The cause of edema formation in the nephrotic syndrome has been an area of intense interest by nephrologists for decades. Klisic et al. (1) in this issue of JASN have added an interesting and important new finding to the complexity of our understanding of the nephrotic syndrome. They demonstrate that apical albumin directly stimulates NHE3 (sodium hydrogen exchanger 3), the major apical transporter responsible for proximal tubule sodium reabsorption.

The relationship between edema and proteinuria was probably first noted in 1764 by Domenico Cotugno (Dominicus Cotunnuis), who described a 28-yr-old soldier with, “...a wonderful eruption of intercutaneous water...whose urine when evaporated over fire formed itself into a white mass, like the soft of an egg when boiled” (2). Classically, the edema formation of nephrotic syndrome was considered to be secondary to increased sodium retention from intravascular volume depletion from low plasma oncotic pressure. In recent years, this has been referred to as the “underfill” hypothesis. However, beginning in the 1940s and particularly in the past two decades, many studies have supported the conceptually opposite idea, the so-called “overfill” hypothesis of primary sodium retention in at least some patients and in certain experimental models. As thoroughly reviewed before (3,4), although some patients with minimal change nephrotic syndrome have low plasma volumes, many patients with the nephrotic syndrome do not manifest many of the expected findings of the underfill hypothesis (e.g., low measured plasma volume, elevation of sodium-retaining hormones, etc.).

The most direct demonstration of sodium retention resulting directly from proteinuria per se were classic studies by Chandra et al. (5) and Ichikawa et al. (6). These studies showed that unilateral renal PAN (puromycin aminonucleoside) infusion led to both unilateral proteinuria and sodium retention by that kidney. This demonstrated that the sodium retention was not dependent on systemic factors or hypoalbuminemia (which was not present) since the opposite nontreated kidney had normal sodium handling. The studies by Ichikawa et al. (6) further examined segmental sodium transport by micropuncture; sodium transport was actually slightly decreased in the proximal tubule. Sodium delivery to the end of the superficial distal tubule was the same in both the PAN-treated and nontreated kidneys, implying that the sodium retention in the proteinuric kidney occurred in the collecting duct.

The mechanism of increased sodium reabsorption by the collecting duct in proteinuric kidneys has also been examined. Doucet’s group have observed increased sodium transport and Na-K-ATPase in collecting ducts in vitro from kidneys with proteinuria (7,8). Other studies have shown that cGMP phosphodiesterase activity in the collecting ducts (and glomeruli) of proteinuric animals is increased, leading to resistance to ANP actions (9,10).

Only a few studies have supported the proximal tubule as the site of increased sodium reabsorption in the nephrotic syndrome (11). However the present in vitro studies on NHE3 was preceded by a recent study from the same group that demonstrated that the PAN model of nephrosis increases NHE3 in vivo (12). The current studies by Klisic et al. (1) show that NHE3 is activated in vitro at several levels (functional activity, mRNA, trafficking) by albumin. There is a complicated interaction with hydrocortisone, which itself activates NHE3 at multiple levels. These studies are particularly valuable in demonstrating that the effect of albumin is direct and not a consequence of secondary in vivo effects.

What do these studies tell us about the nephrotic syndrome? The findings are difficult to reconcile with the previous findings on the prominent role of the collecting duct. Perhaps the main implications are in another direction: linkage to fibrosis and inflammation in some nephrotic diseases. Previous studies have linked increased albumin endocytosis (protein overloading) in the proximal tubule and NHE3 (13); inhibition of NHE3 in vitro decreases albumin endocytosis (13), and NHE3-dependent albumin endocytosis is partially linked to activation of nuclear factor-κB (NF-κB)(14). Therefore, activation of NHE3 by albumin may be related to the renal inflammation and fibrosis, which has been postulated to lead to both progression of renal disease and salt retention (15,16).

The sodium retention leading to edema formation in the nephrotic syndrome likely has a spectrum of pathogenic mechanisms, some underfill some overfill, among patients. A number of mechanistic components have been previously identified; now increased NHE3 joins the enigma.
References


See related article, “Albumin Regulates the Na⁺/H⁺ Exchanger 3 in OKP Cells,” on pages 3008–3016.