REVIEWS

Adv Clin Exp Med 2011, **20**, 2, 217–220
ISSN 1230-025X

Edyta Gołembiewska, Joanna Kabat-Koperska, Kazimierz Ciechanowski

Aquaporin-1 – New Perspectives in Peritoneal Dialysis

Akwaporyna 1 – nowe perspektywy w dializie otrzewnowej

Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland

Abstract

Peritoneal dialysis is an important method of renal replacement therapy for patients with end-stage renal disease. The rate of fluid removal from the patient, i.e. ultrafiltration, depends on the concentration of the osmotic agent (most often glucose) in the dialysate. According to the „three-pore model" of peritoneal transport, ultrasmall pores (aquaporins) are water-specific, and during a hypertonic dwell they can contribute up to 50% of the total ultrafiltration. Experimental studies on animal models have demonstrated the role of aquaporin-1 in water transport and its regulation by hyperosmolality, and have proved the influence of corticosteroid administration on aquaporin-1 function. Experimental studies have also demonstrated other aquaporin-1 properties, such as its role in cell migration, wound healing and tumor growth, and suggested that aquaporin-1 may play a role in leukocyte recruitment during peritonitis. Future studies in peritoneal dialysis patients should assess the influence of aquaporin-1 gene polymorphism on the variability of free water transport and the course of peritonitis (**Adv Clin Exp Med 2011, 20, 2, 217–220**).

Key words: aquaporin-1, free water transport, ultrafiltration, peritonitis.

Streszczenie

Dializa otrzewnowa jest ważną metodą leczenia nerkozastępczego u pacjentów ze schyłkową niewydolnością nerek. Usuwanie nadmiaru płynu z organizmu, tj. ultrafiltracja, zależy od stężenia związku osmotycznie czynnego w dializacie (najczęściej glukozy). Zgodnie z „trójporowym modelem" błony otrzewnowej pory ultramałe (akwaporyny) transportują tylko wodę, a podczas wymiany z płynem hipertonicznym transportowana przez nie woda może stanowić nawet 50% całkowitej ultrafiltracji. Badania doświadczalne na modelach zwierzęcych wykazały rolę akwaporyny 1 w transporcie wody i jego regulację w hiperosmolalnym środowisku. Potwierdziły również wpływ podaży glikokortykosteroidów na funkcję kanałów akwaporynowych. Badania doświadczalne wykazały również inne właściwości akwaporyny 1, takie jak rola w migracji komórek, gojeniu ran i wzroście guzów nowotworowych. Sugerują one również, że akwaporyna 1 może odgrywać rolę w regulacji napływu leukocytów podczas zapalenia otrzewnej. Przyszłe badania u pacjentów dializowanych otrzewnowo powinny ocenić wpływ polimorfizmu genowego akwaporyny 1 na zmienność wielkości transportu wolnej wody i przebieg dializacyjnego zapalenia otrzewnej (**Adv Clin Exp Med 2011, 20, 2, 217–220**).

Słowa kluczowe: akwaporyna 1, transport wolnej wody, ultrafiltracja, zapalenie otrzewnej.

Peritoneal dialysis (PD) is an important method of renal replacement therapy for patients with ESRD (end-stage renal disease) and is used by approximately 15% of the total number of patients on dialysis worldwide [1]. After the implementation of a catheter in the peritoneal cavity, the removal of fluid excess and uremic toxins is performed continuously through frequent exchanges of the infused dialysate. The dialysate (which contains physiological concentrations of sodium, chloride, calcium, magnesium and a buffer) remains in the peritoneal cavity for several hours and then is drained out. The solutes and water move between the blood and the dialysate through the peritoneal membrane.

The "Three-Pore Model" of Peritoneal Transport and Peritoneal Dialysis

Anatomically, the peritoneal membrane (PM) consists of three main components: the capillary wall, the interstitium (mainly a mucopolysaccha-

ride matrix and collagen fibers) and the mesothelium. The transport of solutes is predominantly diffusive and the rate at which it occurs depends on their concentration gradient. Fluid removal from the patient, i.e. ultrafiltration (UF), depends on the concentration of osmotic agent in the dialysate – most often glucose, used at concentrations of 1.36%, 2.27% or 3.86%. Transport during PD is best explained by the "three-pore model", based on computer simulations and proposed by Rippe [2]. According to this model, the most important transport barrier of the peritoneal membrane is the capillary wall, which contains three different types of pores. „Small pores" are probably the clefts located between endothelial cells, with a radius ranging from 40 to 50 Å. They are responsible for the diffusion of small-molecule substances such as urea, creatinine and glucose. "Large pores" (with a radius of around 250 Å) correspond to the interendothelial gaps and represent less than 0.01% of the total number of pores. They participate in the transport of large molecules such as proteins and immunoglobulins. "Ultrasmall pores" are specific for water and play an important role in osmosis. Because of their small radius (< 3 Å), these pores are not permeable to osmotic agents such as glucose and glycerol. They are located in the membranes of endothelial cells. It is assumed that during the first hour of a hypertonic dwell (3.86% glucose) the amount of water transported by these pores accounts for approximately 50% of the total UF obtained. The presence of ultrasmall pores explains the dissociation between sodium and water transport and the phenomenon known as "sodium sieving": the marked fall in the ratio of sodium in dialysate/plasma as a result of the movement of free water into the peritoneal cavity [3, 4].

The Identification of Aquaporin-1

The identification of aquaporines, a family of membrane proteins present in bacteria, plants and mammals, provided new evidence for the "three-pore model" of peritoneal transport. It also explained some of the mechanisms responsible for water transport across biological membranes. Aquaporin-1 (AQP-1), a 28-kDa protein, was the first identified member of the aquaporin family, found in the human erythrocyte membrane [5]. So far 13 aquaporins have been identified in mammals, with different expression in different tissues. Most aquaporins are permeable only for water, but some isoforms (AQP-3, AQP-7, AQP-9 and AQP-10 – called "aquaglyceroporins") can also transport glycerol and urea [6].

Apart from its localization in erythrocytes, proximal tubules and the descending thin limb of Henle's loop of the kidney, AQP-1 presence has been found in the apical and basolateral membranes of the endothelial cells lining the capillaries in many tissues [7]. In a study by Mobasheri and Marples, tissue microarray technology confirmed the presence of AQP-1 in the endothelial barriers of almost all tissues (cardiovascular, respiratory, gastrointestinal, hepatic and pancreatobiliary, oral, salivary, nasal, mammary, endocrine, genital tract and nervous system) [8]. The distribution of AQP-1 in the capillary endothelium – the most important barrier in the transport of substances across the peritoneal membrane during dialysis – confirms the pore-membrane model. Electron microscopy shows that the membrane structure of aquaporin-1 fits the size of "ultrasmall pores" (3.8 Å) in the peritoneal membrane. AQP-1 is a homotetramer, with each monomer containing six tilted α-helices surrounding a single central pore. The selectivity of AQP-1 for water is mainly due to its narrow constriction and arginine residue lining the pore and providing a positive charge that creates electrostatic repulsion for protons [9, 10].

Experimental Studies

The Role of AQP- 1 in Water Transport Across the Peritoneal Membrane

The similarity of the distribution of AQP-1 in the peritoneal membrane (PM) of mice and humans, as well as the similarity of the influence of glucose exposure on the PM in those two species, has led to many experimental studies on AQP-1 function [11, 12]. Proof of the role of AQP-1 in water transport was provided by the study of Yang et al. on AQP-1 knockout mice [13]. In this study, osmotically driven water transport across the PM was significantly lower in AQP-1 knockout mice (AQP-$1^{-/-}$) than in AQP-4 knockout mice (AQP-$4^{-/-}$). In a study by Ni et al. [14], AQP-$1^{-/-}$ mice had significantly lower ultrafiltration than AQP-$1^{+/+}$ mice in the first and the second hour of a hypertonic dwell, and heterozygous mice (AQP-$1^{+/-}$) showed intermediate values of ultrafiltration. Interestingly, AQP-1 deficiency had no influence on the peritoneal membrane structure, including the density and diameter of the capillaries. In a study by Ota et al. [15], AQP-1 expression in mesothelial cells was found to be dependent on exposure to osmotic substances, such as glucose and glycerol. They suggested that hyperosmolality increased AQP-1 dependent water permeability in peritoneal

tissues by regulating translocation from the perinuclear region to the plasma membrane and the synthesis of AQP-1 protein.

Interestingly, the promoter of the mouse AQP-1 gene contains glucocorticoid response elements (GREs) [16]. Glucocorticoid receptors are also present in the peritoneal membrane. In a study by Stoenoiou et al. [16] it was observed that administering high doses of corticosteroids to rats led to increased expression of AQP-1 in the peritoneal capillaries and increased free water transport, reflected by higher ultrafiltration.

Other AQP-1 Properties

Peritonitis is a frequent complication of peritoneal dialysis. It is associated with a loss of ultrafiltration, resulting in overhydration and increased morbidity and mortality of peritoneal dialysis patients.

In studies on animal models it was found that peritonitis was associated with increased transport of small solutes due to proliferation of the vascular bed. The increased effective peritoneal surface area increases glucose reabsorption and decreases the osmotic gradient, resulting in peritoneal ultrafiltration failure [17].

In a study by Saadoun et al. [18], the authors demonstrated the role of AQP-1 in cell migration, wound healing and tumor growth. In this study, melanoma cells were implanted in AQP-1 knockout mice. They observed reduced tumor growth due to lower microvessel proliferation, and improved the survival rate of the mice. Angiogenesis was also altered when AQP-1 knockout mice were implanted with angiogenic factors. At the same time, implanting cells containing AQP-1 accelerated cell migration and wound healing *in vitro*. This suggests that AQP-1 can accelerate the turnover of cell membrane protrusions at the leading edge of cells. The ion uptake at the tip of a cell may create local osmotic gradients, driving AQP-mediated water influx, which may increase local hydrostatic pressure, causing cell membrane protrusions [19]. In a study by Nishino et al. [20], the authors showed that in mice with peritonitis and lacking the AQP-1 gene, angiogenesis and the increased transport of small solutes was significantly lower compared to control mice with "wild" alleles of AQP-1. Furthermore, in AQP-1$^{-/-}$ mice they observed a lower number of infiltrating macrophages and a lower inflammatory response. These observations may suggest that AQP-1 may play a role in leukocyte recruitment during peritonitis.

Conclusions

Ultrafiltration failure and peritonitis are serious complications of peritoneal dialysis, contributing to higher morbidity and mortality of PD patients. Assessment of the function of AQP-1, reflected by free water transport, is important for both clinically stable patients and for patients with complications. Many mathematical models have been created to assess water transport through "ultrasmall" pores [21–23]. In a study by Stachowska-Pietka et al. [23], in peritoneal dialysis patients the values of free water transport changed with the dwell time, which is consistent with the findings of Ota et al. [15]. The results of the research presented in this article suggest that apart from water transport across the peritoneal membrane, AQP-1 may participate in vessel proliferation and leucocyte recruitment during peritonitis. The possibility of regulating AQP-1 expression by corticosteroid administration may open new perspectives in the treatment of ultrafiltration failure in PD patients. Future studies should also assess the influence of AQP-1 gene polymorphism on the variability of free water transport, and on the frequency and course of peritonitis.

References

[1] **Grassmann A, Gioberge S, Moeller S, Brown G:** ESRD patients in 2004: Global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant 2005, 20, 2587–2593.

[2] **Rippe B, Stelin G, Haraldsson B:** Computer simulations of peritoneal fluid transport in CAPD. Kidney Int 1991, 40, 315–325.

[3] **Rippe B, Venturoli D, Simonsen O, de Arteaga J:** Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. Perit Dial Int 2004, 24, 10–27.

[4] **Blake PG:** The remarkable interface between aquaporins and peritoneal dialysis. Perit Dial Int 2010, 30 (2), 131–132.

[5] **Preston GM, Agre P:** Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: member of an ancient channel family. Proc Natl Acad Sci 1991, 88, 11110–11114.

[6] **Krane CM, Goldstein DL:** Comparative functional analysis of aquaporins/glyceroporins in mammals and anurans. Mamm Genome 2007, 18, 452–462.

[7] **Nielsen S, Smith BL, Christensen EI, Agre P:** Distribution of the aquaporin CHIP in secretory and resorptive epithelia and capillary endothelia. Proc Natl Acad Sci 1993, 90, 7275–7279.

[8] **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, 529–537.
[9] **Murata K, Mitsuoka K, Hirai T, Walz T, Agre P, Heymann JB, Engel A, Fujioyoshi Y:** Structural determinants of water permeation through aquaporin-1. Nature 2000, 407, 599–605.
[10] **Nishino T, Devuyst O:** Clinical application of aquaporin research: aquaporin-1 in the peritoneal membrane. Eur J Physiol 2008, 456, 721–727.
[11] **Yong-Lim K:** Update on mechanisms of ulgtrafiltration failure. Perit Dial Int 2009, 29 (S2), 123–127.
[12] **Devuyst O, Yool AJ:** Aquaporin-1: new developments and perspectives for peritoneal dialysis. Perit Dial Int 2010, 30 (2), 135–141.
[13] **Yang B, Folkesson HG, Yang J, Matthay MA, Ma T, Verkman AS:** Reduced osmotic water permeability of the peritoneal barrier in aquaporin-1 knockout mice. Am J Physiol 1999, 276, C76–81.
[14] **Ni J, Verbavatz JM, Rippe A, Boisde I, Moulin P, Rippe B, Varkman AS, Devuyst O:** Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. Kidney Int 2006, 69, 1518–1525.
[15] **Ota T, Kuwahara M, Shuling F, Terada Y, Akiba T, Sasaki S, Marumo F:** Expression of aquaporin-1 in the peritoneal tissues: localization and regulation by hyperosmolality. Perit Dial Int 2002, 22, 307–315.
[16] **Stoenoiu MS, Ni J, Verkaeren C, Debaix H, Jonas JC, Lameire N, Varbavatz JM, Devuyst O:** Corticosteroids induce expression of aquaporin-1 and increase transcellular water transport in rat peritoneum. J Am Soc Nephrol 2003, 14, 555–565.
[17] **Coester AM, Smit W, Struijk DG, Krediet RT:** Peritoneal function in clinical practice: the importance of follow-up and its measurement in patients. Recommendations for patients information and measurement of peritoneal function. Nephrol Dial Transplant Plus 2009, 2, 104–110.
[18] **Saadoun S, Papadopoulos MC, Hara-Chikuma M, Verkman AS:** Impairment of angiogenesis and cell migration by targeted aquaporin-1 gene disruption. Nature 2005, 434, 786–792.
[19] **Belge H, Devuyst O:** Aquaporin-1 – a water channel on the move. Nephrol Dial Transplant 2006, 21, 2069–2071.
[20] **Nishino T, van Loo G, Moulin P, Beyaert R, Verkman AS, Devuyst O:** Aquaporin-1 modulates vascular proliferation and inflammatory response during acute infection. J Am Soc Nephrol 2007, 18, 112A.
[21] **La Milia V, di Filippo S, Crepaldi M, del Vecchio L, dell'Oro C, Andrulli S, Locatelli F:** Mini-peritoneal equilibration test: A simple and fast method to assess free water and small solute transport across the peritoneal membrane. Kidney Int 2005, 68, 840–846.
[22] **Waniewski J, Debowska M, Lindholm B:** Ultrafiltration and absorption in evaluating aquaporin function from peritoneal transport of sodium. Perit Dial Int 2007, 27, 687–690.
[23] **Stachowska-Pietka J, Waniewski J, Vonesh E, Lindholm B:** Changes in free water fraction and aquaporin function with dwell time during continuous ambulatory peritoneal dialysis. Artif Organs 2010, 34 (12), 1138–1143.

Addres for correspondence:

Edyta Gołembiewska
Al. Powstańców Wielkopolskich 72
70-111 Szczecin
Poland
Tel./fax: +48 91 466 11 96
E-mail: irys@sci.pam.szczecin.pl

Conflict of interest: None declared

Received: 29.11.2010
Revised: 18.01.2011
Accepted: 24.03.2011