Mechanisms of oedema in nephrotic syndrome: old theories and new ideas

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Interstitial oedema is a common clinical expression of nephrotic syndrome. Expansion of the interstitial compartment is secondary to the accumulation of sodium in the extracellular compartment, due to an imbalance between oral or parenteral sodium intake and urinary sodium output, along with alterations of fluid transfer across capillary walls.

Molecular mechanism of sodium retention

The intrarenal site of sodium retention was determined by an in vivo micropuncture study in the unilateral model of puromycin aminonucleoside (PAN)-induced proteinuria, which allows the study of a nephrotic and a normal control kidney within the same animal. Sodium delivery to the collecting duct was not different in the two kidneys while the urinary excretion of sodium was 3-fold lower in the nephrotic kidney compared with the control kidney, suggesting that stimulation of tubular sodium reabsorption originated in the collecting duct [1]. The molecular mechanisms of renal sodium avidity have been elucidated recently. The hydrolytic and transport activities of Na,K-ATPase are increased 2-fold in the cortical collecting duct of PAN nephrotic rats [2,3]. The stimulation of Na,K-ATPase is restricted to the cortical collecting duct (CCD) [4] and is associated with decreased urinary sodium excretion, positive sodium balance and generation of ascites [5]. Moreover, a linear inverse correlation between urinary sodium excretion and CCD Na,K-ATPase activity has been observed in three different experimental models of nephrotic syndrome [5]. The Na-pump stimulation relies on increased synthesis and basolateral plasma membrane delivery of Na,K-ATPase subunits [4]. Indeed, the proportional increase in Na,K-ATPase activity, cell surface expression and total cellular content is associated with increased amounts of α and β subunit mRNAs in CCDs from PAN nephrotic rats [4]. In addition to the stimulation of Na,K-ATPase activity, amiloride-sensitive transepithelial voltage and sodium transport measured by in vitro microperfusion are increased in CCDs from PAN nephrotic rats [6]. Patch–clamp analysis of the apical membrane of CCD principal cells from PAN nephrotic rats revealed increased ENaC activity in the absence of transcriptional induction of the mRNAs encoding any of the three ENaC subunits [7]. To summarize, sodium retention in the nephrotic syndrome takes place in the CCD and relies on a coordinated overactivity of Na,K-ATPase and ENaC. The renal sodium retention should normally be counterbalanced by enhanced secretion of sodium in the inner medullary collecting duct, brought about by the release of atrial natriuretic peptide (ANP). This regulatory pathway is curtailed in patients and rats with nephrotic syndrome by enhanced catabolism of cyclic GMP following phosphodiesterase activation [8].

Role of systemic factors

The historical theory of nephrotic oedema generation postulates that stimulation of the renin–aldosterone axis in response to hypovolaemia mediates sodium retention through the following sequence of events: low serum albumin with decreased plasma oncotic pressure results in an imbalance of Starling forces in capillaries leading to interstitial leakage of fluid, hypovolaemia and stimulation of the renin–aldosterone system [9]. However, a large body of clinical and experimental findings is opposed to this theory.

(i) Analbuminaemic patients and rats develop neither oedema nor sodium retention despite low plasma oncotic pressure [10,11].
Mechanism of oedema generation

The extracellular volume expansion subsequent to the renal sodium retention of nephrotic syndrome is not symmetrical between the interstitial compartment and the blood volume. Indeed, the blood volume does not increase in proportion with the major enlargement of the interstitial compartment [24]. This asymmetry is accounted for by an abnormal fluid balance between these two compartments. The fluid rate through the capillary wall is determined by the Starling law [25]:

\[ J_v = L_p S \times (P_c - P_i - \sigma (p_p - p_i)) \]

where \( J_v \) is the transcapillary fluid flow rate, \( L_p \) the hydraulic conductivity of the capillary, \( S \) the capillary exchange surface, \( P_c \) the capillary hydrostatic pressure, \( P_i \) the interstitial hydrostatic pressure, \( \sigma \) the capillary reflection coefficient for plasma proteins, \( p_p \) the plasma oncotic pressure and \( p_i \) the interstitial oncotic pressure.

Asymmetric extracellular expansion was classically attributed to the decrease in plasma oncotic pressure and the subsequent increase in transcapillary oncotic gradient. However, as already mentioned, the absence of oedema in analbuminaemic rats and patients raises the question of the role of low oncotic pressure in the determinism of oedema formation [10,11]. The transcapillary oncotic gradient is unchanged in patients with nephrotic syndrome (6.2 vs 8.7 mmHg in normal people) and in animal models of low plasma oncotic pressure, such as analbuminaemic rats (11.3 ± 0.7 vs 12.2 ± 0.3 mmHg in control rat) and dogs undergoing plasma exchange against a protein-free solution and fed with a low protein diet [10,26,27]. In addition, oncotic pressures of the plasma and interstitium exhibit a linear relationship [27]. Moreover, the association of two diuretics (furosemide and amiloride) results in oedema removal despite persistent low plasma oncotic pressure and unaltered transcapillary oncotic pressure gradient (6.5 ± 1.5 vs 6.2 ± 1.7 mmHg before and after natriuresis, respectively) [27]. Similarly, to the transcapillary oncotic pressure gradient, the transcapillary hydrostatic pressure gradient is not modified in nephrotic patients [28]. This observation relies on the high compliance of subcutaneous and muscle tissues in response to overfilling [29]. Conversely, the capillary filtration capacity is higher in nephrotic patients than in controls, suggesting an impairment of capillary conductivity [28]. Capillary hydraulic conductivity is determined by intercellular macromolecular complexes between endothelial cells, namely tight junctions made of occludin, Claudins and ZO proteins, and adherens junctions made of cadherin, catenins and actinin. These junctional complexes are closely related to the actin cytoskeleton [29]. In diabetes, protein kinase C (PKC) activation leads to increased capillary permeability through changes in occludin phosphorylation [30,31]. A similar mechanism may also increase the capillary hydraulic conductivity in nephrotic patients, owing to an abnormal level of a circulating plasma protein targeted to tight junctions. One of these proteins could be tumour necrosis factor \( \alpha \), whose plasma level is increased in nephrotic patients and which is able to alter capillary permeability through PKC activation [32,33]. In addition, hypoalbuminaemia and increased circulating ANP occurring in nephrotic syndrome enhance the capillary hydraulic conductivity through alterations of intercellular junctional complexes permeability [34,35].
Moreover, albumin extravasation into the interstitial compartment, whereby the reflection coefficient is studied, is increased in nephrotic syndrome and may also account for imbalanced Starling forces [36].

To summarize, the asymmetry of volume expansion, which has been traditionally attributed to the decrease in plasma oncotic pressure, is more likely due to an alteration of the capillary hydraulic conductivity, possibly linked to functional changes at the level of intercellular junctions. The low plasma oncotic pressure does not unbalance the transcapillary oncotic gradient and cannot be considered as a determining factor in oedema generation or as a resistance factor for oedema resorption. Therefore, diuretics preventing renal sodium retention remain the cornerstone of treatment of nephrotic oedema. Accordingly, the association of amiloride and furosemide provides a powerful treatment allowing progressive removal of oedema from nephrotic patients [37].

References

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