Aquaporin-1 Facilitates Transmesothelial Water Permeability

Subjects: Biophysics

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Mesothelial cells in human peritoneum express the water channel aquaporin 1 (AQP1) at the plasma membrane, suggesting that, although in a non-physiological context, it may facilitate osmotic water exchange during peritoneal dialysis (PD).

aquaporin 1 | mesothelial cells | peritoneal dialysis | water transport | three-pore model

1. Introduction

The peritoneal membrane is considered as the first-line barrier that provides a protective, non-adhesive surface on the abdominal cavity and organs. The peritoneal membrane is structured by a layer of squamous-like and cuboidal ciliated mesothelial cells with microvilli and cell-cell junctional complexes, an interstitium containing bundles of collagen and mucopolysaccharides, and a dense network of capillaries, blood vessels, and lymphatics [1]. Mesothelial cells are mesodermal in origin and possess both epithelial and mesenchymal features, which allows for them to play numerous and important functions.

In addition to providing a protective and friction-free interface for the free movement of opposing organs and tissues, the mesothelium is involved in initiation and resolution of inflammation, tissue repair, release of factors to promote both the deposition and clearance of fibrin, and antigen presentation [2].

While this physiological role of the peritoneum was described long ago, more recently attention has focused on the possibility of exploiting the peritoneum as a selective membrane for performing peritoneal dialysis (PD). However, the role of mesothelial cells in mediating exchanges between blood capillaries and PD solutions is still unclear.

PD is a kidney replacement therapy for patients with end-stage renal disease. In principle, the technique is based on the introduction into the patient's peritoneal cavity of a hypertonic solution capable of attracting, through the peritoneal capillaries, excess water and toxins which the patient cannot eliminate due to impaired renal function. Considering the structure of the peritoneum, the pathway available for the water and solutes bidirectional diffusion from plasma to the PD solution includes the capillary endothelium, the sub-mesothelial interstitium, and the mesothelial layer [1][3]. According to the three-pore model [4][5][6][7], the major transport barrier in the peritoneum is the capillary endothelium. In particular, the water-selective "ultrasmall pores", expressed on the endothelial cells, and later on identified as the water channels aquaporin 1 (AQP1) [8][9][10], have been predicted to mediate half of the water ultrafiltration (UF) during crystalloid osmosis [5][6][11]. It has to be underlined that the three-pore model

and most of the scientific literature on the PD field do not consider mesothelial cells of the peritoneum as a functional barrier regulating the rate of water diffusion in PD [11][12][13][14][15][16].

2. The Function of Aquaporins

Since the discovery of the AQP1 water channel in 1992 [17], scientists have sought to understand the function of the 13 aquaporins cloned to date, in the various tissues where they are expressed. In addition to maintaining cell volume, rapid water exchange across cells enables tissues and organs to secrete and/or absorb water as part of their physiological function. AQP1 is detected in the endothelium lining peritoneal capillaries, venules, and small veins [18]. The physiological function of AQP1 in mesothelial cells of the peritoneum could be to secrete water into the peritoneal cavity which, together with glycosaminoglycans and lubricants, facilitates intracoelomic movement of organs. In recent decades, with the increase in the clinical practice of PD, it has been understood that, although in a non-physiological context, the presence of AQP1 in the peritoneal capillaries is a key element ensuring the dialysis process [11].

Currently, the widely accepted model that describes water and solute transport during PD is represented by the ‘three-pore model’, a computer-based simulation elaborated by Rippe and Stelin [4][5][6][7].

The three-pore model assumes that the only limiting barrier regulating the major transport in the peritoneum is the capillary endothelium which contains, indeed, three types of pores: (a) the ‘small pores’, corresponding to clefts between endothelial cells, with an average radius of 40–50 Å, accounting for the 95% of the hydraulic conductivity (L_pS); (b) the ‘large pores’ represented by venular interendothelial gaps, average radius 250 Å, accounting for 5% of the L_pS; (c) the ‘ultra-small’, water-selective pores associated with the plasma membrane of endothelial cells, radius 3–5 Å, accounting for only the 1–2% of the transcellular L_pS. The latter, was subsequently identified as the water channel aquaporin-1 (AQP1) [8][10][17], and since they reject solutes but only facilitate water transport, they mediate half of the water UF during a crystalloid osmosis, as it occurs during a dwell with hypertonic glucose [11]. Later on, Flessner and Rippe implemented the three-pore-model taking into account the barrier effect of the matrix of fibers in the interstitium [19]. Even in this novel computational model, a possible role of mesothelial cells as a third functional barrier to water movement during PD was not considered. Yet, the abundant expression of AQP1 on human mesothelial cells [20], and the fact that, the hydraulic conductivity (L_pS) of the mesothelium is comparable to that of the endothelium of the peritoneal capillaries [21] would suggest that the transport of water through the mesothelium, exploits the transcellular rather than the paracellular pathway, and, therefore, it may be strictly dependent on the availability of AQP1. Indeed, a positive correlation was showed between the amount of AQP1 released in the PD effluent by mesothelial cells and UF, free water transport and Na^+-sieving [20].

3. HMC Monolayers: The Transmesothelial Water Tansport Model

An immortalized mesothelial cell line of human peritoneal origin was exploited due to the limitation of primary cell lines which already start to transform at the third passage and did not survive beyond passage six in culture [22]. In fact, human mesothelial cell line (HMC) showed strong Zo-1 tight junctional bands at the cell-cell contacts and express the tetraspan TJ protein occludin, an important determinant for the regulation of paracellular permeability [23], which is responsible for sealing intercellular TJs [24]. This evidence suggests that the presence of occludin might reduce the paracellular route for water movement. Of note, endogenous expression of TJ proteins Z0-1 and occludin in human peritoneal mesothelial cells has been previously reported [25][26][27] and their role in limiting the paracellular passage of water and solutes has been demonstrated in bovine retinal endothelial cells [28] and in cultured human peritoneal mesothelial cells [29].

Epithelial cell polarity is essential for the establishment and maintenance of vectorial transport of ions and fluids that provides the basis for appropriate reabsorptive and secretory function. Interestingly, basolateral but not apical, addition of ouabain (100 μM), significantly reduced the I_{sc} and increased R_t, as assessed by voltage clamp technique. The existence of amiloride-sensitive apical Na^+ conductance was previously shown by Ussing experiments in mesothelial cells of human parietal peritoneum, sheep visceral peritoneum, human and sheep parietal pleura [30]. Altogether, these findings in HMC indicated a vectorial transepithelial transport of Na^+ and are consistent with the establishment of a polarized monolayer suitable for studying the role of AQP1 water channel in the transmesothelial water transport.

The lack of endogenous expression of AQP1 in HMC is not surprising as it is quite common that, in particular for AQPs, the lack of osmotic challenge in culture condition can downregulate AQPs expression. In fact, it has been reported by several groups that some AQPs, including AQP1, are regulated via osmotic response elements and hypertonicity [31][32][33][34]. The lack of endogenous expression of AQP1 in HMC gave the opportunity to test the rate of transmesothelial water transport in the absence and in the presence of AQP1, given that, besides $HgCl_2$ which is highly toxic to cells, specific drugs that inhibit AQPs function are still lacking.

Indeed, the abundant expression of AQP1 in mesothelial cells in vivo might indicate that these cells need a water channel at the plasma membrane to speed up transcellular water transport, because the paracellular pathway is not per se sufficient to guarantee adequate flow.

It is possible that the minor importance attributed so far to the mesothelium as a functional barrier toward the passage of water may be due, in some cases, to artifacts of the conventional fixation procedure, that induce loss of mesothelial cells, cells shrinkage, and appearance of intercellular gaps [35], erroneously suggesting that the mesothelium could not be a functional barrier to the passage of water.

In conclusion, (1) in vivo the mesothelium could represent a limiting barrier controlling the transcellular diffusion of water from the submesothelial interstitium to the peritoneal cavity during PD with crystalloid osmolytes and that AQP1 facilitates this process; (2) HMCs can be considered a good in vitro model to study transmesothelial transport phenomena. A number of drugs have been shown to upregulate AQP1 expression in patients [36][37][38][39]. In addition, the notion that AQP1 is upregulated by hypertonicity [34] but downregulated by glucose degradation

products [40], contained in conventional glucose-based PD solutions, suggests that new solutions with osmotic agents other than glucose, in addition to being more biocompatible [41], could better preserve the integrity of mesothelium and its AQP1 content, thus resulting in more efficient water UF.

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