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Water-only pores and peritoneal dialysis

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The article by Ni *et al.* solidifies the important role of aquaporin-1 in the process of fluid removal from anephric patients treated with peritoneal dialysis. The presence of the water-only channel in the subperitoneal endothelia provides the mechanism for solute-free ultrafiltrate observed early in dialysis and accounts for approximately half of all the filtration observed in dialysis.

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An essential part of the transport barrier for peritoneal dialysis (PD) is the blood capillary endothelium. Although animal studies have clearly shown that the elimination of the peritoneum does not alter solute or water transport, the size-discriminant portion of the barrier is located in the microvasculature, which is distributed within the tissue adjacent to the peritoneum.[1] The 'pore theory' of capillary transport was developed by Pappenheimer and colleagues[2] nearly 60 years ago. This theory hypothesized that there are small pores that permit smaller solutes such as sugars and ions to pass through the endothelium, while a lesser number of large pores allow proteins and macromolecules to transfer. Occasionally, these investigators mentioned a third pore or water-only pore, which was deemed relatively unimportant in the normally isotonic milieu on both the luminal and the interstitial side of the vascular barrier.

In contrast to the normal tissue environment, during PD the interstitial side of the blood capillaries has a markedly increased osmotic pressure due to the influx of glucose from the PD solution into the tissue surrounding the cavity.[1] Because of the difference between osmotic pressure in the interstitium and that in the capillary lumen, osmosis or ultrafiltration occurs from the lumen into the interstitium. This excess interstitial fluid transports from the tissue into the peritoneal cavity and is subsequently removed from the patient.

The decrease in sodium concentration during the first 10 to 20 minutes of a hypertonic dialysis has led researchers to the hypothesis of the water-only channel. Rippe[3] was the first to the importance of the third pore or water-only channel in his mathematical formulation of transperitoneal transport. Computer simulations of the osmosis observed during patient studies were derived from this theory, termed the 'three-pore model,' and predicted that approximately 50% of the water flow into the peritoneal cavity occurred across the water-only or transcellular pore. This was despite the fact that a very small percentage of the total pore area in the capillary wall (~2%) was made up of these transcellular pores.

Figure 1 demonstrates a modification of the original three-pore theory and illustrates the major transcellular forces across each portion of the endothelial barrier. The following multi-pore version of Starling's law describes the filtration flow across peritoneal capillaries:

$$J_v = L_p S(P_{plasma} - P_{if} - \sum_{i,j} \alpha_j \sigma_{i,j}(\pi_{i,plasma} - \pi_{i,if}))$$

where J_v is flow (flow/area), L_p is hydraulic conductivity; S is total pore area; P_{plasma} is intraluminal capillary hydrostatic pressure in plasma; P_{if} is interstitial hydrostatic pressure; α_j is the fraction of total pore area that is made up of the j^{th} pore ($\alpha_{transcellular\ pore} \approx 0.02$; $\alpha_{small\ pore} \approx 0.95$; $\alpha_{large\ pore} \approx 0.03$);[3] $\sigma_{i,j}$ is reflection coefficient of the j^{th} pore for the i^{th} solute; $\pi_{i,plasma}$ is osmotic pressure in plasma due to the i^{th} solute; and $\pi_{i,if}$ is osmotic pressure in the interstitium due to the i^{th} solute. Because $\sigma_{i,j}$ is approximately 0 for glucose transporting across the equivalent of the large pore, there is essentially no osmotic force across it, and P dominates during PD. In the small-pore equivalent, sodium and glucose have a $\sigma_{i,j}$ of approximately 0.02–0.05,[3] and a small fraction of the osmotic pressure difference exerts its force. The transcellular, water-only pore has a $\sigma_{i,j}$ of 1, making osmosis 20 to 50 times as efficient through it as across the small pore. As solutes do not follow the water through this water-only channel, solute-free filtration occurs, resulting in lowered sodium in the dialysis fluid during the early period of peak osmosis.

Discovery of *aquaporin-1* (*AQP1*) by Agre and colleagues[4] opened up an entirely new area of research in the peritoneum. Carlsson *et al.*[5] first demonstrated that *in vivo* inhibition of *AQP1* channels with mercuric chloride during PD resulted in a significant decrease in the volume of fluid filtered from the tissue into the peritoneal cavity. Subsequently, Yang *et al.*[6] used transgenic *AQP1* knockout mice to demonstrate a decrease of approximately 60% in the filtration when dialysis was carried out with a hypertonic solution; this agreed closely with predictions by Rippe and colleagues.[3] In clinical dialysis, the loss of solute-free filtrate during the initial period of the dwell has been linked to ultrafiltration failure.[7] These results implied loss of functional *AQP1*, but Goffin *et al.*[8] demonstrated that a 67-year-old man on PD for 11 years had apparently normal expression of *AQP1* despite the diagnosis of ultrafiltration failure. Therefore, there still remained a question of the linkage between expression of *AQP1* and ultrafiltration failure.

In this issue, Ni and colleagues[9]

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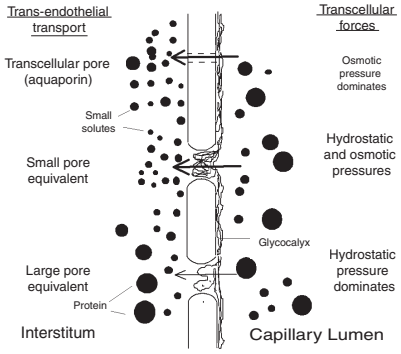

Figure 1 | The endothelial barrier to water transport during peritoneal dialysis. The barrier is portrayed as three points of transfer across the endothelium: (1) transcellular, water-only aquaporin; (2) intercellular gap lined by a dense glycocalyx (equivalent to the 'small pore' of Rippe's model);[3] (3) intercellular gap with a less dense glycocalyx that permits macromolecules to pass (equivalent to the 'large pore' in Rippe's model). The dominant transcellular forces for water transport are listed to the right for each penetration in the endothelium. The magnitude of the water transport is indicated by the thickness of the arrow.

clearly show the important role of *AQP1* in the removal of fluid from the body during PD. Using reverse transcriptase–polymerase chain reaction and immunogold electron microscopy, they demonstrate that *AQP1* is expressed in the mouse peritoneum and, in particular, in the capillary endothelium of the tissue adjacent to the peritoneum. The *AQP1* staining has been noted in the mesothelium in prior studies, but Ni *et al.*[9] have clearly demonstrated that *AQP1* is exclusively in the endothelium. Therefore, the imposition of the glucose gradient on the cells within the tissue is assumed to make only a minuscule contribution to the solute-free water. The solute-free water volume during the first hour of hypertonic dialysis (3.86% dextrose solution) has been estimated to be 135 ml of the total 404 ml of ultrafiltrate.[7] Therefore, this volume has to come from the blood capillaries, which continually circulate new fluid through the tissue.

Ni and colleagues[9] dialyzed normal mice and mice deficient in *AQP1* to directly demonstrate the flow through *AQP1* in PD. Although they measured no difference in microvascular density or the structure of capillary membrane or capillaries, the *AQP1*-deficient mice showed no sodium sieving, a 50% decrease in the net fluid removal, and a 70% decrease in the initial solute-free ultrafiltration. Heterozygous mice showed intermediate values for sodium sieving and initial ultrafiltration but had cumulative ultrafiltration similar to that of normal mice. These data provide clear evidence of the essential role of *AQP1* and the ultrafiltration phenomena during PD.

Marked changes in the filtration of solute-free water, overall net ultrafiltration, and glucose transport have been recorded during cases of peritonitis or chronic peritoneal inflammation. There is still the major question of the mechanism of this loss of ultrafiltration. Is it due to a decrease in functional aquaporin or to the injury of the glycocalyx, which lines the inter-endothelial clefts to form the transport paths of the small-pore and large-pore equivalents (Figure 1)? In the pore-matrix theory,[10] a cell-surface glycocalyx determines the permeability of the spaces between the cells. Most of these spaces are densely lined and allow only small molecules to transport (small-pore equivalent). However, occasionally the glycocalyx is decreased in density and larger molecules can pass through (large-pore equivalent). During inflammation, cytokines cause major changes in the glycocalyx and the permeability of capillaries.[11] Other questions concern the nature of the capillary barrier during angiogenesis, which has been demonstrated to occur in the submesothelial layer during episodes of inflammation. It may be that during peritonitis or chronic peritoneal inflammation, the so-called small-pore equivalent becomes hyper-permeable because of the loss of the glycocalyx. Although loss of *AQP1* would certainly decrease the observed ultrafiltration, alteration of the glycocalyx would markedly increase the permeability of these channels to solutes such as glucose or sodium. If this sodium were transported from the capillary lumen to the interstitium and out into the cavity at the same rate at which solute-free water was transferred through the aquaporin, there would be no solute-free ultrafiltration. Simultaneously, rapid transfer of glucose across the endothelium would rapidly dissipate the osmotic gradient and diminish ultrafiltration.

At this point, the complete mechanism of ultrafiltration failure at the cellular and the capillary level is unknown. The delineation of the function of *AQP1* in this mouse model is the first step in unraveling the mysteries of the peritoneal barrier at the molecular level. The functional role of a glycocalyx in normal conditions and during peritoneal inflammation, the role of the interstitium and of possible signaling between mesothelial, interstitial, and endothelial cells, and the role of the generalized fibrosis that occurs in the submesothelial compact zone all require investigation before we can fully understand ultrafiltration during PD and its failure under inflammatory conditions.

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