Pathophysiology and treatment of edema in adults with the nephrotic syndrome

Esmat Abdollahpour, MD, nephrologist, academic member, Shariati Hospital, TUMS

Nephrotic syndrome:
Edema (+ proteinuria, hypoalbuminemia, dyslipidemia)

Incidence of nephrotic syndrome in adults: approximately 2.7–3 new cases per 100,000 people per year

serious implications:

- symptomatic or asymptomatic pulmonary congestion
- cardiovascular risk
- Hypertension
- Risk of local or systemic infections
- anasarca, including nephrosarca
- impaired mobility

underfill hypothesis

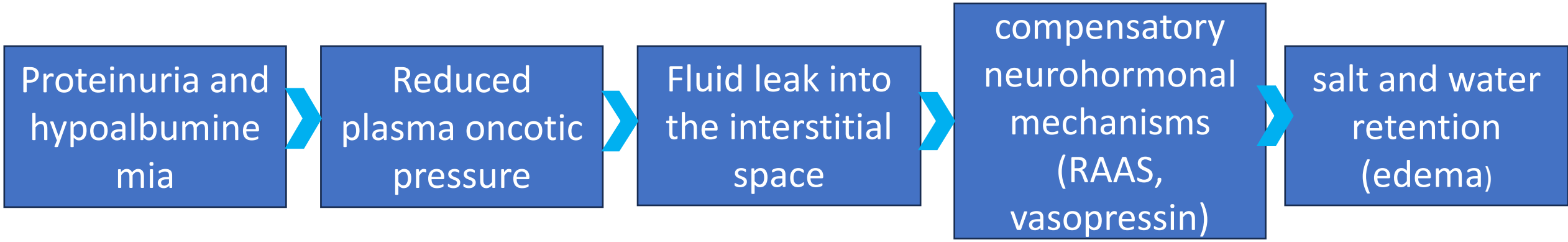
- The basic mechanism of the underfill hypothesis is explained by proteinuria leading to hypoalbuminemia, which results in reduced plasma oncotic pressure, which further induces fluid to leak into the interstitial space and thus causes edema

overfill hypothesis

- kidney-limiting mechanism of sodium retention in the presence of proteinuria

- These two hypotheses are not entirely separated but actually interact with each other, with one of them being more pronounced in individual patients
- Determining them is the most important step in the treatment of nephrotic edema because, ultimately, the goal of treatment is to eliminate excess water with minimal complications

Underfill hypothesis


Proteinuria and hypoalbumine mia
Reduced plasma oncotic pressure
Fluid leak into the interstitial space
compensatory neurohormonal mechanisms (RAAS, vasopressin)
salt and water retention (edema)

Edema development, a dynamic process involving three steps

Step 1

- Initial proteinuria without edema but with increased aldosterone levels, increased renal flow and sodium retention

Step 2

- Hypovolemia with edema and persistently increased aldosterone levels and sodium retention

Step 3

- Edema without hypovolemia or sodium retention and normal plasma aldosterone

- At first, edema is absent because of compensatory factors such as increased lymphatic flow and increased interstitial hydrostatic pressure due to fluid movement from the intravascular space, and these factors simultaneously act like a protective shield against further fluid entry and reduced interstitial oncotic pressure, which thus minimizes the transcapillary pressure gradient

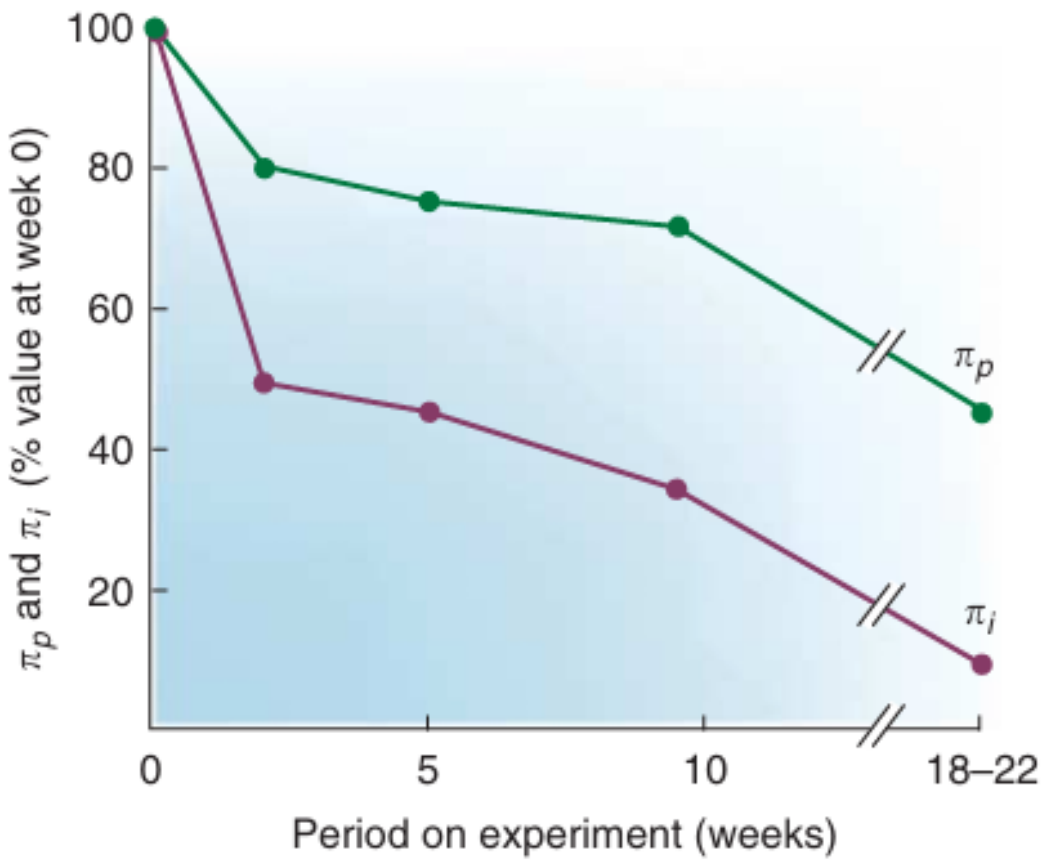
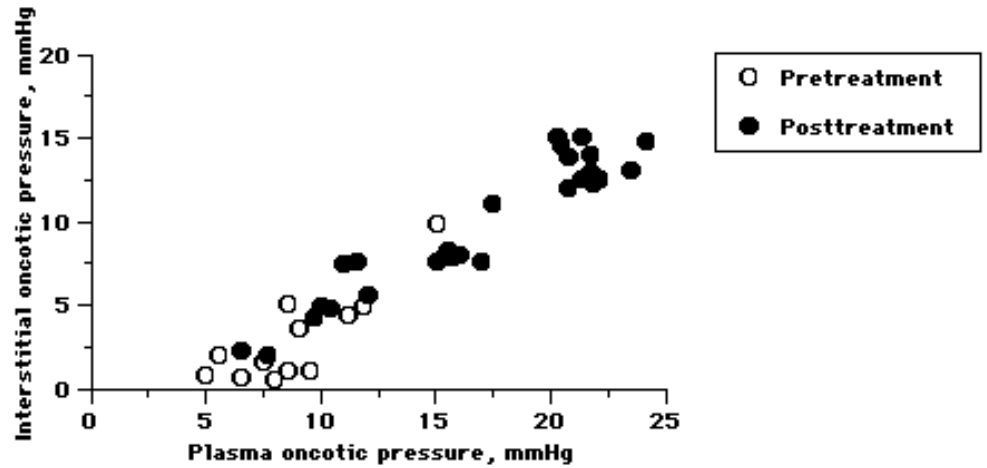


Figure 1 | As serum oncotic pressure declines, there is a parallel decline in interstitial oncotic pressure of greater magnitude in rats fed a very low protein diet (adapted from Fiorotto and Coward[7]).

Kidney International (2012) 82, 635–642

Little change in oncotic pressure gradient in nephrotic syndrome



Relation between plasma and interstitial oncotic pressures in patients with the nephrotic syndrome due to minimal change disease before (open circles) and after (closed circles) steroid-induced remission of the proteinuria. Both parameters are reduced in the nephrotic state, resulting in little change in the transcapillary oncotic pressure gradient and therefore little tendency to promoting edema formation.

Data from Koomans, HA, Kortlandt, W, Geers, AB, Dorhout Mees, EJ, Nephron 1985; 40:391.

Hypoalbuminemia

In patients receiving steroid treatment, volume tends to correct itself well before albumin does

Hypovolemia

Using radioactive albumin in patients with nephrotic syndrome showed normal or increased plasma volume, implying that hypovolemia is only a minor cause of salt retention

RAAS

- Patients with nephrotic syndrome can have high, low, or even normal renin levels, mainly because edema is a dynamic process
- patients with high renin levels have tubular dysfunction leading to sodium retention and a generalized increase in capillary leakage that prevents volume expansion, changes most commonly observed in MCD.
- Patients with low renin levels have decreased sodium excretion due to impaired glomerular filtration, leading to volume expansion, as is the case for most glomerulonephritis
- The role of angiotensin II in the proximal tubular uptake of sodium via AT1 in nephrotic syndrome is controversial.
- angiotensin II increases sodium reabsorption in the CCD system through ENaC aldosterone-independent stimulation
- localized mechanism to explain edema rather than a systemic factor such as hyperaldosteronism
- ENaC activity was correlated with increased aldosterone levels

arginine vasopressin

- Increased serum osmolality or decreased arterial blood volume stimulates AVP secretion, as may be the case in nephrotic edema
- there are studies and case reports indicating apparently elevated ADH in "overfill" patients, suggesting a possible pathological increase in ADH in nephrotic syndrome patients

sympathetic nervous system activity

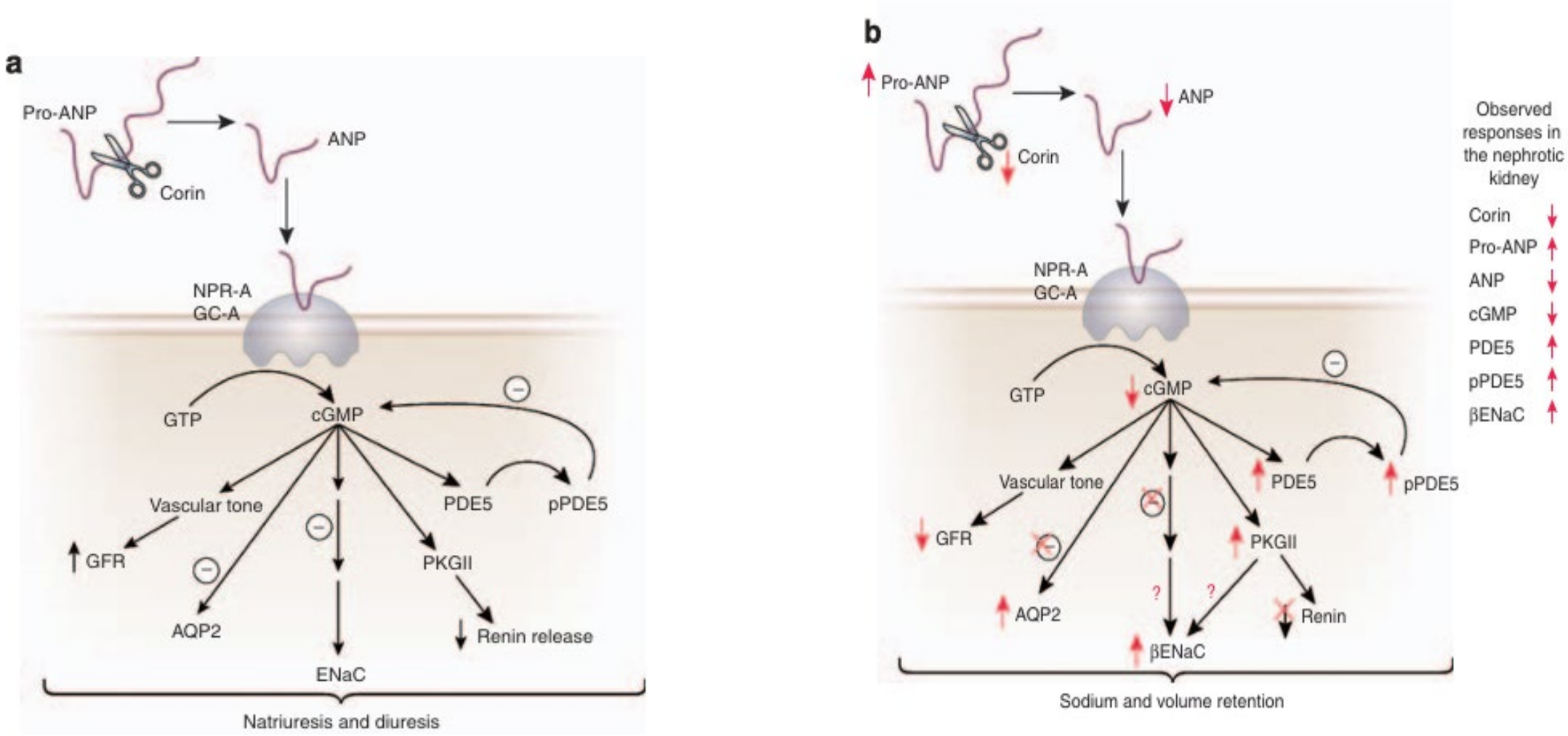
- Physiological responses to hypovolemia include increased SNS activity, which in turn leads to increased renin secretion
- another mechanism: the inhibitory effect of the cardiopulmonary baroreflex on the sympathetic nervous system, decreased cardiopulmonary reflex in nephrotic syndrome with an attenuated inhibition of renal sympathetic activity, possibly due to increased RAAS activity

Atrial natriuretic peptide

- Volume expansion causes atrial-wall stretching, and, in response, cardiac muscle cells in the heart's atria produce ANP.
- Main function: to decrease extracellular fluid intake by stimulating natriuresis in the collecting duct.
- Nephrotic edema has specific resistance to ANP

Three possible mechanisms:

1. the rapid degradation of ANP via cGMP as a result of plasmin loss, which activates phosphodiesterase (PDE).
2. an increase in levels of a cyclophilin-like protein, which decreases sodium excretion. Nephrotic syndrome and higher ANP levels cause an upregulation of this protein
3. corin, a serine/threonine protease that cleaves the pro-form of ANP into active ANP. Atrial cardiomyocytes secreted corin. both ANP and corin are present in the kidney.



| Influence of corin in the nephrotic kidney

- Decreased corin and ANP levels in the nephrotic kidney.
- Higher ENaC activity was linked to lower corin levels.
- The importance of corin and ANP in treating nephrotic edema

Kidney International (2010) 78, 635 – 637. doi: 10.1038/ki.2010.223

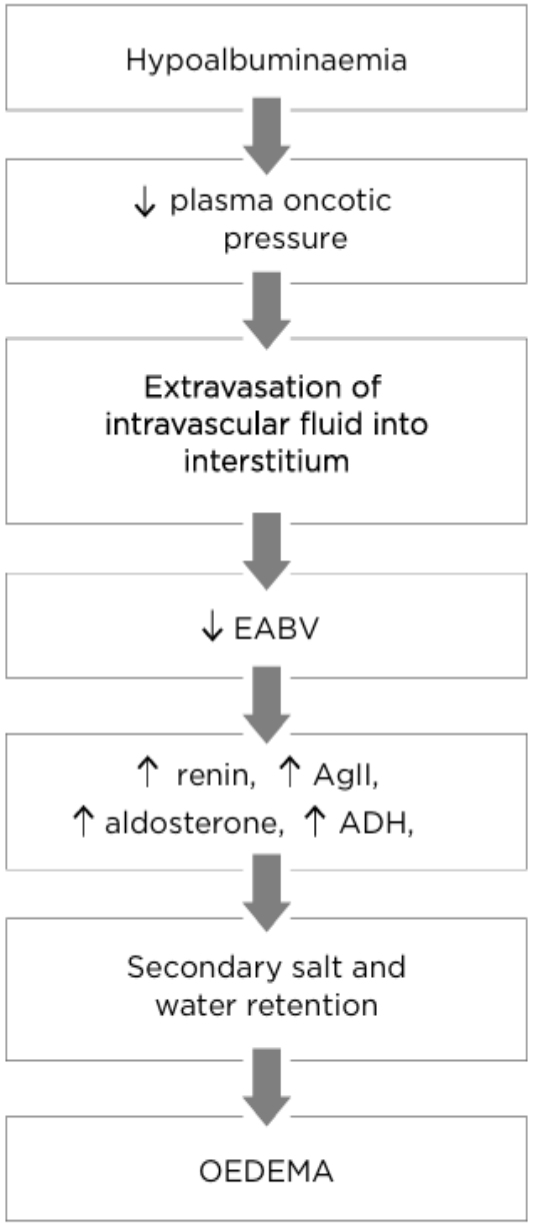


Figure 1: The pathophysiology of oedema formation according to the 'underfill' theory.

EMJ Urol. 2021;9(1):107-117.

Overfill hypothesis

Three main targets:
NHE3
ENaC
Na/K ATPase

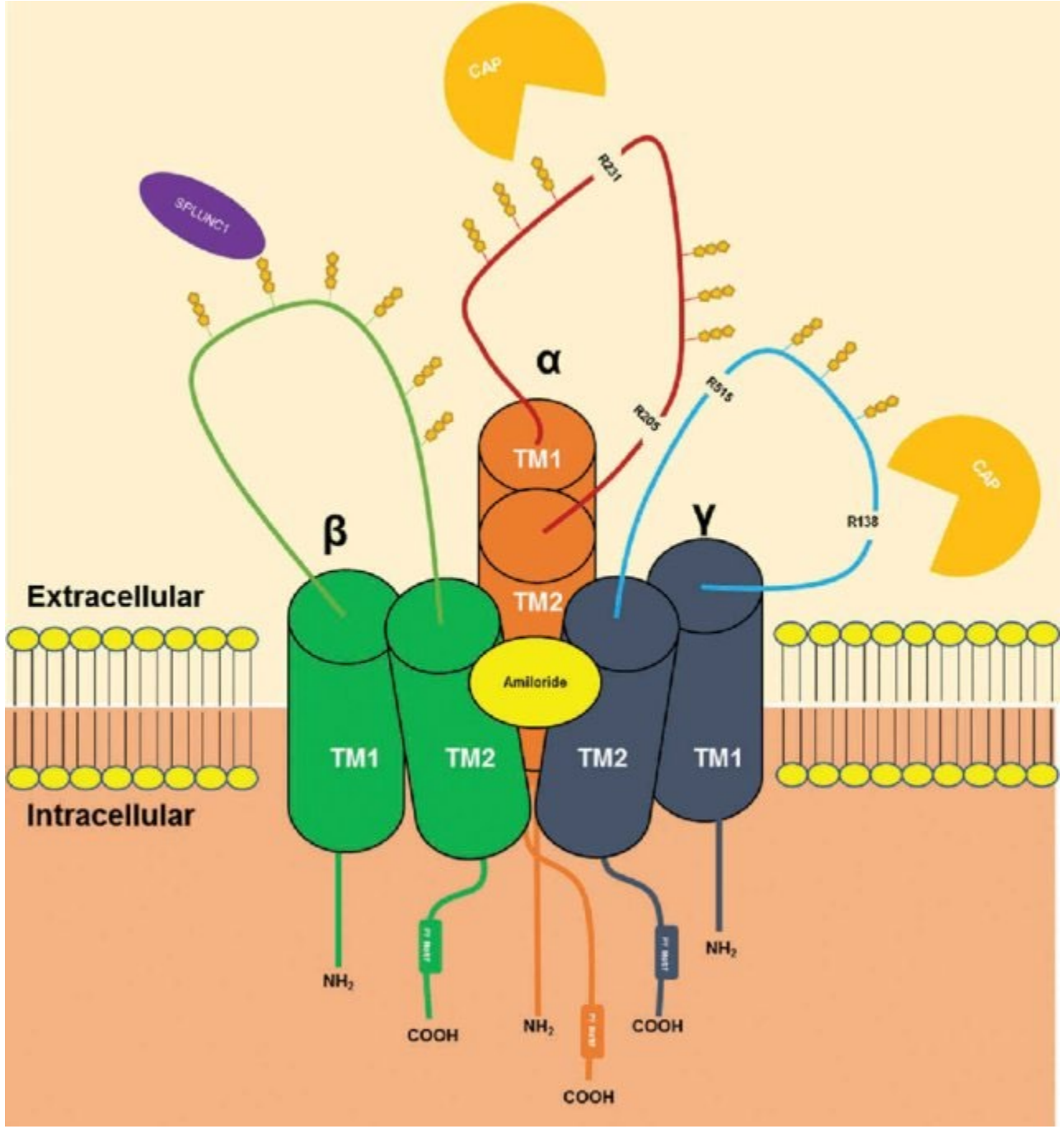
Increased NHE3 activity in nephrotic syndrome or non-nephrotic proteinuria

- The megalin receptor and the inactive form of NHE3, which is bound to megalin
- In the case of proteinuria, megalin attempts to reabsorb proteins as much as possible, releasing NHE3.
- NHE3 is recycled back to the cell surface from the endosome when albumin is present, leading to increased sodium retention in the proximal tubule

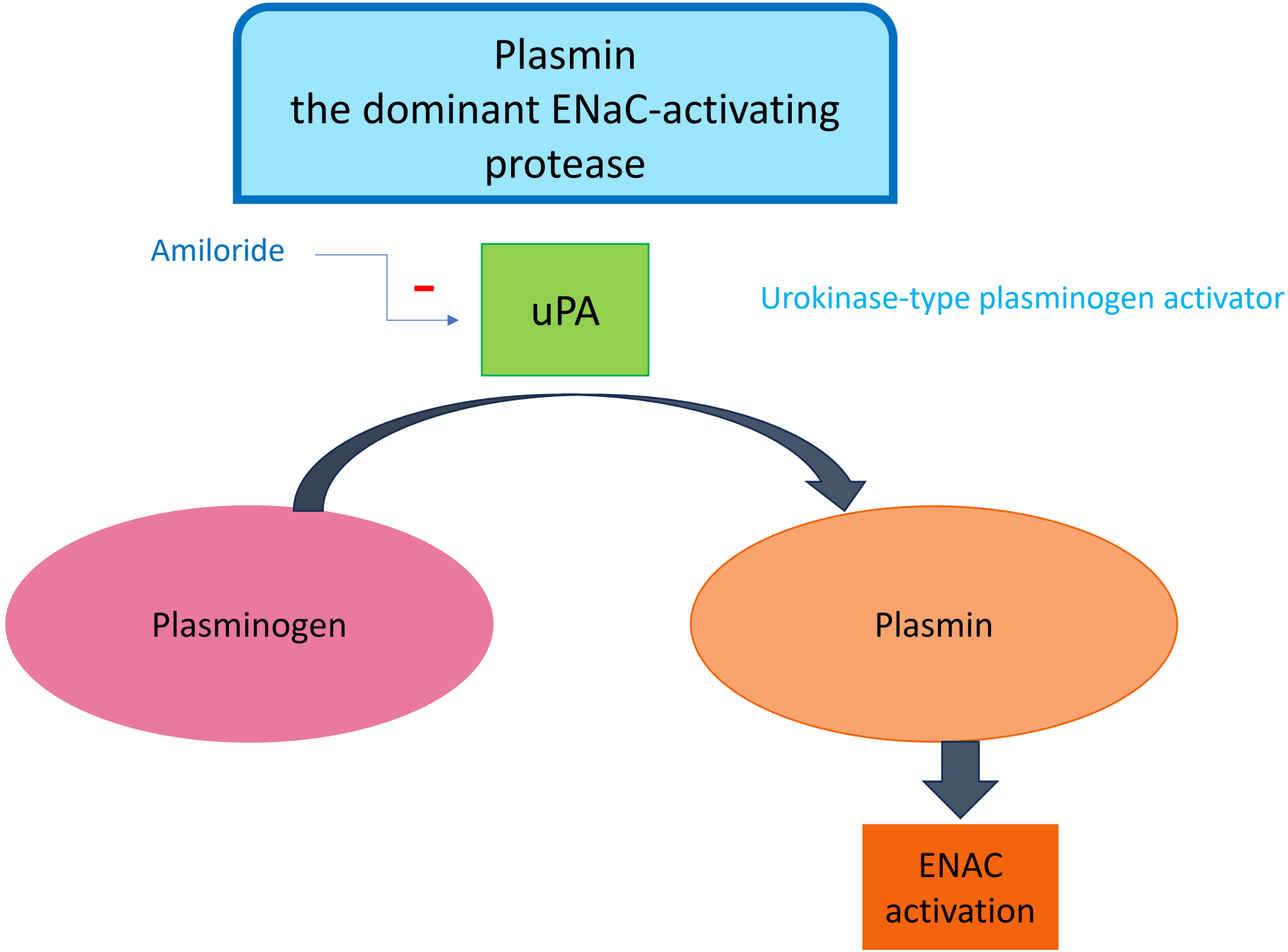
Serin Proteases

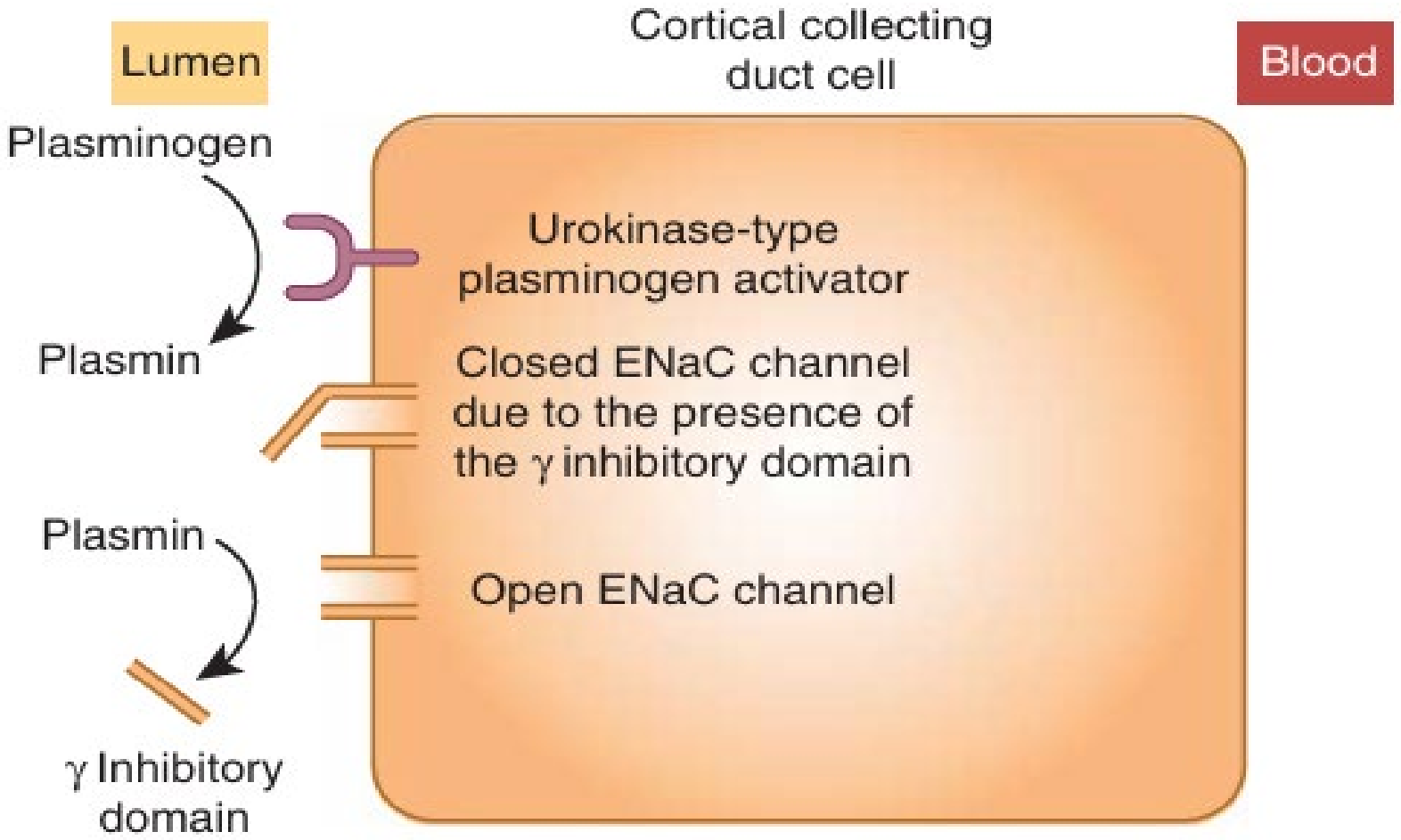
The ENaC has three types of subunits—alpha (α), beta (β), and gamma (γ). Each subunit possesses two transmembrane domains that form an extracellular loop with both carboxyl and amino termini in the cytoplasm.

Structural features of the epithelial Na + channel (ENaC). ENaC exists as a heterotrimer consisting of α, β, and γ subunits. Each subunit contains two membrane spanning domains with intracellular N-and C-termini. The extracellular domains contain sites for proteolytic cleavage while the PY motif in the C-termini is the site for ubquination.



- Trypsin or chymotrypsin: a two- to threefold increase in sodium reabsorption.
- These proteases either directly or indirectly (via hormonal, paracrine, or trafficking pathways) regulate the ENaC because it was not possible to demonstrate direct cleavage of the ENaC extracellular loop
- The ENaC undergoes proteolysis due to trypsin or chymotrypsin.


Plasmin
the dominant ENaC-activating protease
Amiloride
-
uPA
Urokinase-type plasminogen activator
Plasminogen
Plasmin
ENAC
activation



Kidney International (2012) 82, 635–642

- uPA activity is not mandatory for sodium retention.
- Hypervolemia is developed, mainly through the action of other proteases, such as kallikrein.
- volume expansion due to serine proteases encompasses not only nephrotic syndrome but also other proteinuric clinical conditions, such as preeclampsia and diabetic nephropathy

- ENaC maturation involves the proteolytic processing of the alpha and gamma subunits
- Gradual activation of the ENaC requires cleavage at different sites in the extracellular domains of both the alpha and gamma subunits.
- Proteolytic cleavage plays an important role in regulating these channels' activity by increasing their opening probability.
- Channels lacking proteolytic activity have a low probability of opening.

Furin

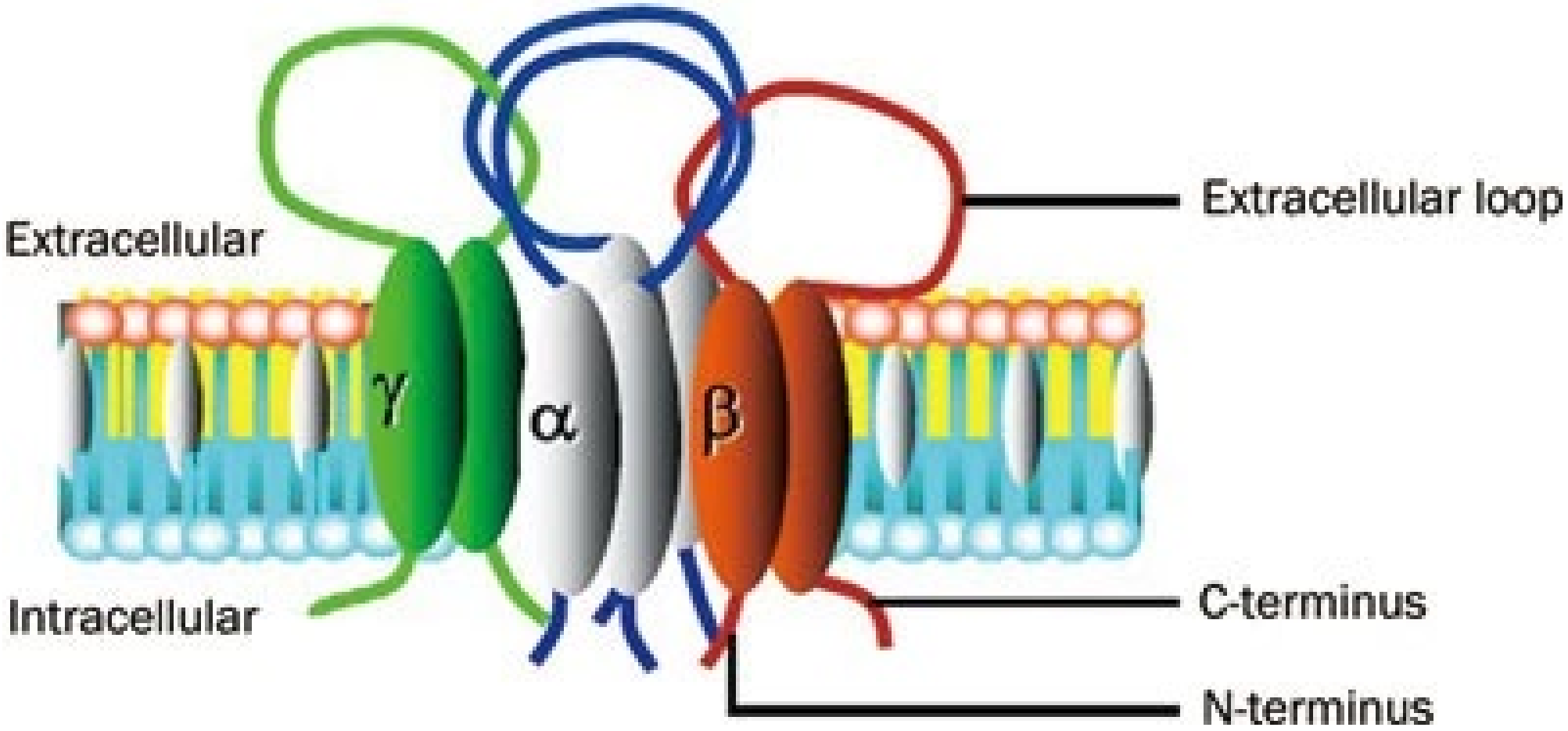
- trans-Golgi network protease
- intermediate probability of opening
- cleaving the alpha subunit of the ENaC at two different sites and its gamma subunit at one site

Prostasin

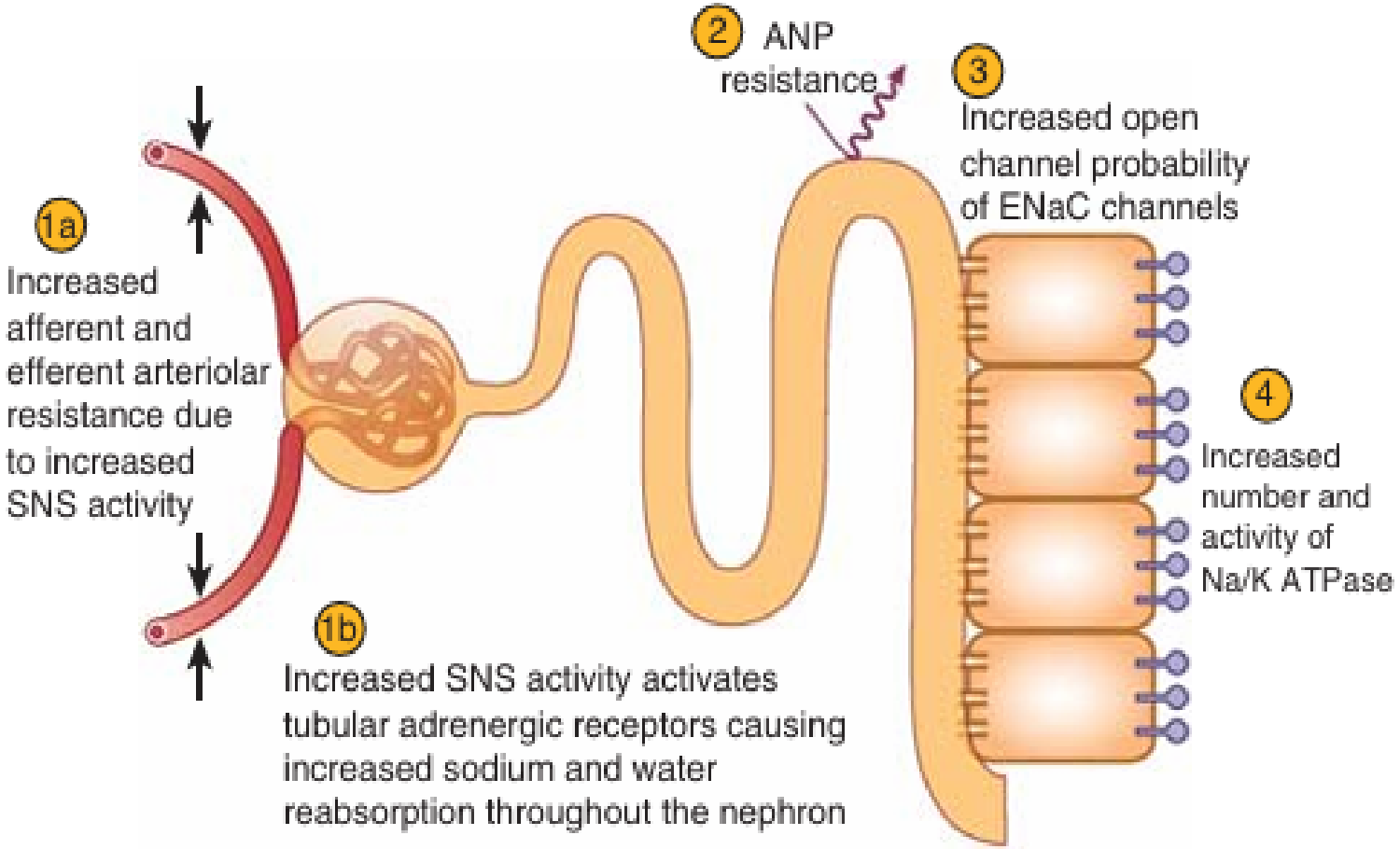
- Dual gamma-subunit cleavage via a second protease, such as prostasin
- vast list of additional proteases, capacity to cleave the gamma subunit (TMPRSS4, matriptase, cathepsin B, elastase, kallikrein and plasmin)

higher levels of furin-cleaved ENaC in diuretic-treated subjects

Furin + Prostasin Furin

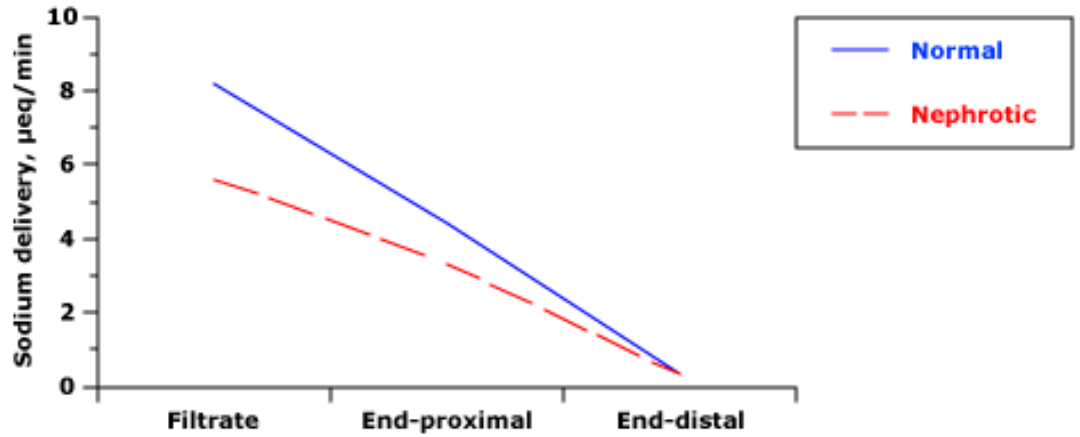


The topology of ENaC. ENaC consists of at least three subunits including α, β, and γ subunits, each of which possesses two transmembrane domains, a large extracellular loop, a cytoplasmic C-terminal domain and an N-terminal domain.



Kidney International (2012) 82, 635–642

Increased collecting tubule sodium reabsorption in nephrotic syndrome



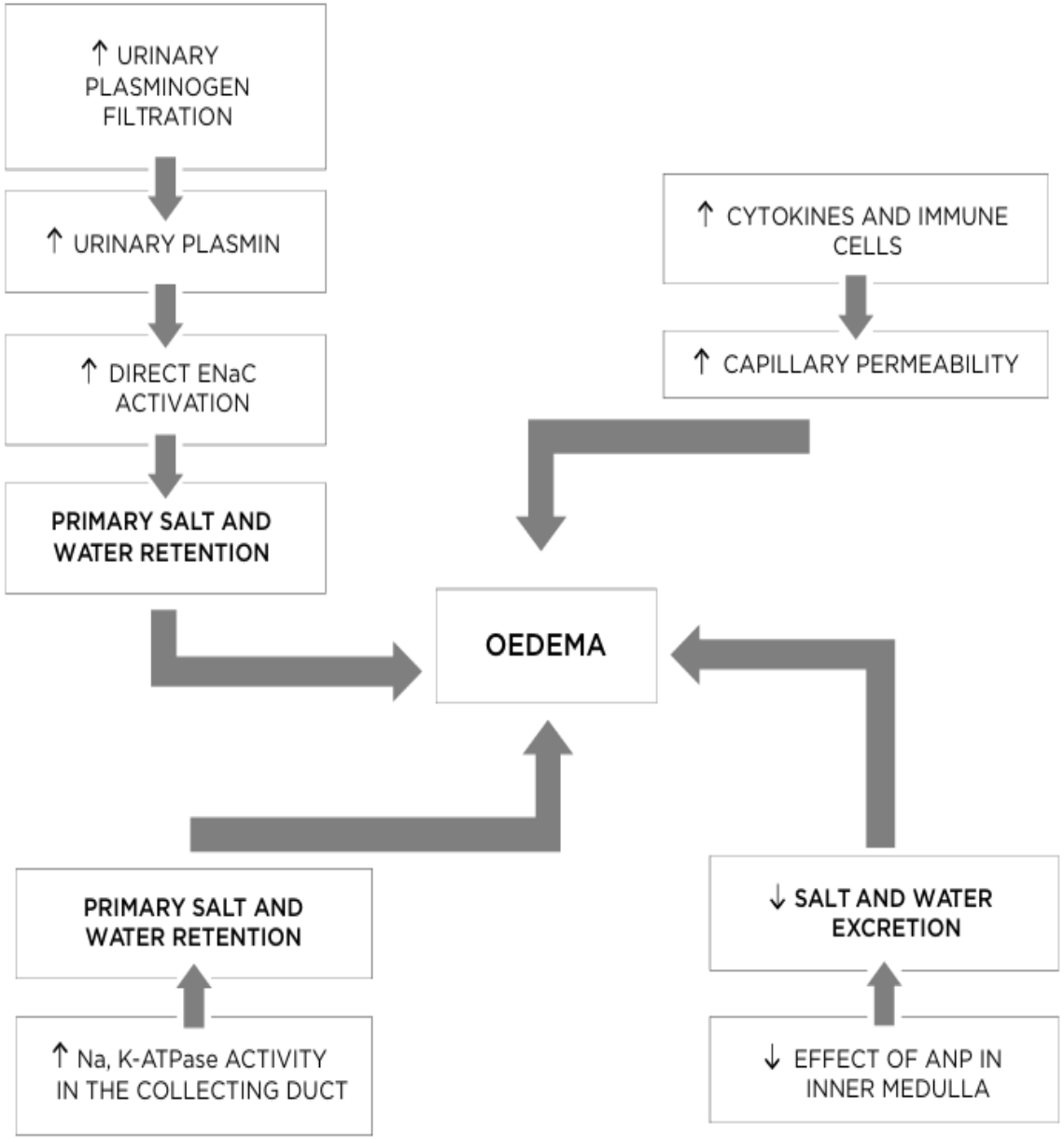


Figure 2: The pathophysiology of oedema formation according to the 'overfill' theory.

EMJ Urol. 2021;9(1):107-117

Assessment of the predominant mechanism involved in nephrotic edema

Certain laboratory markers, such as serum aldosterone, vasopressin, ANP, norepinephrine, and even urinary sodium and potassium

The TTKG index : an indirect measure of serum aldosterone.

Increases in hypovolemia patients

Certain clinical features (signs and symptoms of hypovolemia and hypoperfusion) and accessible laboratory markers (serum albumin, creatinine, eGFR, and hematocrit) help to differentiate between underfill and overfill nephrotic edema.

TABLE 2 | Mechanism of edema formation in nephrotic syndrome: "underfilling."

Clinical characteristics
Neuromuscular weakness, pallor, cool extremities, tachycardia, and other signs and symptoms of orthostatic hypotension, abdominal pain secondary to gut edema, abdominal compartment syndrome, or thrombosis of vena cave or renal veins
Laboratory findings
Reduced urine volume
$FE_{Na+} < 0.2\%$
$UK^+/UK^+ + Na^+ > 60\%$ (increased TTKG index)
Reduced urinary Na^+ and high potassium concentration
Very low serum albumin (≤2 g/dL)
Low serum creatinine level
GFR > 75 mL/min/1.73 m^2
Hemoconcentration
High circulating PRA, aldosterone, vasopressin, and norepinephrine
Low ANP concentration

FE_{Na+}, fractional excretion of sodium; UK^+ and UNa^+, urinary potassium and sodium concentrations; TTKG, transtubular potassium gradient; GFR, glomerular filtration rate; PRA, plasma renin activity; ANP, atrial natriuretic peptide.

Ellis D (2016) Pathophysiology, Evaluation, and Management of Edema in Childhood Nephrotic Syndrome. Front. Pediatr. 3:111. doi: 10.3389/fped.2015.00111

TABLE 3 | Mechanism of edema formation in nephrotic syndrome: "overfilling."

Clinical findings
Normal or elevated BP without tachycardia or orthostatic symptoms, and no signs to indicate distal extremity hypoperfusion
Laboratory findings
FE_{Na+} > 0.5% while on no salt restricted diet
$UK^+/UK^+ + UNa^+$ < 60% (decreased TTKG index)
Hematuria and cellular casts
Serum albumin >2 g/dL
Elevated serum creatinine and BUN
GFR < 50 mL/min/1.73 m^2
Decreased vasopressin
Low circulating PRA and norepinephrine
Low or normal plasma aldosterone
High ANP

FE_{Na+}, fractional excretion of sodium; UK^+ and UNa^+, urinary potassium and sodium concentrations; TTKG, transtubular potassium gradient; GFR, glomerular filtration rate; PRA, plasma renin activity; ANP, atrial natriuretic peptide.

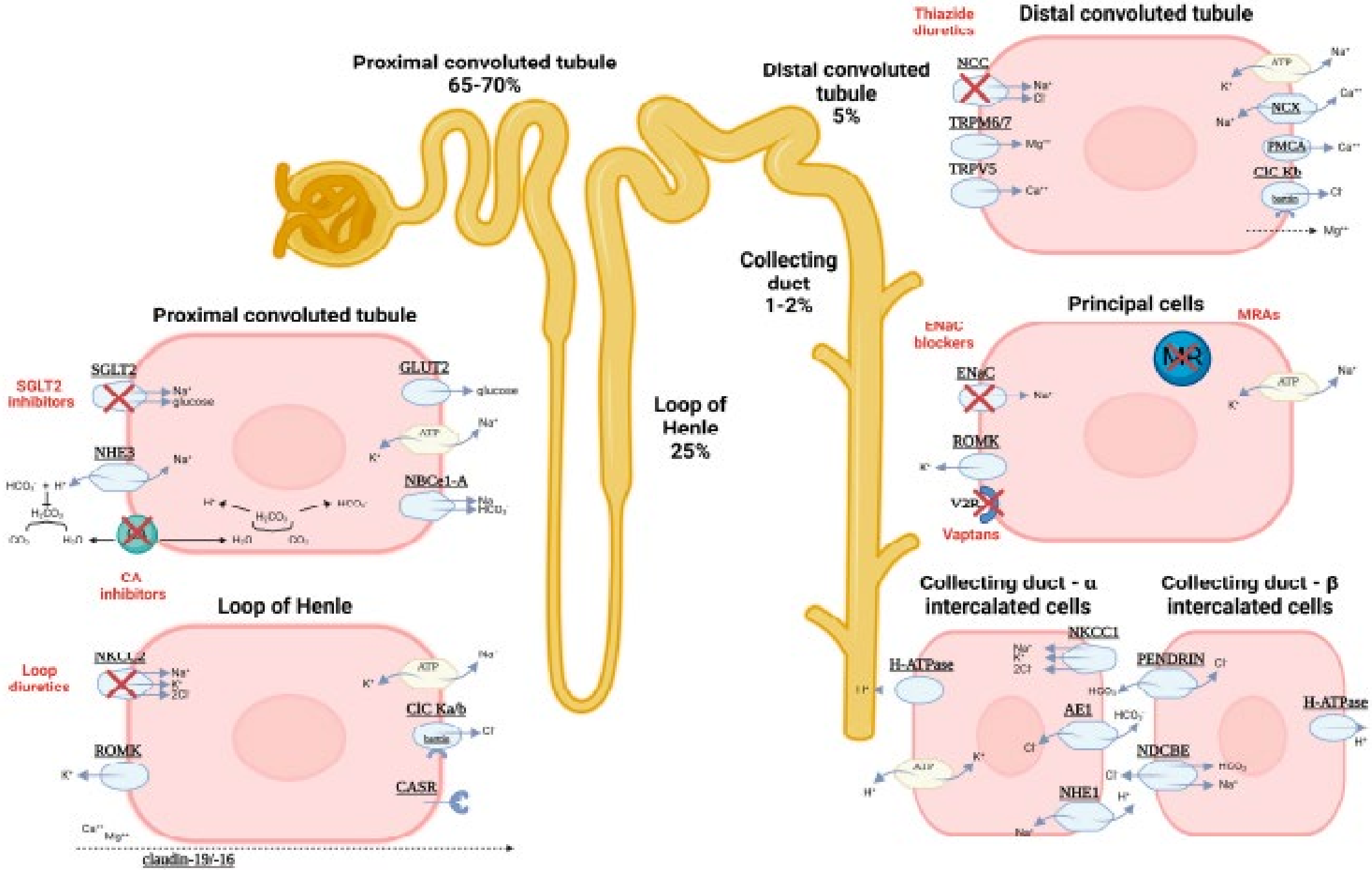
Ellis D (2016) Pathophysiology, Evaluation, and Management of Edema in Childhood Nephrotic Syndrome. Front. Pediatr. 3:111. doi: 10.3389/fped.2015.00111

Treatment

- Differentiation between underfill and overfill nephrotic edema is a very important step, as the treatment differs depending on the predominant underlying mechanism.
- In patients with hypervolemia, diuretic treatment is of utmost importance,
- In patients with underfill hypervolemia, excessive diuretic administration without albumin infusion can have serious deleterious consequences (AKI, dyselectrolytemia, etc.)

Diuretic Treatment

- Diuretics are fundamental for relieving volume overload
- there are no guidelines for the diuretic treatment of nephrotic edema.
- Diuretics comprise several classes: 1. Sulfonamide-loop diuretics, thiazide diuretics, and CA inhibitors; 2. Potassium-sparing diuretic-ENaC antagonists and aldosterone antagonists 3. Vasopressin-receptor antagonists (vaptans); 4. Osmotic diuretics


Proximal convoluted tubule
65-70%
Distal convoluted tubule
5%
Collecting duct
1-2%
Loop of Henle
25%
Thiazide diuretics
Distal convoluted tubule
NCC
TRPM6/7
TRPV5
NCX
PMCA
ClC Kb
Proximal convoluted tubule
SGLT2 inhibitors
SGLT2
GLUT2
NHE3
NBCe1-A
CA inhibitors
Principal cells
MRAs
ENaC blockers
ENaC
ROMK
V2R
Vaptans
Loop of Henle
Loop diuretics
NKCC2
ClC Ka/b
ROMK
CASR
claudin-19/-16
Collecting duct - α intercalated cells
Collecting duct - β intercalated cells
H-ATPase
NKCC1
PENDRIN
AE1
NDCBE
NHE1

Loop diuretics

- High efficacy (increased sodium excretion of 25% of the total filtered sodium) and safety profile
- Usually the first choice of treatment for hypervolemia
- Furosemide is the most commonly used loop diuretic
- variable oral bioavailability and a short half-life, furosemide is much more available than other loop diuretics (such as torsemide).

Thiazide diuretics

- The second most commonly used class of diuretics
- as moderate-efficacy drugs (inhibit the reabsorption of only 5–6% of luminal sodium in the distal convoluted tubule0.
- The widely used clinical agents are hydrochlorothiazide and indapamide, chlorthalidone which are thiazide-like diuretics
- The preferred choice is metolazone, a long-acting thiazide-like diuretic

Potassium-sparing diuretics

- ENaC-blockers or MRAs, they are weak diuretics that inhibit less than 2% of the total filtered sodium load.
- Aldosterone antagonists: little or no improvement in the natriuretic effect in nephrotic patients
- Shapiro et al. demonstrated that spironolactone caused a significant increase in sodium excretion in nephrotic patients compared to a placebo (a small-scale study involving only five patients with nephrotic syndrome)

- Understandably, the inhibition of either component of the RAAS would correct a hypervolemic state.
- No large randomized trials of renin suppression with direct inhibitors or beta-blockers.
- No increase in diuresis or natriuresis after propranolol treatment
- ACE-inhibitors, particularly captopril, failed to increase sodium and water excretion, although marked diuresis was noted in healthy subjects

CA inhibitors

- Reduce sodium and water reabsorption in the proximal tubule, but most of the sodium and water is subsequently reabsorbed in the distal tubule. Therefore, these agents are not effective diuretics

VR antagonists (aquaretics)

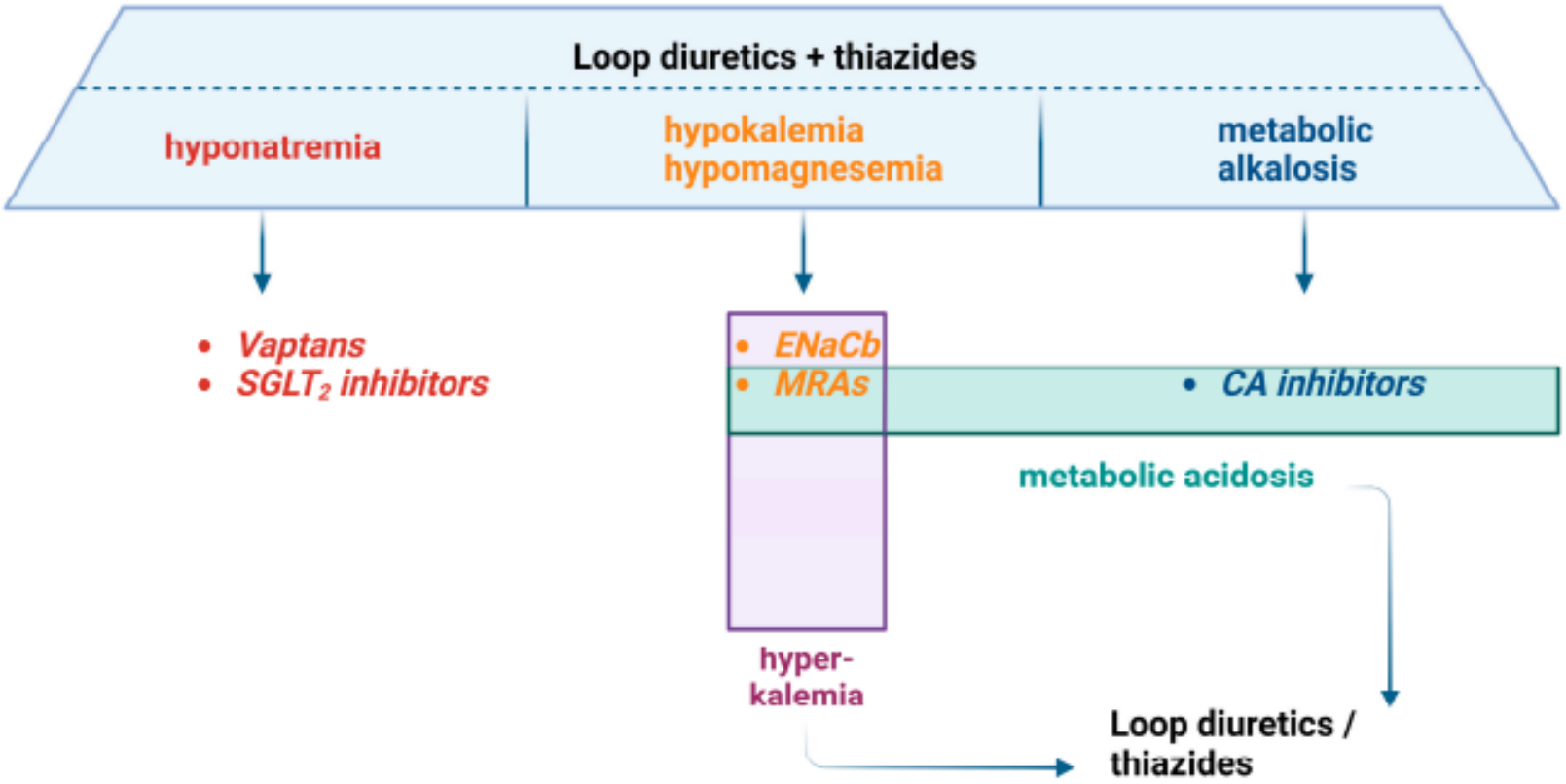
- Tolvaptan, a selective oral AVP V2-receptor antagonist, and conivaptan, a nonselective V1a/V2-receptor antagonist
- treatment of hypervolemic hyponatremia in congestive heart failure and euvolemic hyponatremia in the SIADH.
- These drugs may be potential options for treating nephrotic edema because of their mechanism of action.
- only small studies and case reports have shown the benefit of vasopressin-receptor antagonists.

Osmotic diuretics

- They are freely filtered in the glomerulus and do not act on a specific tubular channel (mannitol, urea)
- These diuretics remain in the tubule and increase tubular osmotic pressure, which inhibits water reabsorption and disrupts countercurrent exchange and the medullary concentration gradient

SGLT2-inhibitors (flozins)

- Act on the SGLT2 protein expressed in the early proximal tubules to reduce the reabsorption of filtered glucose and sodium and promote urinary glucose excretion
- the non-reabsorbed glucose induces an osmotic diuretic effect
- Slowing the progression of diabetic and nondiabetic CKD, possibly through reduced glomerular hyperfiltration and other pleiotropic physiological benefits
- Another potential benefit is that SGLT2-inhibitors help to correct hypervolemia-associated hyponatremia



Major adverse events of diuretics and possible diuretic combinations to overcome them. Abbreviations carbonic anhydrase (CA), epithelial sodium-channel blockers (ENaCb), mineralocorticoid-receptor antagonist, sodium–glucose transport protein 2 (SGLT2).

Correct dosage and timing of diuretics

Treatment generally starts with lower doses of diuretics (loop diuretics are the drugs of choice)

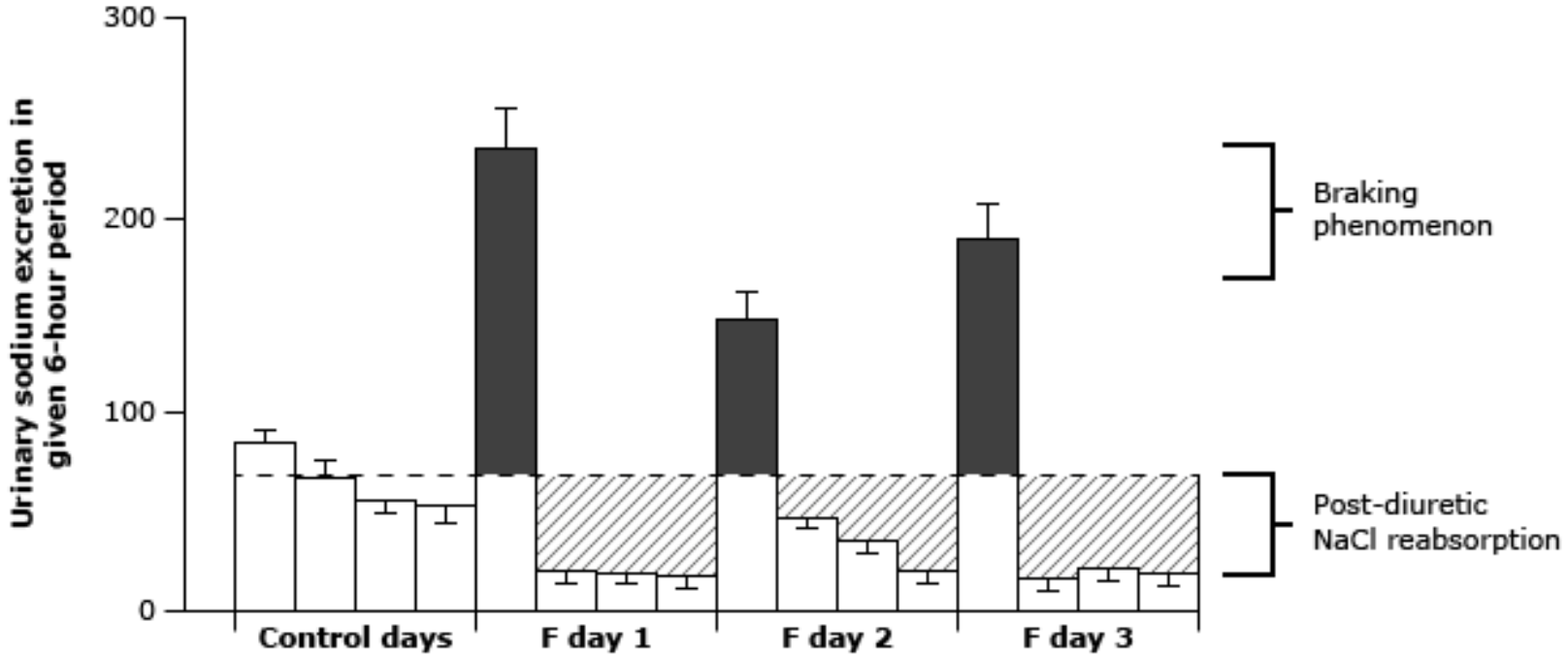
When adequate diuresis does not occur, a stepped-care approach is recommended

gradually increasing doses, based on certain clinical and biological aspects (urine output, hydration status, weight, blood pressure, electrolytes, and serum creatinine, etc)

If diuretic resistance is present, the use of a second diuretic drug that acts on a different nephron segment is often effective

- Drugs from a different class may act synergistically with the first by blocking the adaptive processes that limit the efficacy of diuretics, such as the activation of the RAAS and SNS, excessive NaCl consumption and the remodeling of the distal nephron.
- Distal convoluted tubule hypertrophy and hyperplasia occur due to the workload induced via diuretics

The braking phenomenon as a contributor to loop diuretic resistance after multiple doses



Patients may have a decreased response (ie, a decreased excretion of NaCl, shown in the y-axis) over time (shown in the x-axis) despite using the same dose of a loop diuretic. This is due to enhanced tubular sodium reabsorption in other parts of the nephron (other than the loop of Henle) and is called the "braking phenomenon." Each bar in the figure represents the sodium excreted during a 6-hour period. The horizontal dashed line represents the sodium intake. The black bars represent the 6-hour sodium excretion immediately after diuretic administration.

Diuretic resistance

- Defined as the failure of diuretics to achieve decongestion despite the use of the maximum recommended doses, as evidenced by a low urinary sodium concentration.
- No precise values for the maximum dose of diuretics or for the optimal urinary sodium level.
- An FENa of less than 0.2% in a state of hypervolemia due to any cause is associated with a poor response to diuretics and could be used as a clear definition of diuretic-resistant edema. (Knauf and Mutschler in 1997)
- This finding has not been validated in large clinical trials

Multiple causes of diuretic resistance (pharmacokinetic or pharmacodynamic)

Pharmacokinetics

- All the factors that influence a diuretic's ability to reach its site of action, such as hypoalbuminemia, proteinuria, or intestinal-wall edema.

Pharmacodynamics

- How the kidney responds to a diuretic, such as increased tubular sodium reabsorption in the presence of various proteases (plasmin, furin, and plasminogen, etc.

Multiple considerations in diuretic resistance

- Firstly, it is imperative to ensure the accuracy of the diagnosis of nephrotic syndrome and to exclude other potential causes of peripheral edema, including lymphedema or venous edema.
- Secondly, assessing patient compliance with prescribed medications and adherence to a low-salt diet is essential.
- Subsequently, it is important to identify factors contributing to the decreased transport of diuretics to the renal tubule, such as a low dosage or infrequent dosing of diuretics, impaired absorption due to intestinal-wall edema, or drug administration with food and low serum albumin levels

Step 1

- loop diuretics (2mg/kg/day)
- The aim to increase urine output over the next 2–4 h

Step 2

- Failure to do so means that the natriuretic threshold has not been reached: the initial dose is doubled (6 mg/kg/day) and subsequently increased up to the maximum dose of the diuretic, or the route of administration is switched to intravenous administration (preferred, intestinal wall edema)

Step 3

- Combination diuretic therapy (metolazone, indapamide, chlorthalidone, amiloride, spironolactone, eplerenone, finerenone)

- Properly monitoring for any indication of hypovolemia, such as low blood pressure, high pulse rate, or increased hematocrit.
- In the event of hypovolemia, an albumin infusion should be considered for fluid resuscitation

Ultrafiltration

Furosemide + Albumin

- Furosemide binds to albumin to reach the proximal tubule, where it is secreted into the intratubular space
- Hypoalbuminemia affect their distribution and delivery to the kidneys
- Conflicting results in various RCT
- possible mechanisms postulated by the authors for the increased diuresis: increased renal plasma flow and/or the direct tubular effects of diuretics
- These benefits appear to occur shortly after the infusion of albumin, i.e., between 6 and 24 h.

Pediatric Nephrology (2022) 37:1747–1757
https://doi.org/10.1007/s00467-021-05358-4

SYSTEMATIC REVIEW/META-ANALYSIS

Furosemide and albumin for the treatment of nephrotic edema: a systematic review

Erin Hedin[1,2] · Vid Bijelić[3] · Nick Barrowman[3] · Pavel Geier[2]

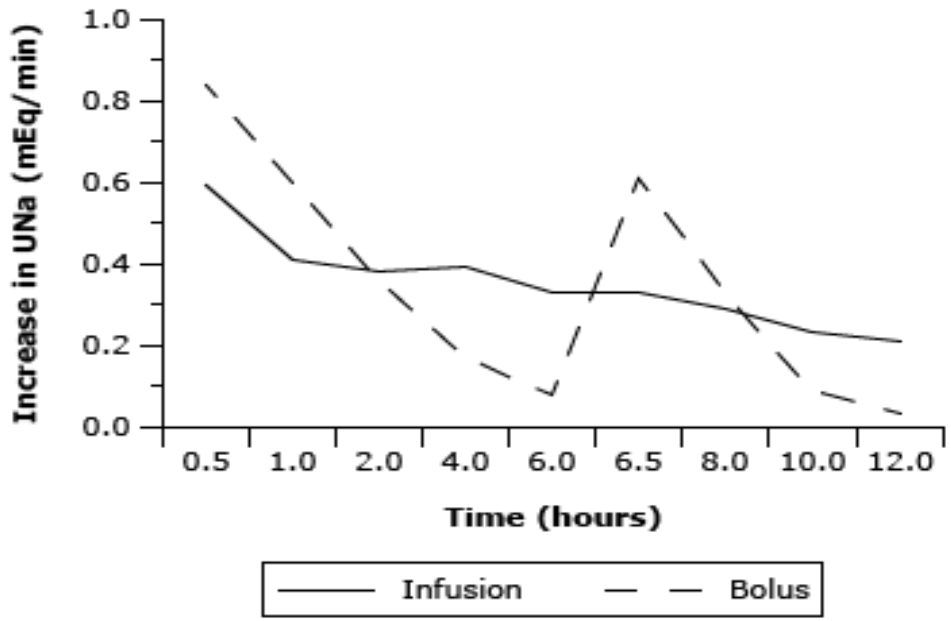
Received: 23 April 2021 / Revised: 7 November 2021 / Accepted: 8 November 2021 / Published online: 3 March 2022

Results The search yielded 525 records, and after screening, five studies were included in the systematic review and four of those studies in the meta-analysis. One study had high risk of bias and the remaining three studies were deemed to have some concerns. Urine excretion was greater after treatment with furosemide and albumin versus furosemide (SMD 0.85, 95% CI = 0.33 to 1.38). Results for sodium excretion were inconclusive (SMD 0.37, 95%CI = −0.28 to 1.02).

Authors' conclusions The current evidence is not sufficient to make definitive conclusions about the role of albumin in treating nephrotic edema. High-quality randomized studies with adequate samples sizes are needed. Including an assessment of intravascular volume status may be helpful.

Trial registration Prospero: CRD4201808979. https://www.crd.york.ac.uk/PROSPERO

Diuresis in continuous versus bolus loop diuretic therapy



Increase in urinary sodium excretion (UNa) after intravenous bumetanide, given as a continuous infusion (solid line) or as a bolus (dashed line), in patients with stable chronic kidney disease. The continuous infusion produced a 30% greater increase in UNa than bolus therapy due to a more favorable rate of diuretic excretion. In addition, the natriuretic response declined over time with both regimens. With the bolus, for example, the peak natriuretic response to the second dose was 25% less than that to the first.

- a randomized trial involving 20 patients with refractory nephrotic edema in which the efficacy of preloading with acetazolamide and hydrochlorothiazide was compared to that of preloading with furosemide and hydrochlorothiazide over a one-week period: improved diuresis, as indicated by differences in the mean weight change and urinary volume
- The importance of pendrin in nephrotic syndrome, paralleling its importance to the ENaC.

Indian Journal of Pediatrics (July 2022) 89(7):699–705
https://doi.org/10.1007/s12098-021-03988-y

ORIGINAL ARTICLE

Efficacy and Safety of Combination Therapy with Tolvaptan and Furosemide in Children with Nephrotic Syndrome and Refractory Edema: A Prospective Interventional Study

- Meena et al. showed that in 10 pediatric patients with steroid-resistant nephrotic syndrome and severe resistant edema, the combination of intravenous furosemide and oral tolvaptan increased urine output while decreasing body weight at 48 h. Renal function was not impaired, but three patients had hypernatremia, with a serum sodium concentration > 145 mEq/L.

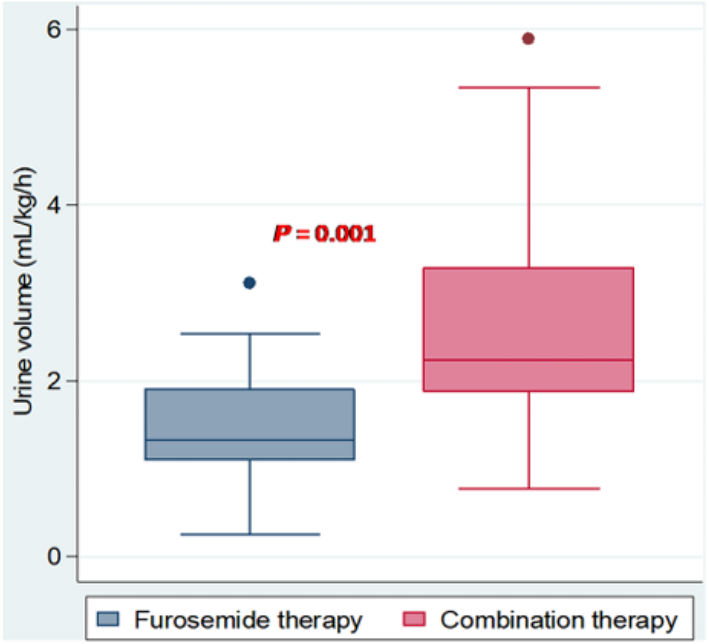
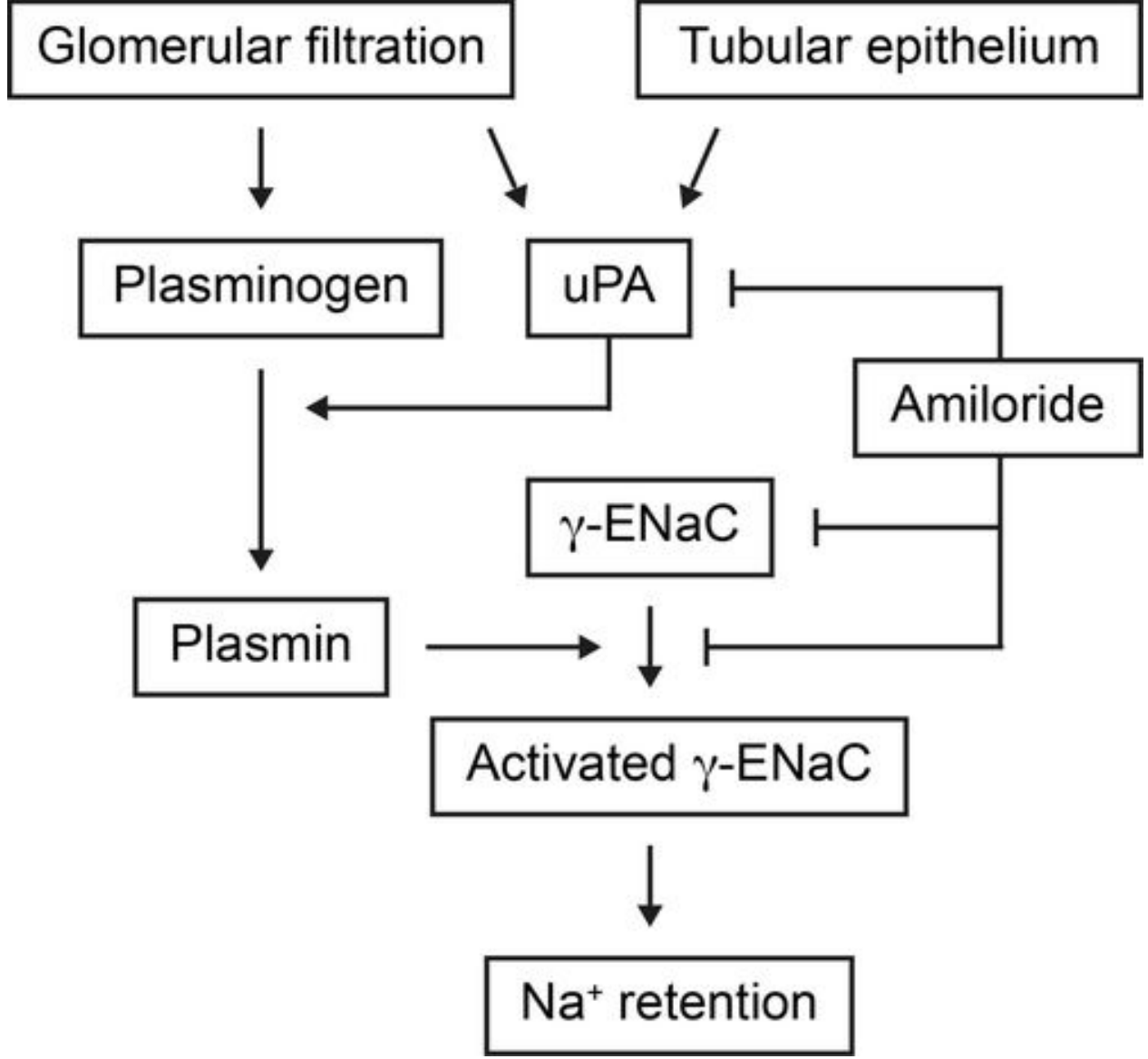


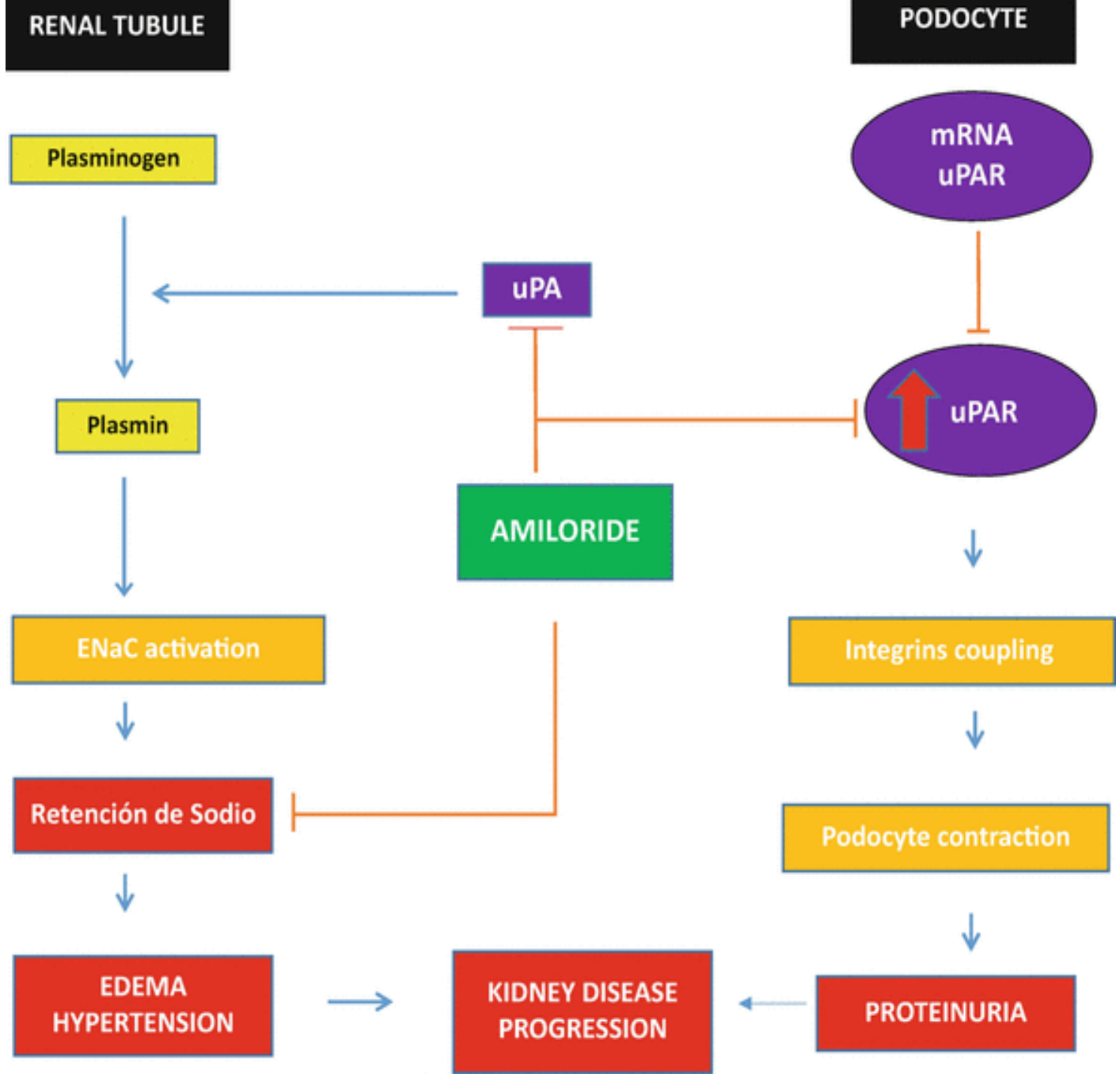
Fig. 2 Comparison of urine volume during 48 h of furosemide and combination therapy

Conclusion The combination of oral tolvaptan and IV furosemide is effective in augmenting diuresis and reducing weight in patients with furosemide refractory edema but requires monitoring of electrolytes and volume status.

- urinary excretion of serine proteases in patients with nephrotic syndrome means that the ENaC can be activated in these patients
- ENaC blockers, such as amiloride and triamterene, may yield a more favorable response
- Amiloride exhibits an additional benefit by decreasing plasmin levels through the inhibition of the urokinase plasminogen-activator receptor (uPAR)
- uPAR is also implicated in the activation of αvβ3 integrin or the vitronectin receptor, resulting in podocyte contraction and subsequent detachment from the glomerulus, leading to proteinuria
- soluble uPAR affects proximal tubular cells and induces fibrosis in an integrin-dependent manner
- The reduction in uPAR levels due to the action of amiloride translates into a decrease in the concentration of soluble uPAR (suPAR), the circulating version of uPAR. This, in turn, inhibits the activation of αvβ3 integrin, ultimately contributing to a decrease in proteinuria



Effect of amiloride on uPA and epithelial sodium channel (ENaC) in nephrotic syndrome. uPA is aberrantly cofiltered with plasminogen through the injured glomerular filtration barrier during nephrotic syndrome and is also thought to be secreted by the tubular epithelium. In the pre urine, uPA activates plasminogen to plasmin. Plasmin may also activate pro-uPA. Plasmin activates the -subunit of ENaC through proteolytical cleavage leading to sodium retention. Amiloride attenuates not only urine uPA activity but also has a direct inhibitory effect on ENaC


RENAL TUBULE
PODOCYTE
Plasminogen
mRNA
uPAR
uPA
Plasmin
uPAR
AMILORIDE
ENaC activation
Integrins coupling
Retención de Sodio
Podocyte contraction
EDEMA
HYPERTENSION
KIDNEY DISEASE
PROGRESSION
PROTEINURIA

REGULAR PAPER

ACTA PHYSIOLOGICA

Urokinase-type plasminogen activator contributes to amiloride-sensitive sodium retention in nephrotic range glomerular proteinuria in mice

Conclusions: Nephrotic range glomerular proteinuria leads to urokinase-dependent intratubular plasminogen activation and γENaC cleavage which contribute to sodium accumulation.

Received: 4 April 2024 | Revised: 14 May 2024 | Accepted: 18 May 2024
DOI: 10.1111/apha.14183

RESEARCH PAPER

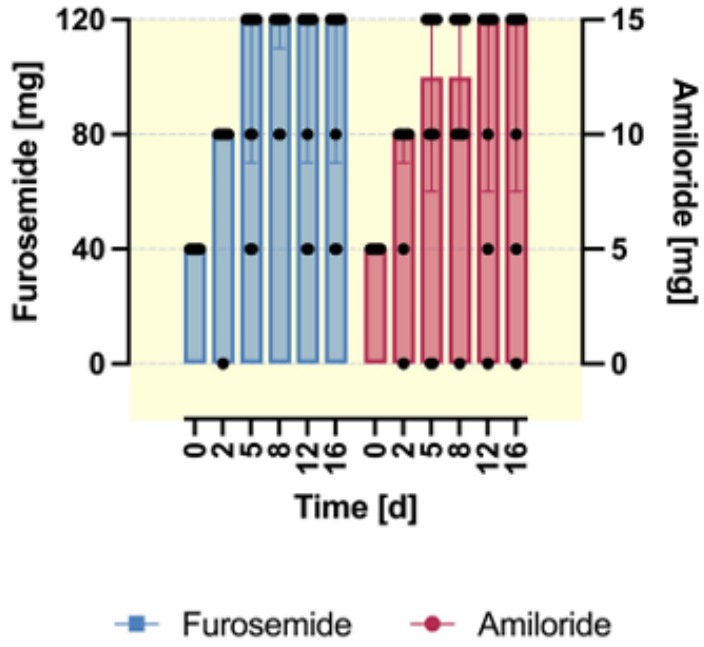
ACTA PHYSIOLOGICA

Amiloride versus furosemide for the treatment of edema in patients with nephrotic syndrome: A pilot study (AMILOR)

Methods: The monocentric randomized controlled AMILOR study investigated the antiedematous effect of amiloride (starting dose 5 mg/day, max. 15 mg/day) in comparison to standard therapy with the loop diuretic furosemide (40 mg/day, max. 120 mg/day) over 16 days. Overhydration (OH) was measured by bioimpedance spectroscopy (BCM, Fresenius). Depending on the OH response, diuretic dose was adjusted on days 2, 5, 8 and 12, and if necessary, hydrochlorothiazide (HCT) was added from d8 (12.5 mg/day, max. 25 mg/day). The primary endpoint was the decrease in OH on d8. The study was terminated prematurely due to insufficient recruitment and a low statistical power due to a low actual effect size.

Results: Median baseline OH was +26.4 (interquartile range 15.5–35.1)% extracellular water (ECW) in the amiloride arm and +27.9 (24.1–29.4)% ECW in the furosemide arm and decreased by 1.95 (0.80–6.40) and 5.15 (0.90–8.30)% ECW after 8 days, respectively, and by 10.10 (1.30–14.40) and 7.40 (2.80–10.10)% ECW after 16 days, respectively. OH decrease on d8 and d16 was not significantly different between both arms.

Conclusion: The AMILOR study is the first randomized controlled pilot study suggesting a similar antiedematous effect as furosemide. Further studies are required to better define the role of amiloride in NS (EudraCT 2019-002607-18).



Journal of
Clinical Medicine

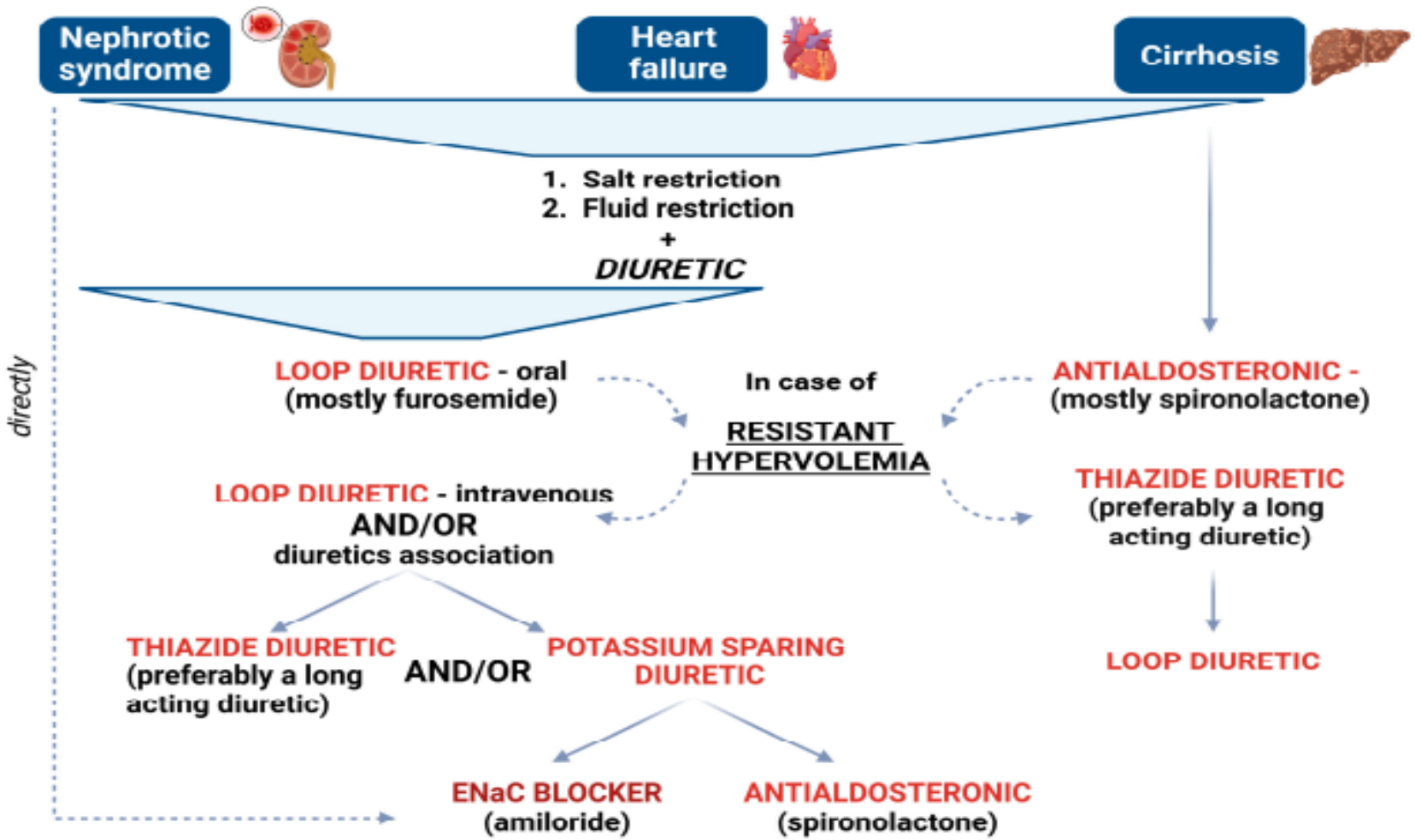
MDPI

Article

Oral Furosemide and Hydrochlorothiazide/Amiloride versus Intravenous Furosemide for the Treatment of Resistant Nephrotic Syndrome

Abstract: Background: Data on diuretic treatment in nephrotic syndrome (NS) are scarce. Our goal was to assess the non-inferiority of the combined oral diuretics (furosemide/hydrochlorothiazide/amiloride) compared to intravenous (i.v.) furosemide in patients with NS and resistant edema. Methods: We conducted a prospective randomized trial on 22 patients with resistant nephrotic edema (RNE), defined as hypervolemia and a FENa < 0.2%. Based on a computer-generated 1:1 randomization, we assigned patients to receive either intravenous furosemide (40 mg bolus and then continuous administration of 5 mg/h) or oral furosemide (40 mg/day) and hydrochlorothiazide/amiloride (50/5 mg/day) for a period of 5 days. Clinical and laboratory measurements were performed daily. Hydration status was assessed by bioimpedance on day 1 and at the end of day 5 after treatment initiation. The primary endpoint was weight change from baseline to day 5. Secondary endpoints were hydration status change measured by bioimpedance and safety outcomes (low blood pressure, severe electrolyte disturbances, acute kidney injury and worsening hypervolemia). Results: Primary endpoint analysis showed that after 5 days of treatment, there was a significant difference in weight change from baseline between groups [adjusted mean difference: −3.33 kg (95% CI: −6.34 to −0.31), $p = 0.03$], with a higher mean weight change in the oral diuretic treatment group [−7.10 kg (95% CI: −18.30 to −4.30) vs. −4.55 kg (95%CI: −6.73 to −2.36)]. Secondary endpoint analysis showed that there was no significant difference between groups regarding hydration status change [adjusted mean difference: −0.05 L (95% CI: −2.6 to 2.6), $p = 0.96$], with a mean hydration status change in the oral diuretic treatment group of −4.71 L (95% CI: −6.87 to −2.54) and −3.91 L (95% CI: −5.69 to −2.13) in the i.v. diuretic treatment group. We observed a significant decrease in adjusted mean serum sodium of −2.15 mmol/L [(95% CI: −4.25 to −0.05), $p = 0.04$]), favored by the combined oral diuretic treatment [−2.70 mmol/L (95% CI: −4.89 to −0.50) vs. −0.10 mmol/L (95%CI: −1.30 to 1.10)]. No statistically significant difference was observed between the two groups in terms of adverse events. Conclusions: A combination of oral diuretics based on furosemide, amiloride and hydrochlorothiazide is non-inferior to i.v. furosemide in weight control of patients with RNE and a similar safety profile.

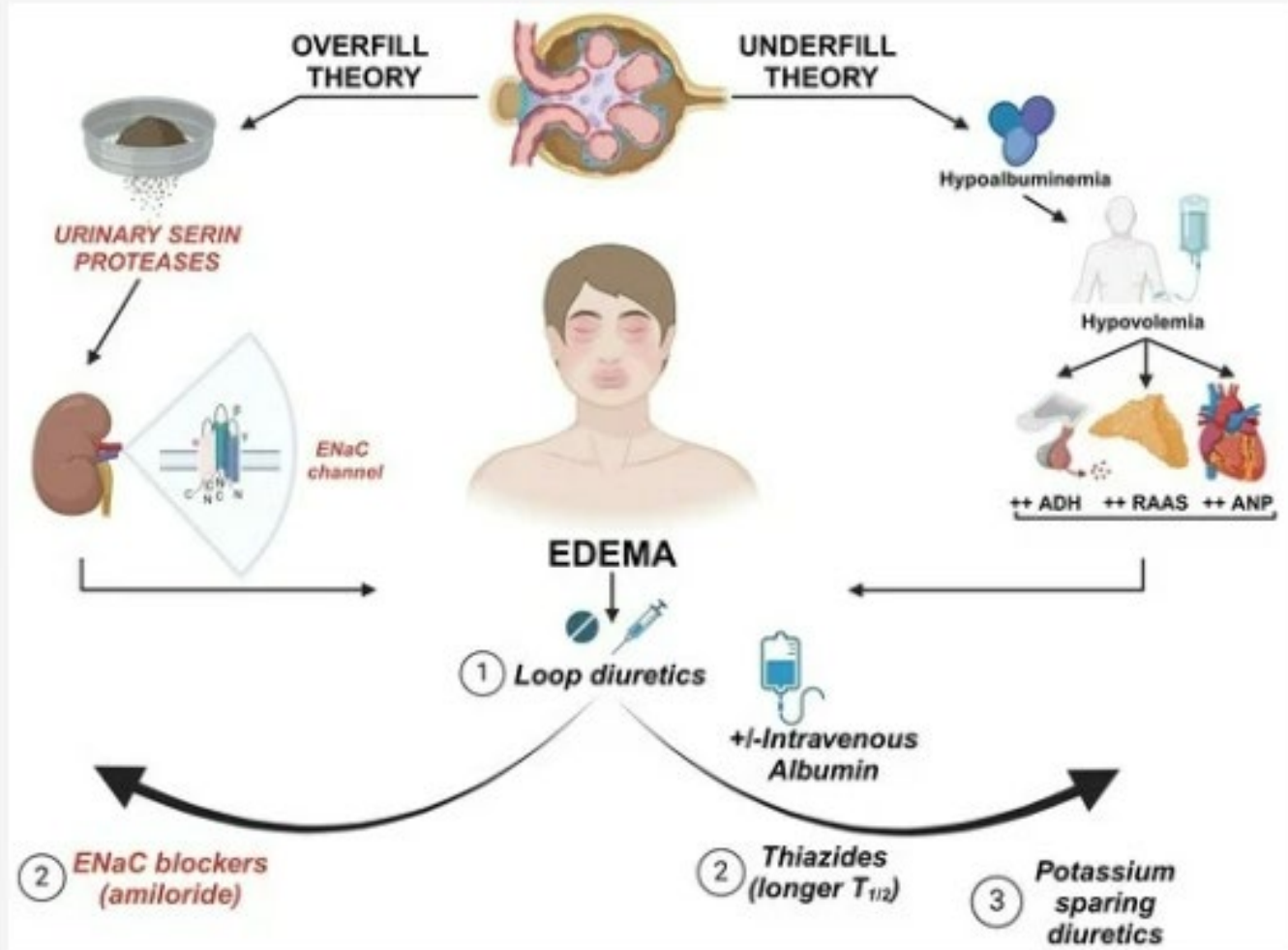
J. Clin. Med. 2023, 12, 6895. https://doi.org/10.3390/jcm12216895



A stepwise approach for diuretic-resistance management of edematous states

New Pharmacological Targets

- Promising pharmacological interventions for overcoming diuretic resistance:
- serine protease inhibitors;
- adenosine A1-receptor antagonists
- urea-transporter inhibitors
- ROMK-inhibitors
- WNK-SPAK-inhibitors
- natriuretic peptide-receptor agonists
- pendrin-inhibitors
- guanylyl-cyclase A-receptor activators
- inhibitors of relaxin, luteolin, and epicatechin



Graphical Abstract