. VRACs and other ion channels and transporters in the regulation of cell volume and beyond. *Nat Rev Mol Cell Biol.* 2016; 17(5):293-307. https://doi.org/10.1038/nrm.2016.29
37. Nielsen S. Renal aquaporins : an overview. *BJU Int.* 2002; 90:2-7. https://doi.org/10.1046/j.1464-410X.90.s3.1.x
38. Park E, Kwon T, Ph D. A Minireview on Vasopressin-regulated Aquaporin-2 in Kidney Collecting Duct Cells. *Electrolyte Blood Press.* 2015; 13:1-6. https://doi.org/10.5049/EBP.2015.13.1.1
39. Kasono K, Saito T, Saito T, Tamemoto H, Yanagidate C, Uchida S, et al. Hypertonicity regulates the aquaporin-2 promoter independently of arginine vasopressin. *Nephrol Dial Transplant.* 2005; 20(3):509-515. https://doi.org/10.1093/ndt/gfh677
40. Matsuzaki T, Yaquchi T, Schimizu K, Kita A, Ishibashi K, Takata K, et al. The distribution and function of aquaporins in the kidney: resolved and unresolved questions. *Anat Sci Int.* 2016; 1-13. https://doi.org/10.1007/s12565-016-0325-2
41. Verkman AS. Lessons on Renal Physiology from Transgenic Mice Lacking Aquaporin Water Channels. 1999; (12):1126-1135.
42. Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. *Nat Rev Neurosci.* 2013; 14(4):265-277. https://doi.org/10.1038/nrn3468
43. Badaut J, Lasbennes F, Magistretti PJ, Regli L. Aquaporins in brain: distribution, physiology, and pathophysiology. J *Cereb Blood Flow Metab.* 2002; 22(4):367-378. https://doi.org/10.1097/00004647-200204000-00001
44. Verkman AS, Binder DK, Bloch O, Auguste K, Papadopoulos MC. Three distinct roles of aquaporin-4 in brain function revealed by knockout mice. *Biochim Biophys Acta - Biomembr.* 2006; 1758(8):1085-1093. https://doi.org/10.1016/j.bbamem.2006.02.018
45. Zador Z, Stiver S, Wang V, Manley GT. Aquaporins. *Handb Exp Pharmacol.* 2009; 190(190):159-170. https://doi.org/10.1007/978-3-540-79885-9
46. Papadopoulos MC, Verkman AS. Aquaporin-4 and brain edema. *Pediatr Nephrol*. 2007; 22(6):778-784. https://doi.org/10.1007/s00467-006-0411-0
47. Beitz E, Zenner HP, Schultz JE. Aquaporin-mediated fluid regulation in the inner ear. *Cell Mol Neurobiol.* 2003; 23(3):315-329. https://doi.org/10.1023/A:1023636620721
48. Verkman AS. More than just water channels: unexpected cellular roles of aquaporins. *J Cell Sci.* 2005; 118:3225-3232. https://doi.org/10.1242/jcs.02519
49. Oshio K, Watanabe H, Song Y, Verkman AS, Manley GT. Reduced cerebrospinal fluid production and intracranial pressure in mice lacking choroid plexus water channel Aquaporin-1. *FASEB J*. 2005; 19(1):76-78. https://doi.org/10.1096/fj.04-1711fje
50. Vilas G, Krishnan D, Kumar S, Malhotra D, Margolis B. Increased water flux induced by an aquaporin-1 / carbonic anhydrase II interaction. *Mol Biol Cell.* 2015; 26:1106-1118. https://doi.org/10.1091/mbc.E14-03-0812
51. Egan JR, Butler TL, Au CG, Tan YM, North KN, Winlaw DS. Myocardial water handling and the role of aquaporins. *Biochim Biophys Acta - Biomembr.* 2006; 1758(8):1043-1052. https://doi.org/10.1016/j.bbamem.2006.05.021
52. Frias T, Duarte R. Aquaporins in physiology and pathology. *TRENDS Sport Sci.* 2014; 3(21):135-144.
53. Fronius M, Clauss WG, Althaus M. Why do we have to move fluid to be able to breathe? *Front Physiol.* 2012; 3(146):1-9. https://doi.org/10.3389/fphys.2012.00146
54. Verkman a. S. Aquaporins in Clinical Medicine. *Annu Rev Med.* 2012; 63(1):303-316. https://doi.org/10.1146/annurev-med-043010-193843
55. McConnell NA, Yunus RS, Gross SA, Bost KL, Clemens MG, Hughes FM. Water permeability of an ovarian antral follicle is predominantly transcellular and mediated by aquaporins. *Endocrinology.* 2002; 143(8):2905-2912. https://doi.org/10.1210/en.143.8.2905
56. Huang HF, He RH, Sun CC, Zhang Y, Meng QX, Ma YY. Function of aquaporins in female and male reproductive systems. *Hum Reprod Updat.* 2006 ;12(6):785-795. https://doi.org/dml035 [pii]\r10.1093/humupd/dml035
57. Yeung C-H. Aquaporins in spermatozoa and testicular germ cells: identification and potential role. *Asian J Androl.* 2010; 12(4):490-499. https://doi.org/10.1038/aja.2010.40
58. Laforenza U. Water channel proteins in the gastrointestinal tract. *Mol Aspects Med*. 2012; 33(5-6):642-650. https://doi.org/10.1016/j.mam.2012.03.001
59. Verkman AS. Aquaporins : translating bench research to human disease. *J Exp Biol.* 2009; 212:1707-1715. https://doi.org/10.1242/jeb.024125
60. Mobasheri A, Marples D. Expression of the AQP-1 water channel in normal human tissues: a semiquantitative study using tissue microarray technology. *Am J Physiol Cell Physiol.* 2004; 286(3):C529-C537. https://doi.org/10.1152/ajpcell.00408.2003
61. Mobasheri A, Marples D, Young IS, Floyd R V., Moskaluk CA, Frigeri A. Distribution of the AQP4 water channel in normal human tissues: Protein and tissue microarrays reveal expression in several new anatomical locations, including the prostate gland and seminal vesicles. *Channels.* 2007; 1(1):29-38. https://doi.org/10.4161/chan.3735
62. Boury-Jamot M, Sougrat R, Tailhardat M, Varlet B Le, Bont?? F, Dumas M, et al. Expression and function of aquaporins in human skin: Is aquaporin-3 just a glycerol transporter? *Biochim Biophys Acta - Biomembr.* 2006; 1758(8):1034-1042. https://doi.org/10.1016/j.bbamem.2006.06.013
63. Verkman AS. Mammalian aquaporins: diverse physiological roles and potential clinical significance. *Expert Rev Mol Med.* 2008; 10:e13. https://doi.org/10.1017/S1462399408000690
64. Gresz V, Kwon TH, Hurley PT, Varga G, Zelles T, Nielsen S, et al. Identification and localization of aquaporin water channels in human salivary glands. *Am J Physiol Gastrointest Liver Physiol.* 2001; 281(1):G247-G254. https://doi.org/10.1152/ajpgi.2001.281.1.G247

How to cite this article: Olayinka Rasheed Ibrahim, Olufemi Soladoye. The role of aquaporins in the regulation of body fluids homeostasis. J Clin Med Kaz. 2019; 4(54):15-20