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Review

Aquaporin-1 in the peritoneal membrane: Implications for water transport across capillaries and peritoneal dialysis

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Abstract

Peritoneal dialysis (PD) is an established mode of renal replacement therapy, based on the exchange of fluid and solutes between blood in peritoneal capillaries and a dialysate that has been introduced in the peritoneal cavity. The dialysis involves diffusive and convective transports and osmosis through the highly vascularized peritoneal membrane. Computer simulations predicted that the membrane contains ultrasmall pores (radius < 3 Å) responsible for the transport of solute-free water across the capillary endothelium during crystalloid osmosis. The distribution of the water channel aquaporin-1 (AQP1), as well as its molecular structure ensuring an exquisite selectivity for water perfectly fit with the characteristics of the ultrasmall pore. Treatment with corticosteroids induces the expression of AQP1 in peritoneal capillaries and increases water permeability and ultrafiltration in rats, without affecting the osmotic gradient and the permeability for small solutes. Studies in knockout mice provided further evidence that osmotically-driven water transport across the peritoneal membrane is mediated by AQP1. AQP1 and endothelial NO synthase (eNOS) show a distinct regulation within the endothelium lining peritoneal capillaries. In acute peritonitis, the upregulation of eNOS and increased release of NO dissipate the osmotic gradient and result in ultrafiltration failure, despite the unchanged expression of AQP1. These data illustrate the potential of the peritoneal membrane to investigate the role and regulation of AQP1 in the endothelium. They also emphasize the critical role of AQP1 during peritoneal dialysis and suggest that manipulating AQP1 expression may be used to increase water permeability across the peritoneal membrane.

Keywords: AQP1; Glucocorticoid; Endothelium; Ultrafiltration; Solute transport; Renal failure; Knockout mouse

Contents

1. Peritoneal dialysis and the peritoneal membrane

Renal replacement therapy represents a major health issue. In 2001, more than 1 million patients with end-stage renal disease (ESRD) were on dialysis worldwide, and that number is

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increasing by 7% annually [1]. Over the past 25 years, peritoneal dialysis (PD) has become an established treatment for ESRD, accounting for about 15% of the total number of patients on dialysis worldwide [2]. Recent insights in the physiology and pathophysiology of the peritoneal membrane, as well as technical advances have improved the popularity of PD [3].

Like any dialysis technique, the aim of PD is to remove the excess of water and uremic toxins from the blood of patients with ESRD. To perform PD, a catheter is implanted in the peritoneal cavity, and a solution (called "the dialysate") that contains physiologic concentrations of sodium, chloride, calcium, magnesium, and a buffer (lactate or bicarbonate) is infused through it. The dialysate remains in the peritoneal cavity for some hours and is then drained out before fresh dialysate is reinfused. Dialysis occurs during the stagnation time, when solutes and water move between the blood and the dialysate through the peritoneal membrane. The peritoneal membrane consists of three main anatomical components: the capillary wall, the interstitium (primarily composed by a mucopolysaccharide matrix and bundles of collagen fibers), and the mesothelium (Fig. 1, panel A). Solutes diffuse between blood and dialysate by diffusive and convective transports, according to their concentration gradient. Ultrafiltration (UF), i.e., the amount of water removed from the patient, depends from the presence of an osmotic agent (most often glucose) in the dialysate. Low-molecular weight solutes, such as urea and creatinine, accompany water movements [3].

The parameters influencing the transport of solutes and water across the peritoneal membrane during PD are i) the exchange frequency and volume of the dialysate; ii) the osmolality of the dialysate; (iii) the peritoneal blood flow; iv) the amount of perfused peritoneal capillaries (« effective peritoneal vascular surface area, EPSA »); and v) the microvascular intrinsic permea-bility [4]. The main transport parameters across the peritoneal membrane are routinely evaluated using the peritoneal equilibration test (PET), which is based on the rate of small solutes transport during an exchange [2]. According to these basic principles, any increase in the transport of small solutes across the membrane will cause a rapid dissipation of the osmotic gradient (due to increased reabsorption of glucose, the osmotic agent, from the dialysate) and a loss of UF, causing fluid overload in the uremic patient. Accordingly, the capacity of osmotically-induced UF across the peritoneal membrane is a major predictor of outcome and mortality in PD patients [5]. Failure of this UF capacity is the most frequent abnormality in long-term PD patients, and the main reason for technical failure [6].

2. The capillary endothelium in the PM contains ultrasmall pores selective for water

The exchange of fluid across the peritoneal membrane during PD is best explained by a "three-pore" model based upon

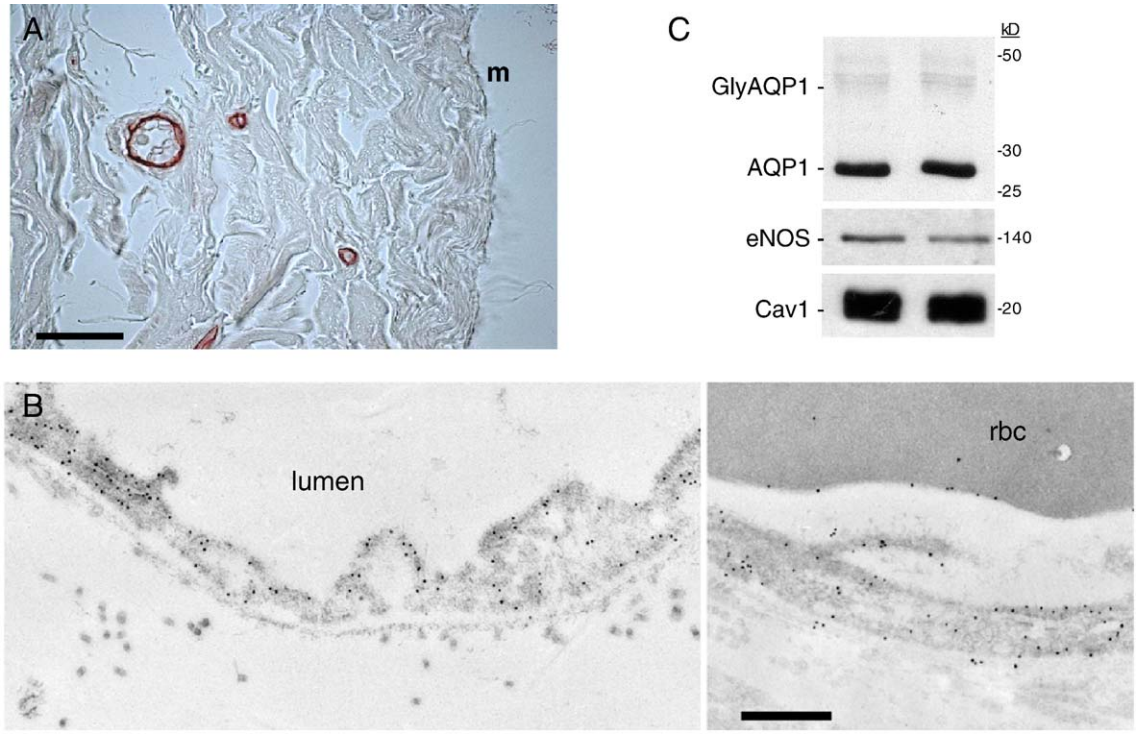

Fig. 1. Structure of the peritoneal membrane and expression and distribution of AQP1. (Panel A) Cross-section of the human parietal peritoneum stained for AQP1. The peritoneal membrane contains three components: a layer of ciliated mesothelial cells (m); the interstitial tissue containing bundles of collagen and mucopolysaccharides; a dense network of capillaries, blood vessels, and lymphatics. AQP1 is detected in the endothelium lining peritoneal capillaries, venules, and small veins. (Scale bar: 40 μm). (Panel B) Immunogold electron microscopy on mouse visceral peritoneum unicryl sections shows a very strong signal for AQP1 in the plasma membrane and plasma membrane infoldings of capillary endothelial cells. Note (right panel) that the density of AQP1 labeling is markedly stronger in endothelial cells than in red blood cells (rbc). (Bar: 500 nm). (Panel C) Immunoblotting of AQP1 and endothelial markers in the mouse visceral peritoneum. The core and glycosylated isoforms of AQP1 are identified, as well as eNOS (140 kDa) and caveolin-1 (20 kDa) in the same samples (20 μg protein/lane).

computer simulations [7]. According to this model, the major transport barrier of the PM is the capillary endothelium, which contains three distinct types of pores [8]. The "small pores" (radius 40 to 50 Å) correspond to the clefts located between endothelial cells. They account for ~95% of the hydraulic conductance (UF coefficient, LpS), i.e., the vast majority of the total pore surface area available for the diffusion of small solutes including urea, creatinine, and glucose. A second population of pores, the "large pores" (radius 250 Å), thought to correspond to the venular interendothelial gaps, accounts for 5% of the UF coefficient. These pores are involved in the transport of macromolecules (proteins, immunoglobulins) and, although they represent only 0.01% of the total number of pores, they mediate an important part of the UF via convection of plasma from blood to the peritoneal cavity. The third population of pores consists in water-specific, "ultrasmall pores" located in the endothelial cells. The ultrasmall pores account only for 1–2% of the hydraulic conductance, meaning an almost insignificant contribution to the overall UF coefficient. However, because they reject solutes but facilitate the transport of water, the ultrasmall pores are extremely important during crystalloid osmosis. Thus, they have been predicted to mediate half of the UF, as well as the "sodium sieving", i.e., the fall in dialysate sodium concentration caused by a rapid transport of water from the blood into the peritoneal cavity during a dwell with hypertonic glucose [7,8] (see Fig. 2, panel B). Understanding the molecular counterpart and the role of the ultrasmall pores has a major clinical importance, since the link between the integrity of the ultrasmall pores and the UF capacity and sodium sieving remains a much debated question in PD [9,10]. According to the three-pore model, the ultrasmall pore should be located in the endothelium lining peritoneal capillaries and post-capillary venules, where most of the water movement during PD occurs [11]. It should also facilitate the water movement while being unpermeable to osmotic agents such as glucose and glycerol, hence have a minimal radius <3 Å [7,8].

3. Aquaporin-1 is the molecular counterpart of the ultrasmall pore

The identification of the aquaporins, a family of integral plasma membrane proteins conserved in bacteria, plants, and mammals, provided critical insights in the molecular mechanisms involved in water permeation across biological membranes [12]. The first identified member of the aquaporin (AQP) family was aquaporin-1 (AQP1), a 28-kDa protein abundantly expressed in the membrane of human red blood cells [13]. To date, 11 members of the AQP family have been identified in mammals, with specific expression patterns and distinct roles in given tissues and cells. Most AQPs are exclusively permeable to water,

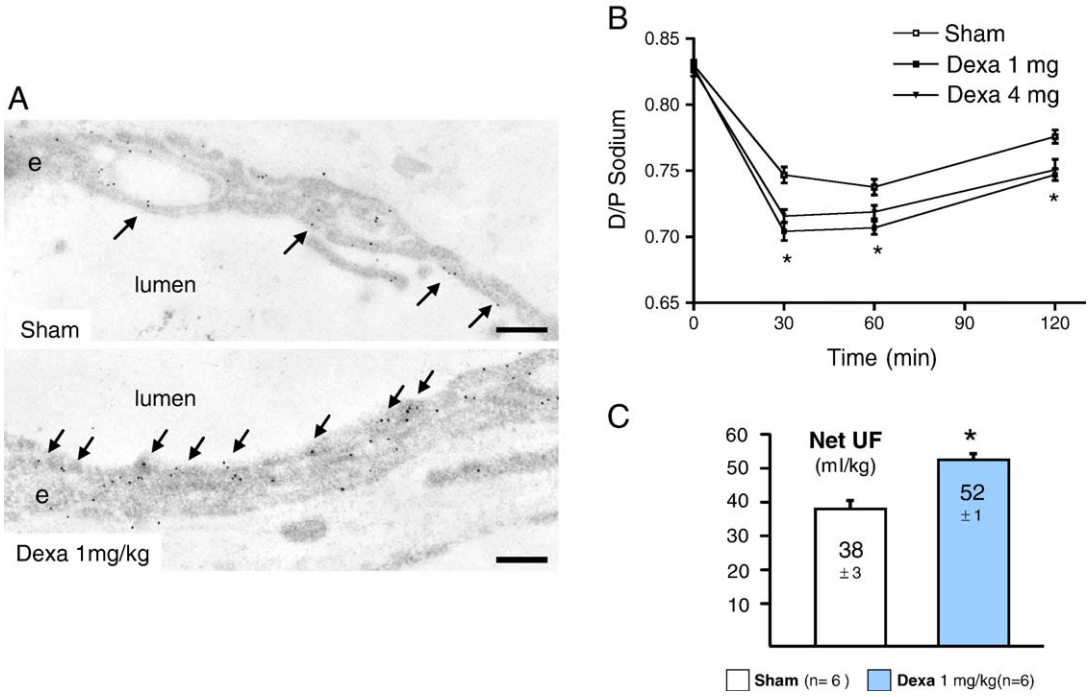

Fig. 2. Influence of corticosteroid treatment on sodium sieving, net ultrafiltration, and AQP1 expression in the capillary endothelium. (Panel A) Ultrathin sections from the visceral peritoneum of rats treated with saline (sham) or dexamethasone (1 mg/kg) for 5 days were incubated with an affinity-purified anti-AQP1 antibody and visualized with goat anti-rabbit IgG conjugated to 10-nm colloidal gold particles. AQP1 labeling is seen in both apical and basal plasma membranes of endothelial cells (e) lining peritoneal capillaries. The abundance of AQP1 in endothelial cells is markedly increased in dexamethasone-treated animals. (Bar: 250 nm). (Panels B–C) Results of the peritoneal equilibration test (PET) performed after 5 days of treatment with saline (sham) or dexamethasone at 1 mg/kg (Dexa 1 mg) or at 4 mg/kg (Dexa 4 mg). The dialysate-to-plasma (D/P) ratios of sodium in sham (□), Dexa 1 mg (■) and Dexa 4 mg (▼) during a 2-h dwell with 3.86% glucose dialysate are shown. The drop in the D/P sodium at 30 min of the dwell ("sodium sieving") is classically used as an index of the free water transport across the ultrasmall pores present in the capillary endothelium (the latter correspond actually to AQP1, see text). Treatment with high-dose dexamethasone induces a significant increase in the sodium sieving, which can be interpreted as an increase in AQP1-mediated water transport, and a significant increase in net ultrafiltration (net UF) across the peritoneal membrane. *$P<0.05$ Dexa 1 mg/kg vs. sham; there were 6 rats in each group. (Modified from Ref. [26]).

whereas some isoforms (AQP3, AQP7, AQP9, and AQP10, called "aquaglyceroporins") transport water, glycerol, and urea [14]. In addition to its abundant expression in proximal convoluted tubules and descending thin limbs of Henle's loop of the mammalian kidney, AQP1 is located in the apical and basolateral membranes of endothelial cells lining non-fenestrated capillaries in a variety of tissues [15] including the peritoneum [16]. Studies in human and rodent peritoneal membrane have confirmed that AQP1 is abundantly expressed the endothelial cells lining capillaries, venules and small veins (Fig. 1), whereas it is not detected in small-size arteries [17,18].

Several lines of evidence support the hypothesis that AQP1 is the molecular counterpart of the ultrasmall pore of the PM.

The distribution of AQP1 in the endothelium lining peritoneal capillaries is consistent with the predicted topology of the ultrasmall pore (Fig. 1). The continuous endothelium lining peritoneal capillaries is the most important barrier for solute transport during PD; within that structure, the ultrasmall pore must be transcellular, i.e., an integral plasma membrane protein [7,8]. In addition, peritoneal capillaries and post-capillary venules represent the principal location for solute and fluid exchange during PD [11].

By principle, the ultrasmall pore is a water-only pathway that reject small solutes such as urea and glucose. The structure of the pore should thus account for the effectiveness of glucose (and glycerol) as an osmotic agent in PD, hence have a minimal radius <3 Å. Expression studies in oocytes of *Xenopus laevis* have demonstrated that AQP1 is indeed a water-specific channel that can be inhibited by mercurials [19]. These results were confirmed by reconstitution of purified AQP1 within proteoliposomes, which also showed that AQP1 is not permeable to urea and glycerol [20,21].

Structural informations about the pore formed by AQP1, based on an atomic model at 3.8 Å resolution obtained by electron cryomicroscopy [22], perfectly fit the postulated size of the ultrasmall pore of the PM. AQP1 is a homotetramer, with each monomer containing six tilted, membrane-spanning a-helices surrounding a single central pore. The selectivity of the pore for water (against protons) is ensured by several elements, including a narrow constriction of 2.8 Å (which allows to accommodate a single water molecule); a conserved arginine residue lining the pore and providing a fixed positive charge that creates electrostatic repulsion for protons; a transient reorientation of the water dipole resulting from the simultaneous formation of hydrogen bonding with the side chains of two conserved asparagine residues (NPA motifs); and two partial positive charges at the center of the channel resulting from two non-membrane-spanning α helices [12]. Of interest is the location of the side chain of a cysteine residue (Cys189) in the AQP1 pore, explaining why the water permeability of many AQPs can be inhibited by mercury compounds [22]. Yet, functional studies conducted in rats and rabbits have shown that peritoneal water permeability is significantly inhibited by $HgCl_2$ under specific experimental conditions (short-term tissue fixation) [16,23].

The promoter of the mouse *Aqp1* gene is known to contain glucocorticoid response elements (GREs) [24], and there is evidence f or AQP1 induction by corticosteroids in perinatal rat lung [25]. Recently, we showed that glucocorticoid receptors are expressed in the peritoneal membrane, and that treatment of rats with high doses of corticosteroids (dexamethasone, 1 to 4 mg/kg daily) is associated with an increased expression of AQP1 in the capillary endothelium, reflected by a significant increase in the sodium sieving and net UF across the membrane (Fig. 2) [26]. These modifications of water transport were observed in absence of any effect on the osmotic gradient, providing a strong argument for the role of AQP1 during PD [26]. These data also suggested that pharmacoregulation of AQP1 could provide a target for increasing UF in PD patients, which is clinically relevant when considering that these patients are often overhydrated [5,6].

Finally, the availability of knockout mice allowed to demonstrate that osmotically-driven water transport across the PM (estimated by the dilution of a tracer) is significantly decreased in AQP1 knockout ($Aqp1^{-/-}$) mice, whereas it remains unchanged in $Aqp4^{-/-}$ mice [27]. Using a PET that has been well-characterized in mouse [28], we recently showed that, in comparison with $Aqp1^{+/+}$ littermates, $Aqp1^{-/-}$ mice had no sodium sieving; a ~70% decrease in the initial, solute-free UF; and a ~50% decrease in cumulative UF [29] (Fig. 3). These modifications occurred despite unchanged osmotic gradient and transport of small solutes in the $Aqp1^{-/-}$ mice. Furthermore, heterozygous $Aqp1^{+/-}$ mice showed intermediate values in sodium sieving and initial UF. The deletion of AQP1 had no effect on the structure of the peritoneal membrane, in particular, the density or diameter of peritoneal capillaries. These data provided the definitive proof for the critical role of AQP1 during PD. They also validated essential predictions of the three-pore model: (i) the ultrasmall pores account for the sodium sieving; and (ii) they mediate 50% of UF during a hypertonic dwell (Fig. 3).

4. Other aquaporins in the peritoneum

We recently used quantitative real-time RT-PCR to document the expression patterns of the AQP gene family (AQP0 to AQP10) in the mouse visceral peritoneum [29]. AQP1 was the most abundant isoform, and the only one located in the capillary endothelium. A significant expression of AQP7 (approximately 2-fold less than AQP1) as well as low levels of AQP9 and AQP5, and traces of AQP3 were also detected [29]. Staining for AQP1 and AQP3 has been inconsistently observed in rat and human mesothelium [16,30]. Recent studies have demonstrated that the expression of AQP1 in mesothelial cells, which may be too low at baseline to be detected by immunostaining, is induced by exposure to osmotic agents such as glucose and mannitol [30,31]. This induction probably reflects the presence of hypertonicity response elements in the AQP1 promoter [32]. Because the mesothelium does not represent a significant functional barrier for water transport in PD, the functional importance of AQPs at that level remains unclear. The water channel could participate in the volume regulation of these cells, which are known to undergo rapid change in volume when exposed to hypertonic dialysates used in PD.

Could aquaporins other than AQP1 play a role in the water permeability of the peritoneal membrane? The only aquaporin

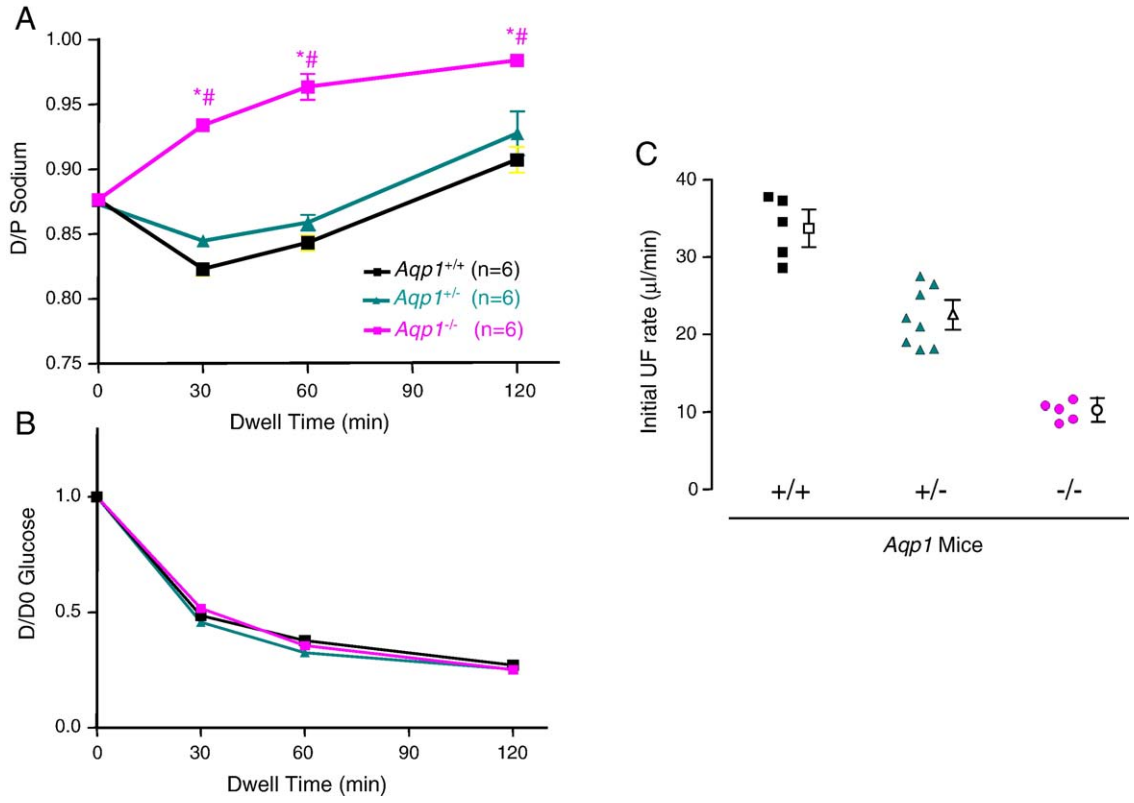

Fig. 3. Effect of AQP1 deletion on the transport of water and small solutes across the peritoneal membrane. Mice with a targeted deletion of *Aqp1* were investigated using a peritoneal equilibration test essentially similar to that performed in patients. The dialysate-to-plasma (D/P) ratio of sodium (panel A), the progressive removal of glucose from the dialysate (D/D0 glucose, panel B), and the initial ultrafiltration rates (solute-free water transport, panel C) were determined in $Aqp1^{+/+}$ mice (black squares), $Aqp1^{+/-}$ mice (green triangles), and $Aqp1^{-/-}$ mice (pink circles) during a 2-h exchange with 2 ml of 7% glucose dialysate. In comparison with $Aqp1^{+/+}$ mice, mice lacking AQP1 show a complete loss of sodium sieving, whereas the glucose reabsorption from dialysate is unchanged. $Aqp1^{-/-}$ mice also show significantly lower initial UF rates. Intermediate values of sodium sieving and initial UF rates are observed in $Aqp1^{+/-}$ mice. *$P<0.05$ vs. $Aqp1^{+/+}$ mice; $^{\#}P<0.05$ vs. $Aqp1^{+/-}$ mice. (Modified from Ref. [29]).

that has been consistently located in the capillary endothelium of the peritoneum is AQP1 [16–18,27–29]. The vasopressin-sensitivity of AQP2, as well as the $HgCl_2$-insensitivity of AQP4 render unlikely their participation in the water permeability of the peritoneum [17,27]. Using well-characterized antibodies, we and others were unable to document any expression of AQP3 and AQP4 in the capillary endothelium of rat peritoneum [18,27]. The fact that glycerol is an effective osmotic agent that can replace glucose in PD [33] argues against a functional role of the aquaglyceroporins in water transport during PD. By contrast, AQP7 could play an important role in the adipocytes of the peritoneum, by acting as a glycerol transporter [34,35].

5. Differential regulation of AQP1 and endothelial nitric oxide synthase in the PM

A decrease in UF, either acute (such as in peritonitis) or chronic (such as in long-term PD), is commonly observed in patients treated by PD. The loss of UF has severe clinical consequences, e.g., increased extracellular fluid volume, and is associated with higher morbidity and mortality in PD patients [5]. As mentioned earlier, AQP1 mediates up to 50% of the UF during the PD procedure. An increased transport of small solutes, due to an increased effective peritoneal surface area, is invariably associated with a higher reabsorption of glucose and an early dissipation of the osmotic gradient, constituting the most common cause of UF failure in PD [4–6]. In recent studies, we investigated the potential contributions of AQP1 and endothelial nitric oxide synthase (eNOS) in these modifications.

Nitric oxide (NO) regulates vascular tone and permeability [36], and early experiments showed that the NO donor nitroprusside increases the effective peritoneal surface area and the intrinsic permeability of the PM [37]. A specific NO synthase (NOS) activity can be detected in the peritoneal membrane, in relation with the expression of the three NOS isoforms—the neuronal NOS (nNOS, NOS1), the inducible NOS (iNOS, NOS2), and the endothelial NOS (eNOS, NOS3) [18,38]. Inflammation of the peritoneum is associated with a marked increase in total and Ca^{2+}-dependent NOS activity, due to upregulated eNOS expression, whereas AQP1 expression is unchanged [17]. Although AQP1 and eNOS are both expressed in the capillary endothelium, eNOS is located in the endothelium lining all types of blood vessels including arterioles, whereas AQP1 is restricted to capillaries, venules and small veins [17,18,28]. The differential regulation of AQP1 and eNOS was further illustrated in the detailed study of a long-term PD patient

characterized by UF failure due to abolition of transcellular water permeability despite an apparently normal expression of AQP1 [39].

Further studies in rat and mouse models of acute peritonitis allowed us to further investigate the role of AQP1 and eNOS in the PM [18,40,41]. These studies revealed that the loss of water permeability and UF in acute peritonitis is due to an increased peritoneal transport for small solutes that appears to be primarily mediated by the increased eNOS, without quantitative nor qualitative evidence for a decrease in AQP1 expression. These data suggest that the release of NO in the capillary endothelium is a major regulator of water permeability across the PM, because it induces a vasodilation (and thus increases the peritoneal exchange surface area and dissipates the osmotic gradient) and promotes angiogenesis [18,41]. However, the lack of total reversibility of the permeability modifications following treatment with L-NAME [40] or in eNOS knockout mice [41] suggests the intriguing hypothesis that increased NO levels, secondary to eNOS upregulation, could modify plasma membrane proteins such as AQP1 and interfere with their functions in endothelial cells [39,40]. Such interaction, probably favoured by the co-localization of AQP1 and eNOS in caveolae [15,16], is also suggested by the intense reactivity for nitro-tyrosine and nitroso-cysteine observed in the capillary endothelium during acute peritonitis [18,40].

6. Conclusions and perspectives

Transcellular water permeability mediated by AQP1 is an essential component of the water removal from uremic patients during PD. Several lines of evidence, culminating with studies in AQP1 knockout mice, have demonstrated that AQP1 is the ultrasmall pore that was predicted by the three-pore model based on computer simulations [7]. This molecular pathway is responsible for ~50% of the UF during PD, and has thus a major clinical relevance for patients treated by PD. The fact that the expression of AQP1 in the PM can be modulated by corticosteroids opens new perspectives for treating UF failure in some PD patients. Furthermore, the peritoneal membrane could represent a useful model to investigate the complex relationships between AQP1, eNOS, and other relevant molecules in the endothelium, and to assess their influence on water transport and angiogenesis [42]. The strict correlation between AQP1 abundance and solute-free water transport across the membrane, that was recently demonstrated using the AQP1 mouse [29], may also be useful for in vivo investigations of drugs targeting the channel.

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