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Potassium homeostasis – Physiology and pharmacology in a clinical context

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ABSTRACT

Membrane voltage controls the function of excitable cells and is mainly a consequence of the ratio between the extra- and intracellular potassium concentration. Potassium homeostasis is safeguarded by balancing the extra −/intracellular distribution and systemic elimination of potassium to the dietary potassium intake. These processes adjust the plasma potassium concentration between 3.5 and 4.5 mmol/L. Several genetic and acquired diseases but also pharmacological interventions cause dyskalemias that are associated with increased morbidity and mortality. The thresholds at which serum K^+ not only associates but also causes increased mortality are hotly debated. We discuss physiologic, pathophysiologic, and pharmacologic aspects of potassium regulation and provide informative case vignettes. Our aim is to help clinicians, epidemiologists, and pharmacologists to understand the complexity of the potassium homeostasis in health and disease and to initiate appropriate treatment strategies in dyskalemic patients.

Abbreviations: 11HSD2, 11-beta-hydroxysteroid dehydrogenase type 2; ACEi, angiotensin-converting enzyme inhibitors; AE1, anion exchanger 1; AKI, acute kidney injury; AME, apparent mineralocorticoid excess; ARB, angiotensin receptor blocker; ASDN, aldosterone-sensitive distal nephron; ATP, Adenosine triphosphate; Bcl-2, B-cell lymphoma 2; BK channels, big potassium channel (large conductance potassium channel); BRAF, serine/threonine-protein kinase B-Raf; BS, Bartter syndrome; CaV1.1, calcium channel, voltage-dependent, L type, alpha 1S subunit; CD, collecting duct; CKD, chronic kidney diseases; ClC-Ka, chloride channel protein ClC-Ka; ClC-Kb, chloride channel protein ClC-Kb; CLOROTIC trial, safety and efficacy of the combination of loop with thiazide-type diuretics in patients with decompensated heart failure trial; CNI, calcineurin-inhibitor; CNT, connecting tubule; Cox-2, cyclooxygenase-2; CTL-4, cytotoxic T lymphocyte–associated protein 4; Cul3, cullin 3; CYP11B1, cytochrome P450 family 11 subfamily B member 1; DASH, dietary approach to stop hypertension; DCT, distal convoluted tubule; DNA, deoxyribonucleic acid; EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; ECF, extracellular fluid; ECG, electrocardiogram; EFSA, European food safety authority; EGFR, epidermal growth factor receptor; ENaC, epithelial sodium channel; ER, emergency room; ESKD, end-stage kidney disease; FDA, food and drug administration; FHHt, familial hyperkalemic hypertension; GFR, glomerular filtration rate; GLUT-4, glucose transporter type 4; GS, Gitelman syndrome; HARMONIZE, hyperkalemia randomized intervention multidose ZS-9 maintenance; HPP, hypokalemic periodic paralysis; ICI, immune checkpoint inhibitors; INTERSALT, International Salt; KCC3a, potassium chloride cotransporter 3a; KCC4, potassium chloride cotransporter 4; KCNJ10, potassium inwardly rectifying channel subfamily J member 10; KCNJ16, potassium inwardly rectifying channel subfamily J member 16; Kir, inwardly rectifier potassium channels; Kir2.6, inward rectifier potassium channel 18; Kir4.1, inward rectifier potassium channel 4.1; Kir5.1, inward pectifier potassium channel 5.1; KLHL3, kelch like family member 3; Kv, voltage-gated potassium channel; MAGE-D2, melanoma-associated antigen D2; MCT1, monocarboxylate transporter 1; MCT2, monocarboxylate transporter 2; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonists; mTOR, mammalian target of rapamycin; mTORC2, mammalian target of rapamycin complex 2; Na^+-K^+-ATPase/NKA, sodium potassium ATPase; NBC, sodium bicarbonate cotransporter; NBCe1, sodium bicarbonate cotransporter 1; NBCe2, sodium bicarbonate cotransporter 2; NCC, sodium-chloride symporter; NCT, sodium-dependent cotransporters; NCX1, sodium calcium exchanger 1; NDA, panel on nutrition, novel foods and food allergens; Nedd4–2, neural precursor cell expressed, developmentally down-regulated 4-like; NHANES, National health and nutrition examination survey; NHE1, sodium hydrogen exchanger 1; NKCC1, sodium potassium 2 chloride cotransporter 1; NKCC2, sodium potassium 2 chloride cotransporter 2; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PHA1, pseudohypoaldosteronism type 1; PKC, protein kinase C; PP1, protein phosphatase 1; PP3, protein phosphatase 3; PT, proximal tubule; PTH, parathyroid hormone; PURE, prospective urban rural epidemiology; RAAS, renin–angiotensin–aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitors; RCT, randomized controlled trial; ROMK, renal outer medullary potassium channel; RTA, renal tubular acidosis; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance; Sgk1, serum-and-glucocorticoid-regulated kinase; *SLC12A3*, solute carrier family 12 member 3; Slc12a6, solute carrier family 12 member 6; *Slc12a7*, solute carrier family 12 member 7; SPAK, STE20/SPS1-related proline/alanine-rich kinase; SPS, sodium polysterene sulfonate; T2DM, type 2 diabetes; TAL, thick ascending limb; TRPM6, transient receptor potential cation channel subfamily M member 6; TRPV4, transient receptor potential vanilloid cation channel 4; TRPV5, transient receptor potential cation channel subfamily V member 5; TTKG, trans-tubular potassium gradient; V-ATPase, vacuolar-type ATPase; WNK1, with-no-lysine(K) kinase 1; WNK4, with-no-lysine(K) kinase 4.

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Contents

1. Introduction

Membrane voltage or potential is pivotal for the function of excitable cells, including neurons, muscle, and endocrine cells. The ratio between the extra- and intracellular potassium concentration is the major determinant of the membrane voltage. Consequently, potassium homeostasis is of uttermost importance and potassium disorders can compromise cell functioning entailing life-threatening conditions.

Potassium (K^+) is routinely assessed in a blood sample that reflects only a small fraction of the total K^+ pool. The plasma K^+ concentration is tightly adjusted between 3.5 and 4.5 mmol/L. Serum values are approximately 0.5 mmol/L higher compared to plasma because of K^+ release from platelets during the in vitro coagulation process. The mean serum K^+ concentration in the 2009–2016 adult National Health and Nutrition Examination Survey (NHANES) was 3.98 mmol/L (Overwyk et al., 2021). Within narrow boundaries, only small diurnal 24-h K^+ oscillations occur with an amplitude of 0.18 mmol/L peaking at 10 am and reaching a nadir at midnight (Sennels, Jorgensen, Goetze, & Fahrenkrug, 2012). In addition, genetic factors modify the serum K^+ concentration, such as heterozygosity for a pathogenic variant in *SLC12A3* encoding the thiazide-sensitive Na–Cl cotransporter (NCC) (Wan et al., 2021).

Potassium homeostasis is safeguarded by balancing the extra−/intracellular distribution and systemic elimination of potassium to the dietary potassium intake. Moreover, interactions between K^+, sodium (Na^+), and acid-base regulation occur with important clinical implications. A variety of conditions cause dyskalemias such as behavioral disorders, genetic abnormalities, pharmacological treatments, acid-base disturbances, and importantly, acute and chronic kidney diseases (CKD). Kidney diseases affect K^+ homeostasis through various mechanisms, including reduced potassium filtration because of decreased glomerular filtration rate (GFR), abnormal potassium reabsorption and secretion from dysregulated cells along the nephron, and several treatments that either increase or decrease renal K^+ excretion. In a large meta-analysis with more than 1.2 million individuals, 4.2% of the CKD patients had serum-K^+ above 5.5 mmol/L compared to only 0.5% of healthy and cardiovascular high-risk individuals without CKD underscoring the significance of CKD as a hyperkalemia risk factor (Kovesdy, et al., 2018). In contrast, hypokalemia below 3.5 mmol/L occurred in approximately 2% of the individuals independently of CKD. However, both lower and higher serum K^+ are associated with increased morbidity and mortality. Despite the U-shaped relationship between serum K^+ and mortality (Kovesdy, et al., 2018), clinicians, for unknown reasons, fear hyperkalemia more than hypokalemia. The thresholds at which serum K^+ not only associates but also causes increased mortality is hotly debated. Consequently, there is an ongoing discussion amongst clinicians about potassium cut-off values at which to intervene therapeutically and what measures are appropriate.

We discuss physiologic, pathophysiologic, and pharmacologic aspects of potassium regulation and provide informative case vignettes. Our aim is to help clinicians, epidemiologists, and pharmacologists comprehending the complexity of the potassium homeostasis in health and disease and to initiate appropriate actions to prevent and treat dyskalemias.

2. Epidemiology of dietary potassium intake

In Palaeolithic times, humans consumed a diet rich in fruits, vegetables, nuts, and seeds, which provided our ancestors with ample amounts of K^+ but very little Na^+. At that time, the average intakes for these two ions were likely in the range of 230–300 mmol/day for K^+ and 1–10 mmol/day for Na^+. This situation changed drastically with the advent of agriculture and modern food processing techniques, which reduced the K^+ content due to K^+ losses during cooking and increased Na^+ content due to additional salting. For these reasons, K^+ intake is nowadays usually low (70–80 mmol/day), while Na^+ intake is high (150–200 mmol/day) (Castro & Raij, 2013; Meneton, Loffing, & Warnock, 2004). The switch from a formerly K^+-rich, Na^+-poor diet to a K^+-poor, Na^+-rich diet occurred within the last 5,000–10,000 years, which is from an evolutionary perspective, a rather short time frame. Hence, it is likely that our genes and homeostatic control systems are still more adjusted to the times when it was necessary to get rid of K^+ and to conserve Na^+. Protective mechanisms that prevented life-threatening serum K^+ increases in Palaeolithic times included cellular K^+ uptake induced by K^+-accompanying sugars (e.g. from dietary fruits and berries) and a switch of the aldosterone response from NaCl retention to K^+ secretion involving WNK kinases and bicarbonate delivery to the distal nephron (e.g. from dietary citrate) (Kamel, Schreiber, & Halperin, 2014). This lack of an evolutionary adaptation likely explains, why our current eating habits with a low K^+ and high Na^+ intake are associated with numerous health problems, including high blood pressure, cardiovascular disease, stroke, kidney stones, osteoporosis, and eventually premature death (reviewed in (Ellison & Welling, 2021; Penton, Czogalla, & Loffing, 2015; Rossier, Bochud, & Devuyst, 2017)).

To reduce the risk for these diet-related sequalae, the world health organization (WHO) recommends that adults should consume per day at least 3.5 g of K^+ and less than 2 g of Na^+ (WHO, 2012a, 2012b). However, these recommendations are rarely met. A recent systematic review and Bayesian meta-analysis of 104 studies from 52 countries indicated that in none of the included countries the average K^+ and Na^+ intake is really in the recommended ranges (Reddin et al., 2023). Moreover, there are significant regional differences. For example, countries in Asia have by far both the lowest K^+ and highest Na^+ intakes, while countries in Eastern and Western Europe reach the recommended K^+ intakes, but still have Na^+ intakes in the upper levels (Powles, et al., 2013; Reddin et al., 2023).

Although, there is a vivid debate about the general need for salt reduction regimes (Batuman, 2013; Cappuccio et al., 2022; Drueke, 2016), there is quite consensus about recommendations for a high dietary K^+ intake (He & MacGregor, 2008; Messerli,

Hofstetter, & Bangalore, 2018). Numerous observational and interventional studies in humans as well as several experimental studies in animal models clearly documented beneficial effects of dietary K^+ (reviewed e.g. in (Penton et al., 2015; Wei et al., 2020). The observational INTERSALT study published in 1988 did already analyze the relation between 24 h urinary K^+ excretion, as a surrogate marker for dietary K^+ intake, and blood pressure. When corrected for confounding factors, this study with more than 10,000 males and females from 32 countries showed a significant inverse relation of blood pressure with urinary K^+ excretion (Intersalt-Cooperative-Research-Group, 1988). More recently, the Prospective Urban Rural Epidemiology (PURE) study, which included data from more than 100′000 adults from 18 countries, further confirmed the beneficial effect of a high dietary K^+ intake on blood pressure (Mente et al., 2014). The authors calculated that each additional gram of urinary K^+ excretion correlates with a drop of systolic blood pressure by more than 1 mmHg (Mente et al., 2014). The blood pressure lowering effect was independent from Na^+ intake, which is consistent with observations from the Dietary Approach to Stop Hypertension (DASH) trial. Also in this interventional study, in which participants eat a diet rich in vegetables and fruits and hence in K^+, blood pressure is significantly lowered irrespective from the amount of Na^+ that is ingested in parallel (Sacks, et al., 2001). The data from the DASH trial as well as those from several other studies do even suggest that the blood pressure lowering effect of dietary K^+ is more pronounced in individuals with high Na^+ intake (Aburto et al., 2013; Krishna & Kapoor, 1991; Mente et al., 2014; Sacks, et al., 2001). The antihypertensive effect of dietary K^+ goes along with a markedly reduced risk for cardiovascular disease and stroke (Aburto et al., 2013).

The observational PURE study demonstrated that the beneficial cardiovascular effects of a K^+-rich diet prevail even after correction for confounding factors such as physical activity, other dietary factors and blood pressure (Mente et al., 2018; O'Donnell et al., 2014). A positive effect of dietary K^+ is also supported by large interventional studies, in which part of the dietary NaCl had been replaced by KCl. Such salt substitution protocols significantly lowered arterial blood pressure (Bernabe-Ortiz et al., 2020) and reduced the risk for cardiovascular death in elderly men by almost 40% in the follow-up time of 31 months (Chang et al., 2006). Likewise, a recent cluster-randomized trial involving 20′995 persons from 600 villages in China demonstrated that salt-substitution lowers the rates of stroke, major cardiovascular events and death from any cause in individuals who had already a history of stroke or were at least 60 years of age and had hypertension (Neal et al., 2021). Apparently, elder and hypertensive people profit most from a high dietary K^+ intake, but do often have also impaired renal function, which may predispose them for the development of hyperkalemia. However, a recent study with 1612 participants in elderly care facilities in China showed that salt substitution only slightly increases mean serum K^+ levels and that this was not associated with an increased rate of adverse outcomes (Yuan et al., 2023).

The blood pressure lowering effect of a high K^+ diet has been attributed to numerous factors including a lowered sympathetic tone (Fujita & Sato, 1984), and direct effects on the vasculature (Oberleithner et al., 2009) and the kidney (Fujita & Sato, 1983), which promotes urinary Na^+ excretion and finally causes a negative Na^+ balance as discussed in more detail under 4.1.

Aside from the effects on the cardiovascular system, high dietary K^+ intake may have additional health benefits. For example, dietary K^+ reduces urinary calcium excretion (Lemann Jr., Pleuss, Gray, & Hoffmann, 1991; Rafferty, Davies, & Heaney, 2005) and hence may prevent kidney stones (Ferraro, Mandel, Curhan, Gambaro, & Taylor, 2016) and may increase bone mineral density (Jehle, Hulter, & Krapf, 2013; Tucker et al., 1999). Moreover, a sufficient K^+ supply was linked to a lowered risk for type-2 diabetes (Conen, Scanni, Gombert, Hulter, & Krapf, 2016). Nevertheless, data on these associations are limited and inconsistent (EFSA NDA Panel (EFSA Panel on Dietetic Products, N. a. A, et al., 2016) and the role of the anion that accompanies the K^+ (e.g. citrate) is unclear. Moreover, at least part of these positive effects are likely related to the general benefits from a K^+-rich healthy diet with fruits and vegetables (Palmer & Clegg, 2016).

In conclusion, the epidemiology of potassium intake highlights the importance of ensuring adequate K^+ consumption for optimal health outcomes. In addition to diets rich in fruits, vegetables, and other potassium-sources, salt substitution might be a cheap and promising strategy to improve human health. Marklund and co-workers modelled this effect for India and calculated that 8% to 14% of annual cardiovascular deaths could be prevented in this country by a nation-wide salt substitution program (Marklund et al., 2022). Salt substitution is also a rather safe approach. With the exception of occasional cases related to excessive K^+ loads (Wetli & Davis, 1978), hyperkalemia is rarely caused by an enhanced dietary K^+ intake (Lehnhardt & Kemper, 2011) because effective homeostatic mechanisms are in place to maintain plasma K^+ levels (see below).

3. Internal and external potassium balance

Potassium is one of the most abundant cations within the human body and plays a critical role in various cell functions including the regulation of intracellular pH, cell volume, DNA and protein synthesis and plasma membrane voltage. The intracellular concentration of K^+ (120–140 mM) is rather high, while the extracellular concentration (3.8–5.0 mM) is rather low (McDonough & Fenton, 2022). This steep K^+ gradient across the cell membrane is important for the resting membrane potential and hence for the normal function of excitable cells in the nervous system, the skeletal muscle and in the heart. Consistently, disturbances in K^+ balance may have severe consequences. For example, hypokalemia (defined as serum K^+ levels below 3.5 mM) can cause muscle weakness, cramps, and irregular heart-rhythm, while hyperkalemia (defined as serum K^+ levels above 5.5 mM) can cause muscle weakness, paralysis, and cardiac arrest.

About 98% of the whole-body K^+ is stored inside the cells (~3500 mmol), while only very small quantities are present in extracellular spaces (70–100 mmol). The amount of extracellular K^+ equals approximately the daily K^+ intake of an adult person (McDonough & Fenton, 2022; Palmer & Clegg, 2019), making every meal to a homeostatic challenge. Nevertheless, although K^+ is rapidly absorbed from the intestinal lumen into the blood, even a K^+-rich meal (e.g. with bananas, raw meat or fish) usually does not cause a major postprandial rise of the extracellular K^+ concentration (DeFronzo, Felig, Ferrannini, & Wahren, 1980). Under these circumstances, maintenance of normal serum K^+-levels is mainly achieved by two mechanism: (i) a rapid shift of K^+ into the cells (internal K^+ balance) and (ii) by an excretion of the extra K^+ via the urine and feces (external K^+ balance) (Giebisch, 2004). K^+ transport across the cell membranes is coupled to the function of specific transport proteins and channels. Nevertheless, K^+ moves rather freely between intra- und extracellular spaces and most (~85%) of the K^+ gets exchanged between compartments within the short half live of 7 h (Zollinger Jr., Van DeWater, Maletskos, & Moore, 1970). Thus, internal and external K^+ balance are closely linked and cooperate for the maintenance of K^+ homoeostasis (Fig. 1).

3.1. Regulation of internal potassium balance

While the final control of K^+ homeostasis is achieved via the kidney, the rapid shift of K^+ from extracellular to intracellular spaces acts as a first-line defense system to avoid life-threatening increases in extracellular K^+ concentrations. The skeletal muscle has by far the highest K^+ storage capacity followed by the liver, red blood cells, and other tissues (Youn & McDonough, 2009). The up-take of K^+ into these cells is mediated by the activity of the Na^+-K^+-ATPase that pumps two K^+ ions into the cell in exchange for 3 Na^+ ions that leave the cell. As the transport

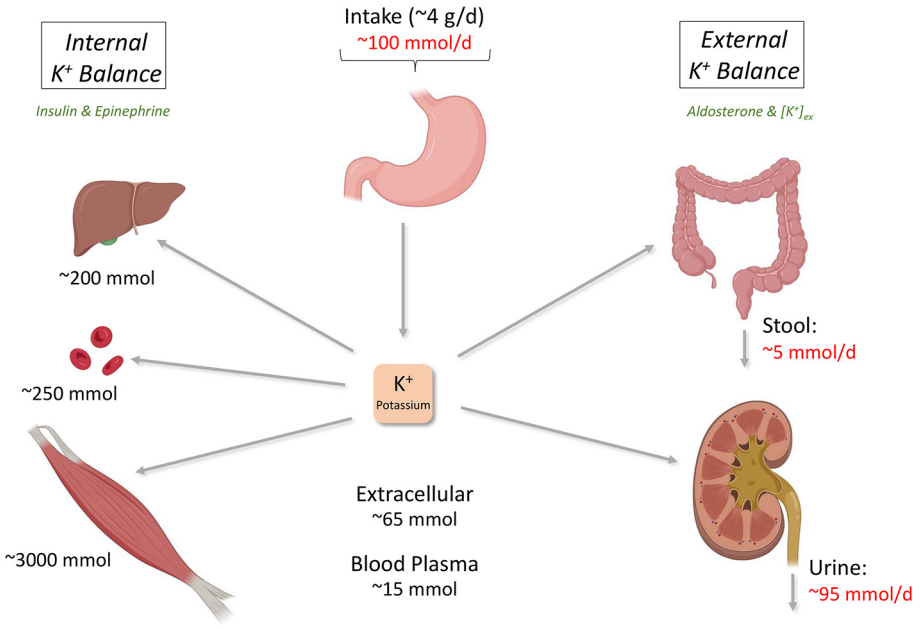

Fig. 1. Internal and external K^+ balance. Depicted are the main organs and cells involved in the maintenance of K^+ homeostasis. Dietary K^+ intake and urinary and fecal K^+ output (all in mmol/d) are shown in red. The main hormones and factors contributing to the regulation of the internal and external K^+ balances are highlighted in green. For details see text. The figure was assembled with licensed images from Bio.Render.com.

occurs against steep electrochemical gradients, this process needs energy provided by ATP produced by mitochondria. The skeletal muscle expresses high levels of the Na^+-K^+-ATPase, possesses numerous mitochondria, and accounts for up to 40% of the whole-body mass. Thus, the skeletal muscle is a huge and perfect sink for the rapid removal of K^+ from the circulation, which is evidenced by its capacity to turn over the entire extracellular K^+ pool in less than half a minute (Cheng, Kuo, & Huang, 2013).

While cellular K^+-uptake is an active, energy-requiring process, the release of K^+ out of the cell occurs passively along the gradient of high intracellular to low extracellular K^+ concentrations. In skeletal muscle cells, the K^+ efflux is mediated via various K^+ channels including inwardly rectifier K^+ channels (Kir) and voltage-gated K^+ channels (Kv) (Lehmann-Horn & Jurkat-Rott, 1999; Vivekanandam, Mannikko, Matthews, & Hanna, 2020). Moreover, skeletal muscle cells express several additional ion transport pathways including a Na^+-H^+-exchanger (i.e. NHE1) (Juel, 1998), Na^+-HCO_3^- cotransporters (e.g. NBCe1 and NBCe2) (Juel, 1997), and monocarboxylate transporters (e.g. MCT1 and MCT2) (Pilegaard, Terzis, Halestrap, & Juel, 1999) that cooperate with the Na^+-K^+-ATPase (Fig. 2).

The internal potassium balance is regulated by a variety of different hormonal and non-hormonal factors. The two hormones most relevant in this context are insulin and epinephrine. A rise of extracellular K^+ concentration stimulates the release of insulin and catecholamines from the pancreas and the adrenal medulla, respectively. This was demonstrated not only in vivo (Rosa et al., 1980; Santeusanio, Faloona, Knochel, & Unger, 1973) but also ex vivo on organ preparations (Baker & Rink, 1975; Grodsky & Bennett, 1966). Insulin binds to the insulin receptor to promote both glucose uptake via the glucose transporter GLUT-4 and K^+ up-take via the Na^+-K^+-ATPase. In contrast to the effects on glucose uptake, the insulin-dependent K^+ uptake remains intact in patients with type-2 diabetes (Nguyen, Maalouf, Sakhaee, & Moe, 2011), suggesting that the effects on Glut-4 and the Na^+-K^+-ATPase occur via different signaling mechanism. Catecholamines may either stimulate the Na^+-K^+-ATPase via β-adrenergic receptors or inhibit the Na^+-K^+-ATPase via α-adrenergic receptors (Aperia et al., 1996). This dual regulation is of particular relevance during intensive physical exercise. Muscle contraction goes along with a considerable efflux of K^+ from the working muscle cells. With intensive exercise (e.g. strenuous running, cycling, rowing), this K^+ release may briefly double plasma K^+ levels and may even cause a larger increase in the interstitial K^+ concentration around the contracting muscle cells (Clausen, 2008). The high extracellular K^+ concentration is not only a challenge for whole body K^+ homeostasis, but depolarizes also the skeletal muscle cells and hence reduces excitability and contractility of the skeletal muscle, which contributes to muscle fatigue (Sejersted & Sjogaard, 2000). Therefore, fast acting mechanisms are needed that limit the increase in extracellular K^+. In fact, exercise is associated with a fast and pronounced release of catecholamines from the sympathetic nervous system and the adrenal medulla. Binding of the released catecholamines to the β-adrenergic receptors on skeletal muscle cells is thought to activate the Na-K-ATPase and to shift at least part of the released K^+ back into the cells to avoid an even more pronounced hyperkalemia (Williams et al., 1985). The strong stimulation of cellular K^+ reuptake during exercise may also explain the rebound hypokalemia that usually occurs within the first few minutes after cessation of an intensive training (Lindinger & Cairns, 2021). Under these circumstances, norepinephrine-dependent activation of α-adrenergic receptors is thought to reduce the activity of the Na-K-ATPase and hence to limit postexercise K^+-uptake and hypokalemia (Williams et al., 1985). Thus, exercise-related changes in plasma K^+ concentrations reflect an intricate balance between K^+ release and K^+ uptake in the contracting muscles. The maintenance of K^+ homeostasis during physical exercise is further supported by cellular K^+ uptake in or release from remote tissues including the resting skeletal muscle and red blood cells (Lijnen et al., 1989; Lindinger & Cairns, 2021). Interestingly, most studies suggest that strenuous exercise does not significantly increase urinary K^+ excretion, which might be explained by the reduced renal blood flow and the lowered glomerular filtration rate during physical training (Poortmans, 1984; Virvidakis, Loukas, Mayopoulou-Symvoulidou, & Mountokalakis, 1986). Consistent with the assumption that K^+ balance during exercise is achieved independent from the kidney is the observation that hemodialysis patients have only moderate increases of plasma K^+ levels during exercise and show a similar postexercise recovery of plasma K^+ concentration as healthy subjects (Tran, Bundgaard, Ladefoged, Haunso, & Kjeldsen, 2013). A significant K^+ loss, however, may occur via the sweat during endurance-type exercise (Lindinger & Cairns, 2021). Although exercise-induced changes in plasma K^+

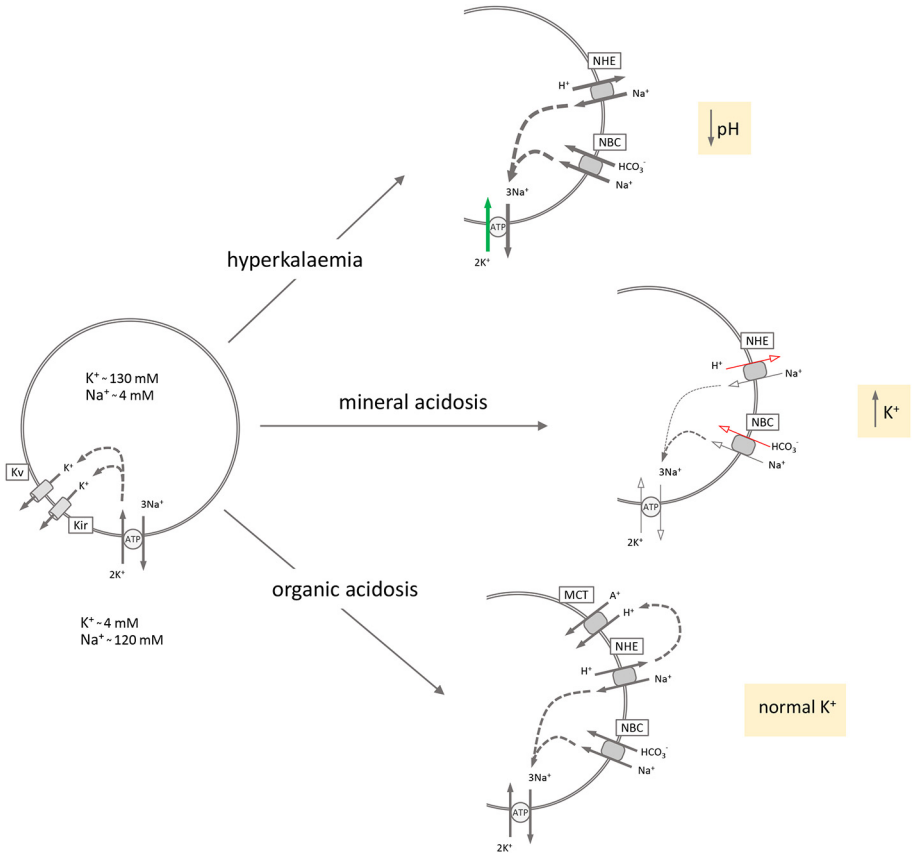

Fig. 2. Ion fluxes controlling internal K^+ balance under control conditions (left), and conditions of hyperkalemia, mineral acidosis, and organic acidosis (right). For details see text.

concentration may impact the heart leading to visible changes to the ECG, relevant cardiac arrhythmia is rare but might be triggered in vulnerable persons (Tran et al., 2013; Tran et al., 2022).

Importantly, insulin and catecholamines have synergistic effects on the Na^+-K^+-ATPase suggesting that both act via different mechanisms (Li & Sperelakis, 1993). Moreover, the mineralocorticoid aldosterone was suggested to impact not only the external K^+ balance (see below), but to modulate also internal K^+ balance in cooperation with insulin and catecholamines (Palmer & Clegg, 2022).

It is general textbook knowledge that acidosis stimulates, and alkalosis suppresses K^+ release in exchange for proton influx or efflux from the cells. However, there is no direct H^+-K^+ exchange mechanism across the cell membrane. Instead, acidosis is thought to primarily suppress the activity of the ubiquitously expressed Na^+-H^+-exchanger (NHE1), and to stimulate the activity of the Na^+-$HCO3^-$ transporter (Palmer, 2015). Both increase the intracellular Na^+ concentration, which lowers the activity of the Na^+-K^+-ATPase and hence cellular K^+ uptake (Fig. 2). Alkalosis has opposite effects.

Extracellular hypertonicity is an additional well-known condition that stimulates K^+ efflux from cells which was nicely demonstrated by the seminal work of Moreno and co-workers already in 1964 (Moreno, Murphy, & Goldsmith, 1969). As isotonic infusions of cell-impermeant mannitol does also cause a K^+ release which parallels water efflux (Moreno et al., 1969), it is likely that at least part of the hypertonicity-related K^+ exit is simply explained by solvent drag. Moreover, hypertonicity-induced cell shrinkage increases the intracellular K^+ and HCO_3^- concentrations (Makoff, da Silva, Rosenbaum, Levy, & Maxwell, 1970) which will provide a more favorable gradient for K^+ efflux via mechanisms discussed above.

3.2. Disease-related modifiers of cellular potassium balance

Hyperkalemia is one of the most common complications of diabetes mellitus and often related to impaired renal function and drug treatment (e.g. with Renin-Angiotensin-Aldosterone-System (RAAS) inhibitors) that reduce the renal K^+ clearance. However, diabetes may also impact internal K^+ balance by shifting intracellular K^+ to extracellular compartments. Several mechanisms are discussed to explain this shift. (i) Reduced plasma insulin levels decrease K^+ uptake directly via a reduced activity of the Na^+-K^+-ATPase. (ii) Hyperglycemia induces a shift of K^+ out of the cell due to cell shrinkage, and (iii) metabolic acidosis decreases K^+ uptake indirectly due to activation of Na^+ uptake via the Na^+-H^+ exchangers and Na^+-$HCO3^-$ transporters as described above (Palmer, 2015). In this context, it is important to mention that organic acidosis (e.g. lactate acidosis) is less prone to cause a K^+ shift from intracellular to extracellular space than mineral acidosis (hyperchloremic, non-ion gap acidosis) (Oster, Perez, & Vaamonde, 1978). As discussed recently, this is most likely related to the activity of the monocarboxylate cotransporters MCT1 and MCT4 that are co-expressed with the Na-K-ATPase and NHE1 in the plasma membrane of skeletal muscle cells (Aronson & Giebisch, 2011). In mineral acidosis, the strong inhibition of NHE1 and NBC lower the activity of the Na^+-K^+-ATPase and hence cellular K^+ uptake leading to a pronounced hyperkalemia. Under conditions of an organic acidosis with high extracellular lactate, MCT1 and MCT4 mediate a lactate and proton influx into the cells, which will lower intracellular pH and hence activate Na^+ influx via NHE1 (Fig. 2). Both, the drop in intracellular pH and the rise in intracellular Na^+ tend to stimulate rather to suppress the activity of the Na^+-K^+-ATPase, which ameliorates the hyperkalemia.

Acute cell or tissue breakdown as it occurs in patients with hemolysis, tumor lysis, or rhabdomyolysis can be also the cause of severe hyperkalemia (Larivee, Michaud, More, Wilson, & Tennankore, 2023; Lehnhardt & Kemper, 2011). The magnitude of this effect can be estimated from the steep differences of intra- to extracellular K^+ concentrations and the fact that the release of 2% of intracellular K^+ will be already sufficient to double extracellular K^+ concentration if not rapidly removed again via renal and extrarenal mechanism.

In contrast to hyperkalemia, hypokalemia is rarely a direct consequence of altered cellular K^+ distribution. Nevertheless, hypokalemia is frequently associated with metabolic alkalosis in patients with intestinal or renal chloride (and acid) losses due to vomiting and treatment with diuretics (Lee Hamm, Hering-Smith, & Nakhoul, 2013). Moreover, hypokalemic metabolic alkalosis is one of the most common findings in critically ill patients (Achanti & Szerlip, 2023). Alkalosis shifts K^+ into the cells by mechanism that are opposite to those described above for acidosis. However, alkalosis has also significant impact on renal K^+ handling (Lee Hamm et al., 2013) and hence the respective contribution of extrarenal vs. renal mechanism is difficult to discern.

Rare causes of hypokalemia due to altered internal K^+ balance are various forms of familial and non-familial hypokalemic periodic paralysis (HPP) (Cheng et al., 2013). HPP typically starts in childhood or adolescence and is characterized by episodes of severe hypokalemia (plasma K^+ 2 mmol/L or even lower) leading to muscle weakness or paralysis (Cheng et al., 2013).

Familial forms of HPP are mostly related to mutations in voltage gated Na^+ ($Na_v1.4$) (Cannon, 2018) or L-type Ca^{2+} ($Ca_V1.1$) channels (Flucher, 2020). As discussed in detail by Cheng and co-workers (Cheng et al., 2013), these mutations cause an inward leak current in skeletal muscle cells that initiates under given conditions a self-reinforcing vicious cycle of hypokalemia and paradoxical depolarization of the plasma membrane, which finally leads to a situation at which K^+ uptake into the cells via the Na^+-K^+-ATPase drastically exceeds the K^+ efflux via Kir channels. Stress, exercise, and carbohydrate-rich meals are known triggers for HPP episodes probably because the elevated catecholamine and insulin levels associated with these conditions stimulate cellular K^+ uptake via the Na^+-K^+-ATPase. In susceptible patients, this causes the slight hypokalemia necessary for the initiation of the mentioned vicious cycle (Cheng et al., 2013).

Non-familial forms of HHP have a similar clinical presentation as the familial forms and occur either spontaneously or in the context of hyperthyroidism. In the latter, the high levels of thyroid hormones are thought to trigger the initial hypokalemia due to an activation of the Na^+-K^+-ATPase (Lin & Huang, 2012). At least some of the affected patients have mutations or polymorphisms in Kir2.6 (Ryan et al., 2010) confirming further that a balanced combination of both K^+-uptake via the Na^+-K^+-ATPase and K^+ efflux via K^+ channels is critical for the maintenance of internal K^+ balance. The critical role of the K^+ exit step is also supported by the observation that intoxication with the K^+ channel blocker barium is associated with hypokalemia and paralysis (Agarwal et al., 1995; Schott & McArdle, 1974).

3.3. Pharmacological modifiers of cellular potassium balance

Several drugs are used in clinical medicine that induce a K^+ shift into cells. These drugs are indispensable to treat patients with hyperkalemia but can also unintentionally produce hypokalemia. The underlying mechanisms employed by these pharmacological interventions to increase the cellular K^+ uptake are based on the physiological principles explained in detail above. We now discuss some more practical issues.

35-years ago, an important study compared the effects of insulin with glucose, epinephrine, and bicarbonate in hyperkalemic chronic hemodialysis patients (Blumberg, Weidmann, Shaw, & Gnadinger, 1988). The 60-min interventions were: a) intravenous (iv) infusion of bicarbonate, either 240 mL 8.4% or 720 mL 1.4%; b) 0.05 μg/kg/min epinephrine iv; c) 100 units (U) insulin (5 mU/kg/min) in 500 mL of 20% glucose iv. After 60 min, insulin/glucose had decreased serum K^+ significantly by 0.8 mmol/L, epinephrine non-significantly by 0.3 mmol/L, and bicarbonate had increased serum K^+ by 0.15 mmol/L. Some important caveats need to be considered: the investigators initially used twice as much epinephrine and noted tachycardia and precordial oppression. This observation is of particular importance for elderly patients with cardiac diseases. Moreover, the insulin had to be reduced to 50 U because of hypoglycemia in some patients. Finally, basal serum HCO_3 was approximately 22 mmol/L and the absence of severe metabolic acidosis may have prevented a decrease in serum K^+ by bicarbonate infusions. Since this seminal study, several modifications of the same therapeutic principles have been reported.

3.3.1. Insulin (+ glucose)

Because of its efficacy, insulin is the first-line treatment for hyperkalemic patients. A main complication is the high incidence of hypoglycemia. This led to the use of concomitant glucose infusions. However, clinicians need to consider that high glucose concentrations facilitate a K^+ efflux from the cells by increasing extracellular osmolarity, thereby inducing a solvent drag. This effect would diminish the K^+-lowering insulin effect. Another point of discussion is insulin adsorption in containers ex vivo. One study found that the use of polypropylene syringes had the highest insulin delivery rate with 80 to 90% (Robert et al., 2021).

A frequently used protocol is the iv administration of 10 U insulin together with 25 g glucose (e.g. 50 mL of 50% glucose). Nevertheless, Apel et al. reported that hypoglycemia occurred in 13% of the treated CKD patients with this treatment protocol (Apel, Reutrakul, & Baldwin, 2014). Several institutions administer additional iv glucose to avoid hypoglycemia, but the disadvantages have been discussed above. Blood glucose monitoring after the initial insulin/glucose administration is mandatory, probably over at least 4 h.

3.3.2. β-mimetics (catecholamines)

We discussed already the K^+-lowering effect of iv epinephrine (Blumberg et al., 1988). As an alternative, β-adrenergic agonists have been applied in nebulized form. Ten chronic hemodialysis patients with plasma K^+ consistently >5 mmol/L underwent a randomized, controlled, double-blind study (Allon, Dunlay, & Copkney, 1989). The patients inhaled either 10–20 mg nebulized albuterol or placebo over 10 min. Albuterol, but not placebo, significantly decreased plasma K^+ within 30 min lasting for at least 2 h. 10 mg resulted in an approximately 0.6 and 20 mg in 1.0 mmol/L plasma K^+ fall. Only minimal increase in blood pressure and heart rate occurred with the β-mimetics. A recent double-blind study randomized hyperkalemic premature newborns with serum $K^+ > 6$ mmol/L to either insulin/glucose or nebulized salbutamol (Saw, Chiu, Chiu, Ji, & Chen, 2019). Serum K^+ decreased in both groups within 3 h without significant differences between the treatments. Again, tachycardia and hypertension were not observed.

It is feasible to combine insulin/glucose with β-mimetics to achieve additive effects on serum K^+.

3.3.3. Bicarbonate administration

Bicarbonate is only recommended for hypokalemic patients with more severe metabolic acidosis (and without volume overload). Study data in CKD patients on the efficacy of this treatment to lower serum K^+ are not convincing (Blumberg et al., 1988; Allon & Shanklin, 1996). Conceivably, in patients with preserved GFR, sodium bicarbonate increases sodium delivery to the distal nephron where it is reabsorbed via the ENaC leading to increased potassium secretion via ROMK. In fact, a controlled study in canines with normal kidney function showed that 8.4% sodium bicarbonate and 8.4% sodium chloride decreased serum K^+ to a similar degree (Kaplan, Braitman, Dalsey, Montgomery, & Mangione, 1997).

A recent Kidney Disease Improving Outcome (KDIGO) Controversies Conference recommended to initiate insulin/glucose and/or β-mimetics

in patients with serum K^+ > 6 mmol/L or at lower values when hyperkalemic EKG changes occur, whereas bicarbonate was only considered for patients with metabolic acidosis and lacking volume overload (Clase et al., 2020).

4. Potassium excretion

In healthy adults, about 95% of the ingested K^+ is excreted via the kidney, while other organs such as the colon and the sweat-glands make only minor contributions. However, K^+ secretion also via these organs may rise under certain conditions such as impaired renal function, diarrhea, or heavy sweating (reviewed in (EFSA NDA Panel (EFSA Panel on Dietetic Products, N. a. A, et al. (2016)).

4.1. Renal potassium handling along the nephron

The kidneys regulate the urinary elimination of K^+ through a process involving filtration, reabsorption, and secretion of K^+ along the nephron (Fig. 3). The K^+ solved in the blood gets initially filtered at the glomerulus. Almost 80% of this filtered K^+ is reabsorbed already by the proximal tubule (PT) in parallel to Na^+ reabsorption facilitated by the apical Na^+-H^+-exchanger 3 (NHE3), various apical Na^+-dependent cotransporters (NCT), and the basolateral Na^+-K^+-ATPase (NKA). The high Na^+ transport rate in PT drives osmotically transcellular and paracellular water fluxes, which are followed by paracellular K^+ reabsorption through solvent drag (Palmer, 2015). While the thin descending limbs of Henle's loop release K^+ into the tubular lumen, the thin ascending limbs reabsorb K^+ (Jamison, Work, & Schafer, 1982), so that the net transport of K^+ along the thin limbs is likely neglectable. The thin limbs are followed by the thick ascending limb (TAL), which reabsorbs an additional ~10% of the filtered K^+. While K^+ transport in PT and TAL is largely unregulated, K^+ transport in the downstream tubules (i.e. the distal convoluted tubule – DCT, the connecting tubule – CNT, and the collecting duct CD) is tightly adjusted depending on the functional needs and can switch between both K^+ reabsorption and K^+ secretion. Under conditions of K^+ deficiency, the DCT, CNT, and CD can reabsorb up to an additional ~2% of the filtered K^+ to minimize renal K^+ loss. Under conditions of a K^+ excess (e.g. after a K^+ rich meal), these segments secrete large quantities of K^+ (~20–180% of the filtered K^+) to keep plasma K^+ concentrations in the normal range (Giebisch, 2009). As the consequence of K^+ secretion and vasopressin-driven water reabsorption, intratubular K^+ concentration increases along the cortical CD, so that in the medullary CD the transepithelial gradient is shifted back towards K^+ reabsorption (Jamison et al., 1982) (Fig. 3).

Small alterations of these K^+ movements may already have severe consequences on the maintenance of K^+ homeostasis. The distal tubules (i.e. the TAL, DCT, CNT and CD) play here a particular role and several human diseases and drugs causing hyper- or hypokalemia interfere with the ion transport processes in these nephron segments. Therefore, before we discuss disease-related and pharmacological modifiers of renal K^+ handling, it is important to recapitulate the complex cellular and molecular architecture of these tubular segments (Fig. 3).

In the TAL, ion and hence K^+ transport relies on the activity of the apical furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) (Castrop & Schiessl, 2014). The Na^+ and Cl^- ions reabsorbed by NKCC2 exit the TAL via the basolateral Na^+-K^+-ATPase and the Cl^- channel ClC–Kb, respectively (Dimke & Schnermann, 2018). The function of ClC–Kb depends on co-expression of barttin that acts as a chaperone to bring ClC–Kb to the cell surface (Stauber, Weinert, & Jentsch, 2012). Part of the reabsorbed K^+ leaves the TAL cells via a basolateral K^+Cl^- cotransport system, that likely corresponds to KCC4 (Slc12a7) based on recent single cell mRNA expression data (Ransick et al., 2019). The main portion of reabsorbed K^+ recycles back to the tubular lumen through apical outer medullary K^+ (ROMK) channels. This K^+ recycling is important to ensure sufficient intratubular K^+ concentrations for the activity of NKCC2. In addition, it turns the TAL lumen

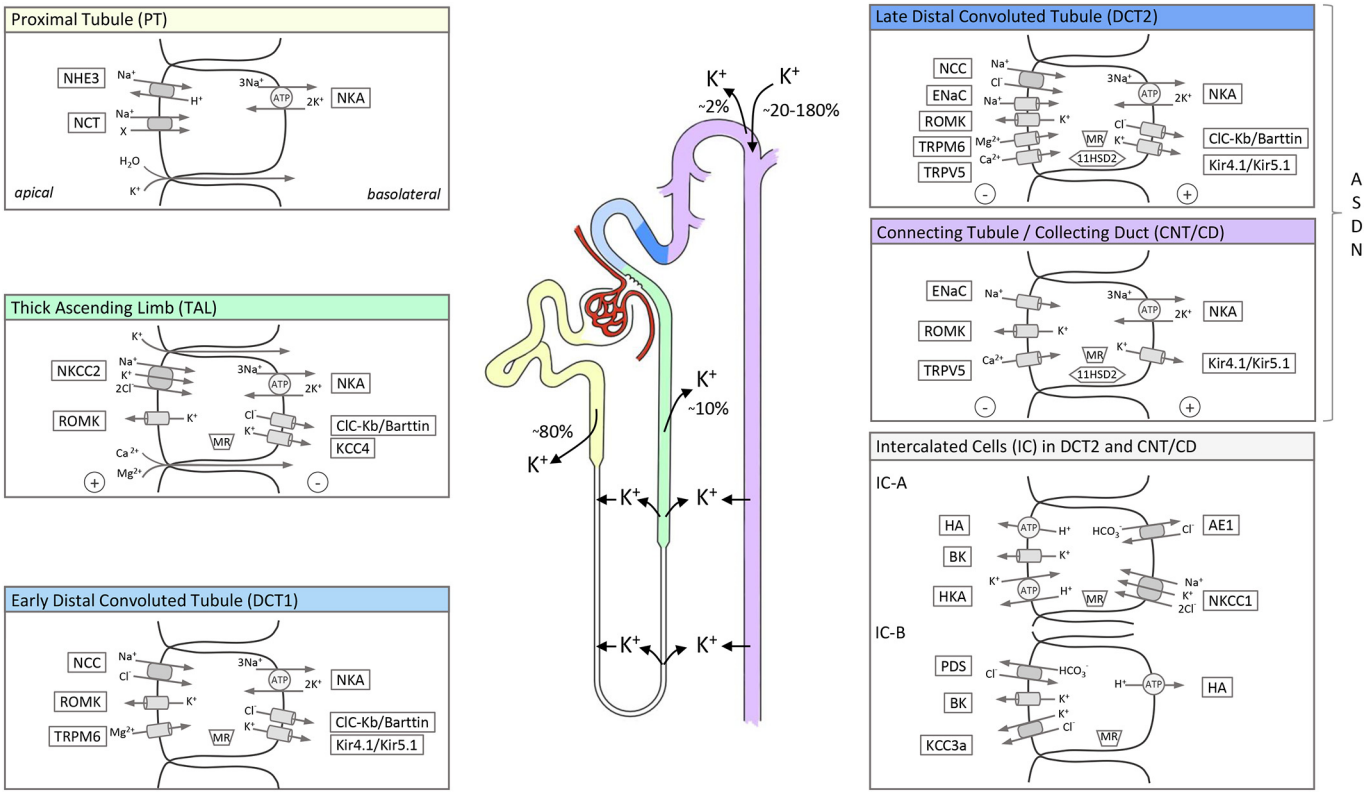

Fig. 3. K^+ handling along the nephron. Depicted are the involved nephron portions, cell types and main ion transport pathways. For details see text. The schematic drawing of the nephron is adapted from Fig. 1 in (Loffing, 2014), for which the author has copyright.

electropositive, which creates the electrochemical driving force not only for the paracellular reabsorption of K^+ but also of magnesium (Mg^{2+}) and calcium (Ca^{2+}) (Palmer, 2015).

The TAL is followed by the DCT that is characterized by the expression of the thiazide-sensitive NaCl cotransporter (NCC). Together with the basolateral Na^+-K^+-ATPase, NCC facilitates transcellular Na^+ reabsorption (McCormick & Ellison, 2015). Like in the TAL, co-transported Cl^- ions leave the cell via a basolateral ClC-Kb channel (Stauber et al., 2012)m. In humans and rodents, the DCT is subdivided into an early DCT (DCT1) and a late DCT (DCT2). In the latter, the apical NCC is progressively replaced by the amiloride-sensitive epithelial Na^+ channel (ENaC), that is also the dominating apical Na^+ entry step in downstream-localized CNT and CD (Bachmann, Bostanjoglo, Schmitt, & Ellison, 1999; Loffing & Kaissling, 2003).

DCT2, CNT and CD form the so-called aldosterone-sensitive distal nephron (ASDN) (Fig. 3). The ASDN was defined as those segments that express high levels of ENaC, the mineralocorticoid receptor (MR), and the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11HSD2) (Loffing et al., 2001). The MR is a ligand-binding nuclear transcription factor that gets activated by both mineralocorticoids (e.g. aldosterone) and glucocorticoids (e.g. cortisol and corticosterone). The 11HSD2 rapidly catalysis the inactivation of corticosteroids and hence confers mineralocorticoid-specificity to the MR. As glucocorticoids circulate at about 1000-times higher concentrations as aldosterone and as the MR is expressed in all cells of the distal nephron (including TAL cells and intercalated cells) (Ackermann et al., 2010), it is the high expression and activity of the 11HSD2 in the segment-specific DCT2, CNT, and CD cells that confers aldosterone-sensitivity to the ASDN.

While the activity of NCC is electroneutral, Na^+ reabsorption via ENaC is electrogenic and turns the tubular lumen electronegative (Pearce, Manis, Nesterov, & Korbmacher, 2022). This sets-up the electrochemical driving force for K^+ secretion via apical K^+ channels (Yang et al., 2021). One of these secretory K^+ channels is ROMK, which is highly abundant in all segment-specific DCT, CNT and CD cells (Mennitt, Wade, Ecelbarger, Palmer, & Frindt, 1997; Xu et al., 1997). The other secretory K^+ channel is the maxi K^+ or big K^+ channel (BK), which is mainly found in intercalated cells and which is critical for flow-dependent K^+ secretion (Carrisoza-Gaytan et al., 2020). Data from mice deficient for either ROMK or BK suggest that both channels can compensate for each other (Bailey et al., 2006; Rieg et al., 2007). Moreover, BK channels have a larger single channel conductance than the ROMK channels. Therefore a few BK channels might be already sufficient to drive a sizable K^+ secretion.

The intercalated cells are morphologically and functionally distinct from the segment-specific cells and are interspersed in DCT2, CNT, cortical and first third of the medullary CD (Chambrey & Trepiccione, 2015; Wall, Verlander, & Romero, 2020). Intercalated cells can be roughly subdivided into two major forms with inverse functional polarities (Fig. 3). Type A intercalated cells secrete protons via an apical H^+-ATPase and reclaim bicarbonate to the blood via the basolateral anion exchanger AE1. Type B intercalated cells secrete bicarbonate via the apical bicarbonate exchanger pendrin and reclaim protons via a basolateral H^+-ATPase (Wall et al., 2020). As such, intercalated cells are critical for the maintenance of acid-base homeostasis (Wagner et al., 2004), but they do also participate to the regulation of renal K^+ handling (Ray et al., 2021), via an extensive functional coupling to the segment-specific cells (Grimm et al., 2015; Pham et al., 2020; Wen et al., 2014). However, as intercalated cells express very little of the Na^+-K^+-ATPase (Brown et al., 1996), it is not yet fully understood how these cells generate sufficient gradients for transcellular K^+ movements. It was suggested that the proton gradient generated by the H^+-ATPase may energize secondary transport systems (Chambrey et al., 2013) that then drive basolateral K^+-uptake via the Na^+-K^+-$2Cl^-$ - cotransporter NKCC1 and apical K^+ release in type A intercalated cells (Liu et al., 2011). Moreover, an apical K^+Cl^+ cotransporter (KCC3a, Slc12a6) may contribute to K^+ excretion in in type B intercalated cells (Ferdaus, Terker, Koumangoye, Wall, & Delpire, 2023).

Interestingly, type A intercalated cells do also express a H^+-K^+-ATPase (HKA) in their apical membrane that can reabsorb K^+ from the tubular fluid in exchange for protons (Greenlee, Lynch, Gumz, Cain, & Wingo, 2010; Walter et al., 2016). As such type A intercalated cells appear to be capable for both K^+ secretion via BK and K^+ reabsorption via the H^+-K^+-ATPase, which could eventually explain the ability of the ASDN to switch between K^+ conservation and K^+ secretion. The close intermingling of segment-specific DCT2, CNT and CD cells with the intercalated cells may also contribute to the close interrelationship between K^+ and acid-base homeostasis (Lee Hamm et al., 2013). As described above, there is also a close coupling of ROMK-dependent K^+ secretion with paracellular Mg^{2+} and Ca^{2+} reabsorption in the TAL.

Interestingly, ROMK is also co-expressed with Mg^{2+} channel TRPM6 in the apical plasma membrane of DCT1and DCT2 and with the Ca^{2+} channel TRPV5 in the apical membrane of DCT2 and CNT. As yet, it is unclear if ROMK activity may interfere with the transcellular Mg^{2+} and Ca^{2+} reabsorption via TRPM6 and TRPV5, respectively. A recent study with mice on either control, high Na^+ or high Na^+/low K^+ diets did not provide evidence for direct effects of the diets on TRPM6 and TRPV5, but suggested that changes to divalent cation transport in DCT and CNT are secondary to effects on paracellular cation reabsorption in proximal tubules and TAL (van der Wijst et al., 2018).

Another functional coupling may exist between the proximal tubule and the ASDN. Hyperkalemia reduces proximal tubular ammoniagenesis. The acidosis may stimulate ENaC and ROMK, as both channels are pH sensitive (Weinstein, 2022).

4.2. Regulation of renal potassium excretion

The regulation of renal K^+ excretion is complex and coupled to many hormonal and non-hormonal factors. The seminal studies of Gerhard Giebisch and co-workers established the basic principles of renal K^+ excretion and of its regulation already more than 50 years ago (Giebisch, 2002; Stanton, 2010). Since then, numerous studies further defined the specific role of involved cell types, ion channels and transporters, and identified the critical molecular players that control their activity as displayed in several excellent recent reviews (e.g. (Castaneda-Bueno, Ellison, & Gamba, 2022; Ellison, Terker, & Gamba, 2016; Hoorn, Gritter, Cuevas, & Fenton, 2020; D. H. Lin, Duan, Zheng, & Wang, 2022; McDonough & Fenton, 2022; McDonough & Youn, 2017; Mutig & Bachmann, 2019; Nomura, Shoda, & Uchida, 2019; Palmer & Clegg, 2019; Su, Ellison, & Wang, 2019; Tabibzadeh & Crambert, 2023; Wei et al., 2020; Welling, 2016)). Based on these studies, the following concepts emerged.

The aldosterone-sensitive distal nephron (ASDN) is the primary site at which K^+ is secreted in response to a dietary K^+ load (Malnic, Klose, & Giebisch, 1964). Under resting conditions or on a low dietary K^+ intake, the ion channels involved in K^+ release (e.g. ROMK, BK and ENaC) are inactive and reside at intracellular sites of the ASDN cells, but get rapidly recruited to the apical plasma membrane after a high K^+ intake (Frindt & Palmer, 2010; Najjar et al., 2005; Wade et al., 2011). Consistently, electrophysiological studies demonstrated that the enhanced urinary K^+ secretion after a K^+ load is mainly achieved by an increase in the number of active channels in the luminal membrane of the ASDN rather than by a change of the conductance and/or the open probability of single channels (Palmer, Antonian, & Frindt, 1994; Palmer & Frindt, 1999). The apical translocation of ROMK and ENaC is accompanied by characteristic posttranslational modifications of the channels, which comprise an increased glycosylation of ROMK (Wade et al., 2011) and a proteolytic cleavage of the alpha- and gamma subunits of ENaC (Ergonul, Frindt, & Palmer, 2006; Jensen, Larsen, Leipziger, & Sorensen, 2016; Terker et al., 2016) which indicate the activation of the channels. The excretion of K^+ in the urine induced by activation of ROMK and ENaC in the segment-specific cells of the

ASDN can be modulated by K^+ excretion via the BK channel or by K^+ reabsorption via the H^+-K^+-ATPase in intercalated cells (Rao, Bhalla, & Pastor-Soler, 2019; Tabibzadeh & Crambert, 2023). Thereby, the effect on intercalated cells may occur independent or dependent from aldosterone and/or the MR (Pham et al., 2020; Shibata, 2016). Interestingly, the MR-dependent effects appear to involve an intercalated cell-specific dephosphorylation of the MR that promotes ligand-binding and eventually increases Cl^- reabsorption and reduces K^+ secretion via intercalated cells (Shibata et al., 2013).

Recent work established that also a dephosphorylation and hence inactivation of NCC in the DCT is a very important component of the renal adaptation to a high K^+ intake (Sorensen et al., 2013; Terker et al., 2015; van der Lubbe et al., 2013). The down-regulation of NCC diminishes Na^+ uptake in the DCT and hence delivers more Na^+ to the downstream localized CNT/CD. In the CNT/CD (and perhaps also in DCT2), this Na^+ can then be reabsorbed via ENaC in exchange for K^+ secretion via ROMK (Fig. 3). This functional coupling between DCT and CNT/CD is thought to significantly accelerate the renal elimination of an excess K^+ load (McDonough & Youn, 2013). The inhibition of NCC also increases the delivery of Cl^- to CNT and CD. This Cl^- can be reabsorbed either paracellular driven by the electrochemical gradient generated by ENaC or transcellular via the apical $Cl^-/HCO3^-$ exchanger pendrin in intercalated cells (Chambrey & Trepiccione, 2015). As not all delivered NaCl is reclaimed, part of it is lost via the urine, which readily explains the previously not well-understood paradox natriuresis and chloruresis after increased K^+ intakes (Tannen, Wedell, & Moore, 1973; van Buren, Rabelink, van Rijn, & Koomans, 1992) and the antihypertensive effect of a K^+ rich diet.

A natriuretic effect of an oral K^+ load is also seen in NCC-deficient mice suggesting that other renal Na^+ transport pathways are downregulated after a K^+ rich meal as well (Sorensen et al., 2013). Indeed, some data suggest that this may include NHE3 in proximal tubules and NKCC2 in TALs (Frindt, Houde, & Palmer, 2011; Jung et al., 2011; Yang et al., 2018).

According to textbooks, aldosterone is the main regulator of K^+ homeostasis. In fact, high plasma K^+ levels directly stimulate aldosterone release from the zona glomerulosa of the adrenal glands (McDonough & Fenton, 2022). Moreover, aldosterone stimulates renal Na^+ reabsorption and K^+ excretion via both an activation of ENaC in the apical membrane and of the Na^+-K^+-ATPase in the basolateral membrane (Pearce et al., 2022). However, there is no clear linear relationship between plasma K^+ concentrations, plasma aldosterone levels and urinary K^+ excretion (Pearce et al., 2022; Young, 1982). Moreover, the kaliuretic response to a K^+ load occurs very rapidly (i.e. in minutes) and usually starts before plasma aldosterone levels increase (Rabinowitz, Green, Sarason, & Yamauchi, 1988). Likewise, experiments on adrenalectomized animals (Palmer et al., 1994; Stanton, Pan, Deetjen, Guckian, & Giebisch, 1987) or mice with a targeted disruption of the aldosterone-synthase (Todkar et al., 2015; Yang, Frindt, Xu, Uchida, & Palmer, 2020) suggested that a K^+ load stimulates urinary K^+ excretion and renal Na^+ and K^+ channels independent from a rise of plasma aldosterone levels. Based on these and several other studies, it appears that the K^+-induced regulation of ROMK and BK is largely, if not completely, aldosterone-independent (Estilo et al., 2008), while the K^+-dependent regulation of ENaC involves both aldosterone-independent (mainly in the early ASDN) and aldosterone-dependent (mainly in the late ASDN) components (Nesterov, Bertog, & Korbmacher, 2022; Yang et al., 2020; Yang et al., 2021). Likewise, the K^+-dependent downregulation of NCC is likely aldosterone-independent, as it occurs similarly in control mice and in mice that lack aldosterone or have no MR expression in the kidney (Canonica et al., 2016; Terker, Yarbrough, et al., 2016; Todkar et al., 2015).

The last ten years brought significant insights into the underlying molecular mechanism that mediate the aldosterone-dependent and aldosterone-independent effects on DCT, CNT and CD as discussed in detail in the reviews mentioned above. In short, many of the molecular event are triggered by a direct sensing of altered plasma K^+ concentrations by the tubular epithelial cells (McDonough & Fenton, 2022). Already small variations around the physiological plasma K^+ concentration may elicit profound effects as demonstrated for the strong inverse correlation of extracellular K^+ and NCC phosphorylation (Penton et al., 2016; Terker et al., 2016). The observed epithelial K^+ sensing critically depends on the ATP-sensitive inward rectifier K^+ channel that is formed by the heterotetrameric assembly of Kir4.1 (KCNJ10) and Kir5.1 (KCNJ16) in the basolateral plasma membrane of DCT, CNT and CD cells (Palygin, Pochynyuk, & Staruschenko, 2018; Su et al., 2019). Under low K^+ diets, the reduced extracellular K^+ concentration favors the efflux of K^+ via Kir4.1/Kir5.1 which hyperpolarizes the basolateral plasma membrane and thereby was proposed to activate the efflux of Cl^- and Ca^{2+} via the basolateral Cl^- channel ClC-Kb (Terker et al., 2015) and the Na^+-Ca^{2+} exchanger NCX1 (Shoda et al., 2020), respectively. Under these conditions, NCC is highly phosphorylated via a cascade of kinases that involves the with-no-lysine(K) kinase WNK4 and the STE20/SPS1-related proline/alanine-rich kinase (SPAK) (Murillo-de-Ozores et al., 2022; Thomson et al., 2020) and a downregulation of KLHL3 (Ishizawa et al., 2016). ENaC and ROMK are inactive and retained inside the CNT/CD cells. Ubiquitylation of ENaC via the ubiquitin-ligase Nedd4–2 (Al-Qusairi et al., 2017) is a central mechanism that keeps the apical abundance of ENaC low (Fig. 3).

With an increased dietary K^+ intake, extracellular K^+ levels rise and reduce the K^+ efflux via the Kir4.1/Kir5.1 channel. This depolarizes the cell membrane and hence decreases Cl^- and Ca^{2+} efflux via ClC–Kb and NCX1, respectively (Hoorn et al., 2020). The increased intracellular Cl^- (Su et al., 2020) binds to the Cl^- binding pocket in WNK4 and thereby inactivates WNK4 and blocks subsequently the SPAK-dependent NCC phosphorylation (Mukherjee et al., 2021). In parallel, the increased intracellular Ca^{2+} binds to calmodulin, which activates protein phosphatase 3 (PP3 or calcineurin) and finally reduces NCC phosphorylation either directly or indirectly via effects on WNK4 (Melnikov, Mayan, Uchida, Holtzman, & Farfel, 2011) and KLHL3 (Ishizawa et al., 2019). In addition to PP3, protein phosphatase 1 (PP1) and perhaps other phosphatases may also contribute to the rapid K^+-induced dephosphorylation of NCC (Banki et al., 2021; Shoda et al., 2017).

In CNT/CD, aldosterone and direct K^+ sensing co-operate to enhance K^+ secretion. Aldosterone binds to the MR and thereby activates the transcription and expression of the regulatory serum-and-glucocorticoid-regulated kinase Sgk1. Sgk1 phosphorylates and thereby inactivates the ubiquitin-ligase Nedd4–2, which eventually enhances the cell surface abundance of ENaC due to the reduced ubiquitination of the channel (reviewed in: (Pearce et al., 2022). Moreover, aldosterone increases the expression of ENaC (mainly alphaENaC) and of the Na^+-K^+-ATPase that will further increase the K^+ (and Na^+) transport capacity of the CNT and CD cells (Pearce et al., 2022; Penton et al., 2015). However, there is also evidence for rapid direct effects of extracellular K^+ on Na^+ reabsorption and K^+ secretion in CNT/CD (Field, Stanton, & Giebisch, 1984; Jensen et al., 2016). Like in the DCT, a rise in extracellular K^+ concentrations might be sensed via basolateral plasma Kir4.1/Kir5.1 (Penton et al., 2020; Wang & Lin, 2022), increase intracellular Cl^- concentrations and activate the WNK4 pathway (Sorensen et al., 2019). However, in contrast to the DCT, the effect of WNK4 is not dependent on its kinase activity. Instead, WNK4 forms together with its homologue WNK1 a scaffolding critical for the activation of the mTORC2 complex (Saha et al., 2022), which increases then ENaC function due to an enhanced phosphorylation and activation of Sgk1 (Sorensen et al., 2019). In parallel, high extracellular K^+ concentrations activate ROMK via mTORC2 and PKC (Grahammer et al., 2016) (Fig. 4) ROMK bears two PKC phosphorylation sites (S4 and S201) that are essential for the cell surface abundance of ROMK (Lin, Sterling, Lerea, Giebisch, & Wang, 2002). Consistent with a critical role of the mTOR pathway for $K^{+\cdot}$ secretion, mice with a targeted inactivation of mTORC2 in the renal distal tubule develop severe hyperkalemia in

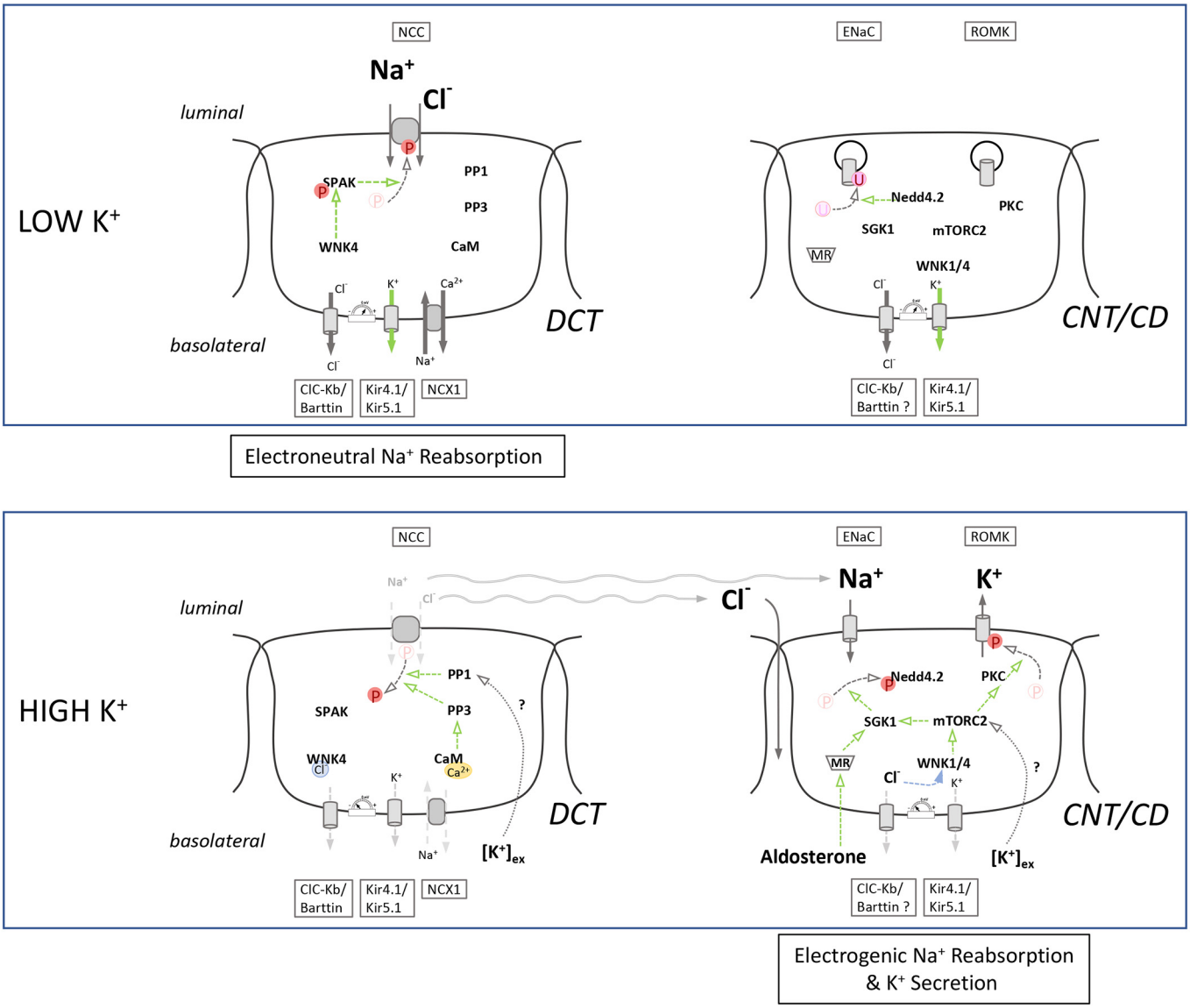

Fig. 4. Molecular signaling pathways and cellular mechanism controlling ion transport in DCT and CNT/CD under low plasma K^+ and high plasma K^+ concentrations, respectively. For details see text.

response to a dietary K^+ load (Grahammer et al., 2016; Saha et al., 2023; Sorensen et al., 2019). The mTOR pathway may also control renal K^+ handling via an altered phosphorylation and activation of the MR in intercalated cells (Shibata et al., 2018).

The aldosterone-independent effects induced by direct K^+ sensing are mainly based on phosphorylation (e.g. Sgk1 and ROMK) and dephosphorylation (e.g. NCC) events that occur very rapid (minutes), while the aldosterone effects are based on altered transcription, which usually implies a certain lag period (hours). This suggests that direct K^+ sensing is particularly important for the immediate response to high K^+ while aldosterone plays a more important role for the long-term response. It had been postulated that the increase in plasma-aldosterone levels and ENaC activity is not only to favor K^+ secretion, but to limit K^+ induced Na^+ losses related to the down-regulation of NCC (Jensen et al., 2016). Observations in adrenalectomized dogs with a fixed replacement dose of aldosterone support this idea. In response to a dietary K^+ load, these dogs cannot increase plasma aldosterone levels and hence develop a more pronounced natriuresis and drop in blood pressure than intact dogs (Young, McCaa, Pan, & Guyton, 1976). An overactivation of the aldosterone - ENaC axis may also explain why a very high K^+ intake associates with high blood pressure despite downregulation of NCC (Little et al., 2023).

A variety of additional hormones were implicated in the regulation of renal K^+ secretion. Glucocorticoids stimulate renal K^+ secretion likely indirectly via increased urinary flow (Stanton, Giebisch, Klein-Robbenhaar, Wade, & DeFronzo, 1985), while vasopressin has direct effects on tubular K^+ release possibly to ensure K^+ secretion also under conditions of antidiuresis (e.g. hemorrhagic shock) (Uyehara & Sarkar, 2013). Moreover, glucagon was suggested to increase in response to a dietary K^+ and to stimulate urinary K^+ excretion in cooperation with insulin (Bankir, Bouby, Blondeau, & Crambert, 2016). In contrast, progesterone levels rise with hypokalemia and are thought to reduce urinary K^+ loss via a stimulation of the H^+-K^+-ATPase in type A intercalated cells (Elabida et al., 2011). Angiotensin II suppresses ROMK, but stimulates ENaC, which may limit renal K^+ secretion and maximize renal Na^+ reabsorption during hypovolemia (Welling, 2013). Furthermore, there is some evidence for a yet not identified humoral kaliuretic factor. In response to a high K^+ diet, this factor may get released from the gut to stimulate renal K^+ secretion even before plasma K^+ levels rise (McDonough & Fenton, 2022).

A intrarenal kaliuretic factor is the serine protease kallikrein, which is highly expressed in the DCT and CNT and which proteolytically activates ENaC. High potassium intake is a strong stimulator of renal kallikrein synthesis and data from knockout mice and humans with partial kallikrein deficiency suggest a contribution of this protease to the regulation of renal K^+ excretion (El Moghrabi et al., 2010; Monteiro et al., 2013).

Another strong aldosterone-independent regulator of renal K^+ excretion is the urinary flow rate. A high urinary flow rate appear to directly activate K^+ secretion in the renal distal tubule (Malnic, Berliner, & Giebisch, 1989). Based on patch-clamp studies on isolated cortical collecting ducts from rabbits, Woda and co-workers suggested that the flow-dependent K^+ secretion is mediated mainly via the BK (or maxi-K) potassium channels (Woda, Bragin, Kleyman, & Satlin, 2001), which are mainly expressed in intercalated cells (Palmer & Frindt, 2007). The activation of BK depends on an increased intracellular Ca^{2+} concentration that elicits the exocytotic insertion of the channel into the apical membrane (Liu, Morimoto, Woda, Kleyman, & Satlin, 2007). The Ca^{2+}-permeable, nonselective cation channel TRPV4 may act here as a flow sensor to activate the BK channel (Stavniichuk et al., 2023). Flow-dependent BK activation may contribute to urinary K^+ wasting in polyuric hereditary diseases such as Bartter syndrome (Bailey et al., 2006) or with thiazide or loop-diuretic treatment (Wen, Cornelius, & Sansom, 2014). However, on a Palaeolithic diet with a low Na^+ and high K^+ intake, furosemide may have a paradox K^+ sparing effect (Wang & Sansom, 2019). The BK channel and flow-dependent activation of renal K^+ secretion likely contributes also to the physiological adaptation of renal K^+ excretion in response to a high K^+ diet. In fact, dietary K^+ does not only enhance the insertion of BK channels into the luminal plasma membrane (Najjar et al., 2005), but does also directly increase urinary flow via a lowered water reabsorption in the collecting system due to a reduced vasopressin sensitivity (Svendsen et al., 2022). These additional adaptive changes to a high K^+ diet likely explain the previous observation (Malnic et al., 1989) that the flow-dependent K^+ secretion is more pronounced on a high than on a low K^+ intake. The critical role of the BK channel for flow-induced K^+ secretion was demonstrated recently also by studies in mice with a targeted deletion of the alpha BK subunit specifically in intercalated cells (Carrisoza-Gaytan et al., 2020).

4.3. Hereditary disease-related modifiers of renal potassium excretion

Several human genetic diseases associated with dyskalemia (Table 1) support the pathophysiological relevance of the molecular players and concepts described above. For example, in Bartter- and Gitelman syndromes mutations in ion transporters and channels in TAL and DCT lead to salt-losing tubulopathies with prominent hypokalemia (Blanchard et al., 2017). As yet, five different types of Bartter-Syndrome (BS) have been described, which are related to loss-of-function mutations in the genes encoding either for NKCC2 (BS 1), ROMK (BS 2), ClC-Kb (BS 3), barttin (BS 4a), ClC-Kb and ClC-Ka (BS 4b), and the melanoma-associated antigen D2 (MAGE-D2) (BS 5) (reviewed in: (Konrad et al., 2021)). BS 1–4 are rare autosomal recessive diseases that directly impact on the ion transporter and channels critical for TAL function (Konrad et al., 2021). BS 5 is an X-chromosomal recessive disease that indirectly reduces the expression and function of NKCC2 and NCC possibly via an altered cyclic AMP-dependent signaling (Laghmani et al., 2016). While BS1–4 usually require life-long therapy including substitution of K^+, BS 5 resolves spontaneously by yet ill-defined mechanisms (Komhoff & Laghmani, 2018). Interestingly, newborns with ROMK mutations (BS 2) are usually hyperkalemic at birth and develop the typical hypokalemia at later stages of life (Bockenhauer & Kleta, 2021). This transient perinatal hyperkalemia is likely explained by the fact that ROMK deficiency does not only impair TAL function but does also diminish ROMK-dependent K^+ excretion in the ASDN. The K^+ loss at later stages is then likely related to increases K^+ fluxes via BK.

Gitelman-Syndrome (GS) is an autosomal-recessive disease related to loss-of function mutations in NCC. In contrast to BS, GS is a rather frequent tubulopathy with a prevalence of ~1–10 per 40′000 people (Blanchard et al., 2017; Ji et al., 2008). So far more than 350 different mutations have been described (Blanchard et al., 2017) and it is estimated that about 1 out of 100 humans is heterozygote for a NCC mutation (Fava et al., 2008). Although heterozygotes have lower blood pressure and increased plasma aldosterone levels (Ji et al., 2008), their plasma K^+ values are not different from controls (Fava et al., 2008) suggesting that the threshold for a deranged K^+ homeostasis is higher than that for Na^+ homeostasis.

The primary defect in BS and GS is an impaired Na^+ reabsorption in the TAL and the DCT, respectively. This Na^+ transport defect causes renal K^+ wasting likely via a combination of several mechanism: (i) The urinary Na^+ wasting activates the RAAS that will then stimulate aldosterone-dependent K^+ secretion; (ii) the enhanced delivery of Na^+ to the ASDN allows that more K^+ can get secreted via ROMK in exchange for Na^+ reabsorption via ENaC, and (iii) the enhanced urinary flow rate activates flow-dependent K^+ secretion.

The critical relevance of NCC and of proteins regulating its function is also evidenced by another group of diseases named familial hyperkalemic hypertension (FHHt), pseudohypaldosteronism type 2 (PHA2), or Gordon syndrome that mirrors the phenotype of GS. FHHt is caused by mutations in WNK1, WNK4 or in two proteins (KLHL3 and CUL3) that are part of an ubiquitin-ligase complex that controls the stability of WNK (Maeoka, Cornelius, & McCormick, 2023). In this disease, NCC activity is increased leading to renal Na^+ retention with hyporenemic arterial hypertension and hyperkalemia.

Two other mirroring genetic diseases underline the importance of ENaC and of the MR for renal K^+ excretion. Patients with autosomal-recessive pseudohypoaldosteronism type 1 (PHA1A) have loss-of-function mutations in one of the subunits of ENaC, which diminishes ENaC-mediated Na^+ reabsorption and hence eliminates the driving force for K^+ and also proton secretion (Furgeson & Linas, 2010). Consistently, patients suffer from renal salt wasting with hypotension, hyperkalemia and acidosis. The syndrome mimics conditions of hypoaldosteronism (e.g. associated with Addison's disease). However, patients with PHA1A do not have low but high plasma aldosterone levels, which explains the name of the disease. The mirroring disease

Table 1
Examples of hereditary diseases with dykalemia.

Hereditary Disease	Affected Protein	Plasma Potassium	Plasma Aldosterone	Extracellular Volume	Acid-Base Status
Bartter	NKCC2, ROMK, ClC-Kb, CLC-Ka, Barttin, MAGE-D2	low	high	low	alkalosis
Gitelman	NCC	low	high	low	alkalosis
FHHt/Gordon/PHA2	WNK1, WNK4, KLHL3, CUL3	high	normal/low	high	acidosis
PHA1A	ENaC	high	high	low	acidosis
PHA1B	MR	high	high	low	acidosis
Liddle	ENaC	low	normal/low	high	alkalosis
Geller	MR	low	low	high	normal
AME	11HSD2	low	low	high	alkalosis
EAST/SeSAME	Kir4.1	low	high	low	alkalosis

to PHA1A is Liddle syndrome. This autosomal dominant disease is characterized by severe arterial hypertension associated with hyperkalemia and alkalosis with normal to low levels of plasma aldosterone. The disease is caused by gain-of-function mutations in ENaC subunits, which impairs the binding of Nedd4–2 to and hence the ubiquitylation of the channel (Rizzo & Staub, 2015). The reduced ubiquitylation increases the cell surface abundance and activity of ENaC, which readily explains the clinical presentation of the disease and why inhibition of ENaC by amiloride is a very effective treatment (Blanchard, 2023).

Moreover, several other genetic diseases interfere with the aldosterone-dependent regulation of ENaC and thereby cause dyskalemia. For example, loss-of-function mutations in the MR cause an autosomal-dominant form of pseudohypoaldosteronism (PHA1B) with hypokalemia (Furgeson & Linas, 2010). Patients with this MR-related PHA1B usually have a less severe phenotype than patients with PHA1A due to ENaC-mutations. The disease improves spontaneously during early childhood suggesting the activation of compensatory mechanism (Kermond, Mallett, & McCarthy, 2023). In contrast to inactivating mutations of the MR, a specific single S810L mutation is associated with an overstimulation of the MR due to an altered hormone binding (Geller syndrome) (Geller et al., 2000). Patients with Geller syndrome show an early onset of hypertension with hypokalemia. In female carriers, pregnancy aggravates the situation because the mutation confers a significant progesterone-sensitivity to the receptor. Likewise, spironolactone becomes a potent agonist of the MR and is hence contraindicated in patients with Geller syndrome (Geller et al., 2000). An overactivation of the MR is also the cause of hypokalemia seen in patients with apparent mineralocorticoid excess (AME). AME is an autosomal recessive disorder due to a congenital defect in the 11HSD2 which leads to an illicit activation of the MR by glucocorticoids. Blockade of the MR with spironolactone is an effective therapeutic option (Funder, 2017). Excessive plasma glucocorticoid levels may also override the capacity of normal 11HSD2 explaining for example the hypokalemia seen in patients with Cushing syndrome (Torpy, Mullen, Ilias, & Nieman, 2002).

The importance of the Kir4.1/Kir5.1-dependent basolateral K^+ sensing mechanism is demonstrated by patients suffering from loss-of-function mutations in Kir4.1 (Lo, Forst, Warth, & Zdebik, 2022). As Kir4.1 is highly expressed in kidney, inner ear and the central nervous system, this autosomal-recessive disease is complex. According to the symptomatology, the syndrome was named either EAST (epilepsy, ataxia, sensorineural deafness, and renal tubulopathy) (Bockenhauer et al., 2009) or SeSAME (seizures, sensorineural deafness, ataxia, intellectual disability, and electrolyte imbalance) (Scholl et al., 2009). Regarding the kidney, patients with EAST/SeSAME syndrome show a Gitelman-like phenotype with renal sodium loss, hypomagnesemia and profound hypokalemia (Lo et al., 2022). Experiments on Kir4.1 deficient mice indicated that the renal phenotype is indeed related to both an inappropriate downregulation of NCC in the DCT (Zhang et al., 2014) and an inappropriate up-regulation of ENaC and ROMK in CNT/CD (Penton et al., 2020) that impairs K^+ sensing by the distal tubule (Cuevas et al., 2017).

4.4. Pharmacological modifiers of renal potassium excretion

4.4.1. Diuretics

Diuretics belong to the most often prescribed drugs. Basically, three main groups of diuretics can be distinguished: (i) loop-diuretics (e.g. furosemide, bumetanide, torasemide), (ii) thiazide- (e.g. hydrochlorothiazide, bendroflumethiazide) or thiazide-like (chlorthalidone, metolazone) diuretics, and (iii) potassium-sparing diuretics (e.g. amiloride, triamterene) (Ellison, 2019). Loop-diuretics block NKCC2 in the TAL. As NKCC2 reabsorbs ~20% of the filtered Na^+ load and contributes significantly to the urinary concentration mechanism, loop diuretics are high-ceiling diuretics, which are preferentially used to wash-out large volumes of Na^+ and fluid in patients with edema due to heart failure or kidney disease. Thiazide- and thiazide-like diuretics are still mainstays of hypertensive therapy due to their natriuretic effect via inhibition of NCC in the DCT. A concern with the use of loop- and thiazide-diuretics is the risk of hypokalemia that arises via the same mechanism as described above for genetic defects in NKCC2 and NCC. In fact, use of these diuretics is perhaps the most common cause of K^+ deficiency in humans (Knochel, 1984). The risk for hypokalemia may even further rise if both types of diuretics are combined for a sequential blockade of Na^+ reabsorption in TAL and DCT as it may become necessary in patients developing loop-diuretic resistance. The CLOROTIC trial evaluated the safety of the combination of loop- with thiazide-diuretics in patients with decompensated heart failure. The prevalence of hypokalemia with plasma K^+ values below 3.0 mmol/L was indeed significantly higher in patients with thiazide cotreatment vs. those without cotreatment (40.6% vs. 16.1%). Nevertheless, the prevalence of plasma K^+ values below 2.5 mmol and the incidence of serious adverse events were not different between the groups (Trulls, et al., 2023).

Loop- and thiazide diuretic induced hypokalemia is often associated with hypomagnesemia. Likewise, patients with salt-losing tubulopathies often have a combination of K^+ and Mg^{2+} deficiency. As the Mg^{2+} deficiency appears to aggravate the hypokalemia by increasing ROMK activity a successful treatment of hypokalemia requires also a correction of the Mg^{2+} deficiency (Huang & Kuo, 2007).

Amiloride and other potassium-sparing diuretics block specifically the epithelial Na^+ channel ENaC in the ASDN and hence lower the driving force for K^+ secretion. For antihypertensive therapy, potassium-sparing diuretics might be combined with thiazide-diuretics to reduce the risk for thiazide-induced hypokalemia. However, severe hyperkalemia has been reported sporadically after both amiloride monotherapy (Maddox, Arnold, & Dewell Jr., 1985) and amiloride/hydrochlorothiazide cotreatment (Jaffey & Martin, 1981). In a recent observational study on 194,456 outpatients, potassium-sparing diuretics were not associated with an increased risk for plasma K^+ levels >5 mmol/L. Actually, the risk for hyperkalemia was lower than with angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi). Not surprisingly, the study found also that loop/thiazide diuretics associated with a decreased risk of hyperkalemia (Chang et al., 2016). Generally, the risk for diuretic-induced dyskalemia varies considerably depending on the choice of the diuretic, the dosage, genetic factors including gender and race, as well as co-medications and various dietary factors (recently reviewed in (Lin, Wong, & Cheung, 2022).

4.4.2. Calcineurin inhibitors

Calcineurin or protein phosphatase 3 (PP3) is a calcium-calmodulin-activated serine-threonine protein phosphatase involved in numerous cellular processes, including the activation and proliferation of T-lymphocytes (Creamer, 2020). Calcineurin-inhibitors (CNI) like tacrolimus and cyclosporine act immune-suppressive and are hence frequently used in patients with solid organ transplantations. However, CNIs have numerous adverse effects including hypertension and hyperkalemia (Higgins et al., 2004). The hypertension and hyperkalemia had been linked to an inappropriate activation of NCC that causes renal Na^+ retention and limits renal K^+ excretion (Hoorn et al., 2011; Hoorn et al., 2012; Ishizawa et al., 2019) . Consistent with a critical role of NCC, tacrolimus has no effect on blood pressure and K^+ homeostasis in mice with a targeted deletion of this transporter (Hoorn et al., 2011). However, mice with a DCT-specific deletion of the calcineurin subunit B are also not hypertensive and hyperkalemic, suggesting that additional mechanism are involved (Banki et al., 2021). In fact, there are reports suggesting that CNIs act also on NKCC2 activity in the kidney (Borschewski et al., 2016; Matsuura et al., 2019) and on aldosterone production in the adrenals (Berber et al., 2023; Ito et al., 2021), which could also impact whole-body K^+ balance.

4.4.3. RAASi

RAAS inhibitors (RAASi) are widely administered to CKD patients providing both cardiovascular and renal protection. RAASi include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and steroidal and non-steroidal mineralocorticoid receptor antagonists (MRA). RAASi increase the risk for hyperkalemia, frequently leading to down-titration or even termination of these medications. Thus, clinicians are often confronted with the question what to do when a CKD patient on RAASi develops hyperkalemia. To our knowledge, no RCT data are available for guidance. In one study, more than 1500 patients admitted to the hospital because of acute heart failure, received daily serum K^+ measurements until day 7 or discharge (Beusekamp et al., 2019). 35% of the patients developed incident hyperkalemia with serum $K^+ > 5.0$ mmol/L, 17% >5.5 mmol/L, and 5% >6.0 mmol/L, respectively. Incident hyperkalemia was not associated with increased all-cause mortality at 180 days but with MRA down-titration. Incident hyperkalemic patients who were discharged after down-titration or discontinuation of these drugs had a 70% higher mortality compared to those with continued or increased ACEi/ARB or MRA dose. Another retrospective cohort study of almost 50,000 older patients analyzed ambulatory interventions for RAASi-related hyperkalemia together with the risk of hyperkalemia recurrence and the occurrence of cardiovascular events and mortality within the 1-year observation period (Hundemer et al., 2021). Interestingly, hyperkalemia with serum $K^+ \geq 5{,}3$ and < 7.0 mmol/L did not lead to pharmacologic interventions in the majority of the patients - clinicians changed the medication in only 23% of the patients. RAASi were stopped in 74% and reduced in 15%, new diuretics prescribed in 3% and increased in 7%, and sodium polysterene sulfonate (SPS) administred in 1% of the patients. Compared to no intervention, the hyperkalemia recurrence risk was lower with RAASi discontinuation and higher with SPS, whereas all other measures had no effect. The higher hyperkalemia incidence with SPS was possibly a consequence of dietary potassium liberation. Interestingly, RAASi discontinuation in this study was not associated with an increased risk for cardiovascular and all-cause mortality at 1 year. The rather short observation periods of both observational studies are limitations. Randomized studies are needed to provide better guidance for clinicians. Adding newer potassium binders provides one way to increase the percentage of patients on RAASi. This topic is discussed later in chapter 6.

4.4.4. Varia medications

4.4.4.1. Co-trimoxazole. Co-trimoxazole is an antibiotic combination of trimethoprim and sulfamethoxazole often used to treat patients with urinary tract infections, and for prophylaxis and treatment of Pneumosystis jirovecii infections, for example in kidney transplantation (Chapman, Dickerson, Daly, Clancy, & Geddes, 2019). Hyperkalemia is a frequent adverse effect of this combination, which is related to an amiloride-like inhibitory effect of trimethoprim on ENaC. A recent study from the Netherlands reported an incidence of hyperkalemia in 20% of hospitalized patients with intravenous administration of co-trimoxazole (Marlicz & Chrzanowska, 1988). Likewise, a randomized controlled trial from the US found significantly higher plasma K^+ values in patients on oral co-trimoxazole treatment compared with patients on placebo. Nevertheless, the increase of plasma K^+ was usually small, but may reach clinically relevant levels in some patients (Chan, Clark, Wilson, Loke, & investigators, T., 2017), in particular, if they have other risk factors for hyperkalemia such as CKD or RAASi co-administration.

4.4.4.2. Licorice. Licorice is a popular candy flavoring and herbal remedy that is derived from the root of the *Glycyrrhiza glabra* plant. When consumed in large quantities or over a prolonged period, licorice can cause hypokalemia, which is often associated with arterial hypertension, low plasma renin activity and reduced plasma aldosterone levels. This type of pseudo-hyperaldosteronism is related to the licorice compound glycyrrhizinc acid, which inhibits the enzyme 11βHSD2 and thereby promotes an inappropriate activation of the MR via glucocorticoids similar to the one seen in patients with hereditary apparent mineralocorticoid excess. In a recent systemic review and meta-analysis, Penninkilampi and co-workers assessed data from18 studies ($n = 337$) in which participants consumed a mean daily dose of glycyrrhizinc acid of 377.9 mg, which equals an estimated amount of 189 g of black licorice/day. The pooled data from nine studies with reported plasma K^+ levels showed a significant drop of the mean plasma K^+ levels from pre- to post-licorice consumption by −033 mmol/L (95% CI -042 to 0.23). However, as pointed out by Yoshino et al., the risk for licorice-associated hypokalemia may vary considerably with age, gender, concomitant medication, and preexisting medical conditions (Yoshino et al., 2021). A derivative of glycyrrhizinc acid is carbenoxolone. Carbenoxolone has anti-inflammatory properties and is used for the treatment of oral, esophageal, and gastric ulcers. Like natural liquorice, carbenoxolone can cause significant hypokalemia (Metcalfe & Entrican, 1987).

4.4.4.3. Azole antifungal agents. Invasive fungal infections pose a serious threat, particularly to immunocompromised patients. Azoles (−conazole) are frequently used as first-line treatments for fungal infections and for prophylaxis in patients at increased infection risk. These drugs are associated with adverse events including hepatoxicity, myositis, peripheral neuropathy, ophthalmologic disorders, nausea and vomiting, and hypokalemia (Benitez & Carver, 2019; de Souza, Santos, & Reis, 2016; Maertens et al., 2021; Pana et al., 2018). Several mechanisms contribute to antifungal azole-induced hypokalemia, such as adrenal insufficiency (Gradon & Sepkowitz, 1991; McCance, Ritchie, Sheridan, & Atkinson, 1987). However, some of the hypokalemic patients present with severe hypertension rather than hypotension that is seen in adrenal insufficiency. Pseudohyperaldosteronism was identified as the underlying disease mechanism explaining both hypertension and hypokalemia. This condition was observed with itra- and posaconazole but not with voriconazole (Brandi, Feltoft, Serup, & Eldrup, 2021; Hoffmann, McHardy, & Thompson 3rd., 2018; Kuriakose, Nesbitt, Greene, & Harris, 2018; Maertens et al., 2021). Itraconazole and Posaconazole lead to mineralocorticoid receptor activation and to subsequent renal potassium secretion although by distinct mechanisms. Itraconazole was shown to inhibit predominantly 11β-HSD2 thereby increasing cortisol, whereas posaconazole inhibited CYP11B1 leading to accumulation of 11-deoxycorticosterone and 11-deoxycortisol (Beck, Telisman, van Koppen, Thompson 3rd, & Odermatt, 2020). These effects were not seen with voriconazole, fluconazole, and isavuconazole.

4.4.4.4. Anticancer drugs. Anticancer drugs are associated with both hyper- and hypokalemia. One hyperkalemia mechanism employed by anticancer drugs is acute kidney injury (AKI). Strongly reduced GFR leads to compromized glomerular potassium filtration and subsequently to hyperkalemia (Rosner & Perazella, 2017). Some of anticancer drugs employ additional mechanisms, such as tumor lysis syndrome with huge potassium release from tumor cells. Moreover, immune checkpoint inhibitors (ICI) are increasingly reported to cause hyperkalemia. ICIs are monoclonal antibodies that block programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte–associated protein 4 (CTL-4), respectively. Blocking these inhibitory co-stimulatory signals increases the capacity of T cells to kill tumor cells. Unfortunately, these drugs also induce autoimmune inflammatory side effects, including adrenalitis (Postow, Sidlow, & Hellmann, 2018). Consequently, ICIs were shown to lead to primary adrenal insufficiency with substantial mortality and morbidity, including hyperkalemia (Barroso-Sousa et al., 2018; Grouthier et al., 2020).

However, hypokalemia is also frequent in cancer patients because of either renal or gastrointestinal potassium losses, or intracellular

potassium shifting. Cisplatin and ifosfamide provide examples for tubular epithelial cell injury with subsequent renal potassium wasting, the former accompanied and facilitated by significant magnesium losses. Hypokalemia is often intractable until the magnesium deficit is substituted. The reason for this interaction is the fact that intracellular magnesium inhibits potassium secretion via ROMK in the distal nephron thereby increasing renal losses. Another example for hypomagnesemia with persistent hypokalemia comes from treatment with monoclonal anti-EGFR antibodies, such as cetuximab (Wang et al., 2015). Moreover, ICIs not only cause hyper- but also hypokalemia. In fact, hypokalemia was with 19% more common than hyperkalemia that was found in 6% of the ICI-treated patients (Wanchoo, Sakhiya, & Jhaveri, 2021). ICI-induced gastritis, colitis, and tubulointerstitial nephritis contribute to hypokalemia through gastrointestinal and renal potassium losses. ICI-mediated hypokalemia occurs frequently together with distal or proximal RTA. In biopsies from ICI-treated patients with distal RTA, deceased V-ATPase pump and anion-exchanger 1 expression was detected in type A intercalated cells, reminiscent of findings in Sjögren patients (Herrmann, Alexander, Romero, & Zand, 2020). Additional anticancer drugs are reported to cause hypokalemia, including tyrosine kinase, Bcl-2, and BRAF inhibitors (van der Lubbe, Lugtenburg, & Hoorn, 2021; Verzicco et al., 2020; Wanchoo, Jhaveri, Deray, & Launay-Vacher, 2016). Consequently, serum-K^+ (and Mg^{2+}) need to be regularly monitored in patients receiving anticancer treatments.

5. Considerations of dietary potassium intake in chronic kidney disease

Given the central role of the kidneys for the external K^+ balance, it is not surprising that patients with CKD are at high risk for the development of hyperkalemia. The risk progressively increases with the decline of glomerular filtration. A large retrospective analysis on 245,808 US veterans revealed an increasing odds ratio for hyperkalemia (> 5.5 mmol/L) from 2.24 for moderate CKD (stage 3; GFR: 30–59 mL/min/1.73m^2), over 5.91 for severe CKD (stage 4; GFR: 15–29 mL/min/1.73m^2), to even 11 for end-stage renal disease (stage 5. GFR < 15 mL/min/1.73m^2) (Einhorn et al., 2009). Likewise, data from the German CKD registry demonstrated a clear inverse correlation of mean plasma K^+ levels with GFR. Remarkably, more than 25% patients of patients with CKD stages 4–5 had plasma K^+ levels above 5 mmol/L, and more than 1.4% had even plasma K^+ levels above 6 mmol/L (Kleophas, et al., 2013). An accompanying therapy with RAASi may further increase the risk for hyperkalemia due to the additional impairment of tubular K^+ secretion. Clinical trials report incidences of 1.9–38.4% for hyperkalemia in CKD patients with RAAS Inhibition. However, the strict inclusion criteria and well controlled settings of clinical trials provide likely numbers that underestimate the real frequency of hyperkalemia in everyday clinical practice (Kovesdy, 2014). As hyperkalemia destabilizes the membrane potential of excitable cells, rises in plasma K^+ make patients prone for cardiac arrhythmia and even sudden cardiac arrest. However, it is interesting to note, that patients with CKD are in fact at high risk for hyperkalemia but that they appear to better tolerate episodes of hyperkalemia than patients with normal renal function. For example, the odds ratio for sudden death within 1 day after a hyperkalemic episode with a plasma K + level above 6 mmol/L is 31.64 for patients without CKD, 19.52 for patients with CKD stage 3, 11.56 for patients with CKD stage 4, and "only" 8.02 for patients with CKD stage 5 (Einhorn et al., 2009). The risk of hyperkalemia led to recommendations for a reduction of dietary K^+ intake in patients with CKD. However, K^+ rich foods (e.g. fruits and vegetables) are usually part of a healthy and tasteful diet. Moreover, there is emerging evidence that dietary K^+ may not only have beneficial effects on the cardiovascular system but also on the kidney and even for patients with CKD. In 2014, data from the ONTARGET/TRANSCEND observational trial with more than 28,000 participants suggested that a higher urinary K^+ excretion as a surrogate marker for dietary K^+ intake, improves all renal outcomes including decline of GFR, doubling of creatinine, progression of proteinuria with only a minor increase of the risk for hyperkalemia (Smyth, et al., 2014). However, it is important to note that the study included mainly patients with mild CKD. A subgroup analysis suggested a loss of the reno-protective effect of a high K^+ diet in patients with more advanced CKD (GFR <45) (Smyth, et al., 2014). Wei and co-workers recently summarized the results from 10 epidemiological cohort studies that analyzed the association between urinary K^+ or urinary Na^+/K^+ excretion and kidney outcomes. Six studies suggested better kidney outcomes, one study suggested a lower mortality, two studies found no association or were inconclusive and only one study reported worse kidney outcomes (Wei et al., 2020). Different mechanism may explain the putative beneficial effect of an increased dietary K^+ intake, including a lowered blood pressure due to the K^+ effects on renal Na^+ handling (see above), an improved GFR due to a direct K^+-dependent relaxation of afferent arteriole, and an improved renal blood flow due to vasodilation via the K^+ activated renal kallikrein system (Jablonski & Kendrick, 2014). These data from cohort studies in humans together with emerging evidence form experimental studies in animal models (reviewed in (Wei et al., 2020)), suggest that patients with CKD may also profit from increasing dietary K^+ and may even question the "do-not-eat-potassium" rule in dialysis.

6. New developments: pharmacological reduction of dietary potassium uptake

Because of the pivotal role of potassium for membrane potentials, hyperkalemia can provoke lethal arrhythmias resulting in sudden cardiac death. CKD patients are at an increased risk for hyperkalemia. Therefore, physicians have used a variety of measures to lower serum K^+, including potassium binders that act in the gastrointestinal tract. Three different potassium binding principles are employed, namely cation-exchanger from polysterene sulfonate with either Na^+ or Ca^{2+} bound to the polymer, and two newer binders, patiromer and zirconium silicate, formerly known as ZS-9. Patiromer is an oral nonabsorbed polymer that binds potassium in exchange for calcium. Sodium zirconium cyclosilicate is a rare earth providing a nonabsorbed nonpolymer functioning as potassium trap that exchanges potassium for Na^+ and H^+.

6.1. Sodium polystyrene sulfonate

In 1958, the FDA approved sodium polysterene sulfonate (SPS), a polymer with a reactive sulfonyl group that can exchange the bound Na^+ for another cation such as K^+, but also Ca^{2+}, Mg^{2+}, and NH_4^+. The exchange occurs mainly in the colon, and the newly bound K^+ is then lost with the stool. One gram of SPS contains 4 mmol Na^+ that are available for the exchange with K^+. Because SPS leads to constipation, it is often combined with sorbitol. At the time of introduction into clinic, efficacy and safety were assumed from small uncontrolled case series with several confounders but not studied in randomized controlled trials (RCT) (Evans, Jones, Milne, & Yellowlees, 1953; Flinn, Merrill, & Welzant, 1961; Scherr, Ogden, Mead, Spritz, & Rubin, 1961). SPS was used with great confidence in industrial amounts around the world for decades, either as an oral or rectal application. In one study, 95% of the patients with serum K^+ ≥ 5.1 mmol/L received SPS, more than 2/3 even as monotherapy, most frequently at a 30 g dose (Fordjour, Walton, & Doran, 2014). In only 14% of the patients, a serum K^+ control was performed within 8 h. Thus, confidence in SPS seemed overwhelming. Approximately 50 years later, an intensive discussion about efficacy and safety started (Kamel & Schreiber, 2012; Sterns, Rojas, Bernstein, & Chennupati, 2010; M. Watson, Abbott, & Yuan, 2010). Careful stool studies established a positive correlation between stool weight and stool potassium excretion (Hayes Jr. & Robinson, 1965). Emmet et al. studied the distinct effects of SPS and laxatives on potassium stool content and found that increasing stool volume led to more enteral K^+ excretion with rather small additional SPS effects (Emmett et al., 1995). Only in

2015, a double-blind randomized clinical trial in 33 chronic hemodialysis patients was performed. Patients received placebo or 30 g SPS/d orally over 7 days (Lepage et al., 2015). Importantly, SPS was dissolved in water without sorbitol. At day 7, serum K^+ had decreased by 0.21 mmol/L in the placebo group and by 1.25 mmol/L in the SPS group. The 1.04 mmol/L difference was statistically significant indicating that SPS, at least when taken over 1 week, lowers serum K^+. Amazingly, this is, and probably will remain, the only randomized placebo-controlled SPS trial. Concerns about rare, but potentially fatal, SPS-related colonic necrosis, in combination with sorbitol and alone, resulted in warnings by the FDA in 2009 closing the circle of a 50-year SPS mythos (Gerstman, Kirkman, & Platt, 1992; Harel et al., 2013; Noel et al., 2019; Watson et al., 2012). In summary, SPS has serum K^+ lowering effects with rare but serious safety concerns. SPS seems insufficient to lower serum K^+ rapidly enough in life-threatening hyperkalemia and should definitively not be used as monotherapy in this setting. New, effective K^+-binders have been developed that were thoroughly studied in well-conducted RCT.

6.2. Patiromer

In 2015, patiromer was tested in hyperkalemic CKD patients who received RAASi with a serum K^+ between 5.1 to <6.5 mml/L (Weir et al., 2015). The rationale for this study was that hyperkalemia is associated with increased mortality and limits RAASi use. In the initial trial phase, all patients received 4.2 or 8.4 g patiromer twice daily. At week 4, serum K^+ significantly decreased by 1.01 mmol/L with is a larger effect in patients with moderate-to-severe compared to mild hyperkalemia. 76% of the study participants reached the serum K^+ target of 3.8 to <5.1 mmol/L. In the subsequent trial phase, the patients who had an initial serum K^+ baseline of 5.5 to <6.5 mmol/L and had achieved the target at week 4, were randomized to either continue patiromer or to placebo. The median serum K^+ increase was significantly greater with placebo then with patiromer, and serum $K^+ \geq 5.5$ mmol/L occurred in 60% of the former but only in 15% of the latter group through week 8. Similar efficacy and safety was established in additional patient cohorts, mainly CKD patients without and with type 2 diabetes mellitus (T2DM), RAASi treatments, and over longer time periods up to 1 year (Agarwal et al., 2019; Bakris et al., 2015; Pitt et al., 2018). Patiromer enabled more patients to use RAASi medication (Pitt et al., 2011; Weir et al., 2015). An interesting question pertains to the patiromer use in acute care settings. Studying three different time intervals up to 24 h, a single patiromer dose delivered as monotherapy was associated with a significant serum K^+ decrease (Di Palo, Sinnett, & Goriacko, 2022). The effect occurred within the first 6-h interval. Although the lack of a placebo control limits the interpretation, the data suggest that patiromer could provide a useful measure to treat patients with acute, non–life-threatening hyperkalemia.

Patiromer releases Ca^{2+} and, in healthies, was associated with increased urine calcium excretion, whereas the urinary excretion of K^+, Na^+, Mg^{2+}, and Ph^{2+} decreased (Bushinsky et al., 2016). In CKD patients, a decrease in urine and serum-Ph^{2+} in a hyperphosphatemic subgroup was observed. Neither urine or serum Ca^{2+}, PTH, or active vitamin D changed in these patients. Oxalate was not measured and the potential clinical significances of these findings remain unclear (Emmett & Mehta, 2016).

6.3. Sodium zirconium cyclosilicate

Sodium zirconium cyclosilicate, has a 25-fold selectivity for K^+ over other cations such as Ca^{2+} and Mg^{2+} (Stavros, Yang, Leon, Nuttall, & Rasmussen, 2014). The drug's efficacy and safety was documented in RCT that included patients with risk factors for hyperkalemia such as CKD, RAASi, T2DM, and heart failure. In the largest study, 754 hyperkalemic patients with serum K+ between 5.0 and 6.5 mmol/L received either placebo or sodium zirconium cyclosilicate at doses ranging from 1.25 to 10 g/trice daily (Packham et al., 2015). At 48 h, serum K^+ decreased by 0.25 mmol/L in the placebo group. Although not reaching statistical significance this finding shows the importance of appropriate controls. However, all sodium zirconium cyclosilicate treatment groups showed a significant dose-dependent serum K^+ decrease. For example, in the 10 g group, serum K^+ fell by 0.7 from 5.3 to 4.6 mmol/L within 48 h, starting already 1 h after the first dose was administered. In the subsequent maintenance study phase, significantly more patients on 5 or 10 g/d sodium zirconium cyclosilicate remained normokalemic over the next 12 days compared to the placebo group. In the HARMONIZE study, the percentage of patients remaining normokalemic with 5 g sodium zirconium cyclosilicate/d was 80% with ZS-9 but only 46% with placebo (Kosiborod, Peacock, & Packham, 2015). These data were confirmed in a subsequent study where 40% of the placebo group but more than twice as many patients on sodium zirconium cyclosilicate were able to continue cardioprotective RAASi treatment (Anker et al., 2015). The potassium lowering effect occurs regardless of the CKD stage (Roger et al., 2021).

The adverse event profile of patiromer and sodium zirconium cyclosilicate seems favorable although a few off-target aspects should be considered. Not surprisingly, both drugs are associated with an increased hypokalemia risk (Spinowitz et al., 2019). Patiromer causes hypomagnesemia in up to 24% of the patients (Pitt et al., 2011). Moreover, patiromer exhibited significant drug-drug interactions with 4 of 12 studied medications, namely ciprofloxacin, clopidogrel, metformin and metoprolol, when administered within a 3 h interval (Lesko et al., 2017). Sodium zirconium cyclosilicate contains sodium and caused edema in up to 14% of the patients when used at 15 g doses (Kosiborod et al., 2015). A post-hoc analysis of RCT data revealed that sodium zirconium cyclosilicate leads to serum bicarbonate increase up to 1.5 mmol/L, most likely by gastrointestinal NH_4^+ binding and increased ammoniagenesis because of decreased serum K^+ (Roger et al., 2021).

In summary, with patiromer and sodium zirconium cyclosilicate clinicians have two novel drugs on hand to effectively lower serum K^+ in hyperkalemic patients and enable more RAASi therapy. However, open questions remain, including the threshold for potassium binder initiation, and whether the new potassium binders translate into hard endpoints. It is conceivable that reversing hyperkalemia improves patient survival and cardiovascular or renal events, but it is also possible that only serum K^+ is reduced but not the hard endpoints. Further studies are needed to clarify these important issues.

6.4. Laxatives

We already discussed aspects of gastrointestinal potassium excretion and the increase of this elimination route by sorbitol and phenolphthalein. A recent analysis of more than 36,000 patients in an advanced CKD stage on transition to end-stage kidney disease (ESKD) explored the association of laxatives and dyskalemia (Sumida et al., 2021). Dyskalemia was defined as serum $K^+ < 3.5$ or >5.5 mmol/L and occurred in 4.0% and 5.0% of the patients, respectively. After multivariable adjustments, patients with laxative intake had an approximately 20% lower risk for hyper- but not for hypokalemia in the last 1-year pre-ESKD period. The data suggests a therapeutic potential of laxatives in hyperkalemia management of patients with advanced CKD stages. Whether laxatives can help to postpone dialysis needs to be tested in an appropriate prospective study design.

7. Illustrating case vignettes

7.1. Case 1

A 85-year-old man presented to the emergency room (ER) with profound muscle weakness and confusion. His past medical history showed T2DM, arterial hypertension, and congestive heart failure. He was

dismissed from the hospital six weeks ago, when his heart failure medication was fine-tuned because of cardiac decompensation. He now was on 10 mg/d ramipril, 2 × 95 mg/d metoprolol, 2 × 10 mg/d furosemide, 1 × 12.5 mg/d hydrochlorothiazide, and 50 mg/d spironolactone. Recently, his general practitioner added the Cox-2 inhibitor rofecoxib because of arthralgias in several joints. Physical examination in the ER revealed a blood pressure of 160/100 mmHg and a rhythmic heart rate of 80/min. He had minor peripheral edema, a 3/6 systolic ejection murmur along the left sternal border, and his lungs were clear. His electrocardiogram is depicted in Fig. 5. Selected laboratory blood values showed Na^+ 136, Cl^- 100, K^+ 10.6 (all mmol/L), and creatinine 473 μmol/L. Arterial blood gases revealed pH 7.19, pO_2 100 mmHg, pCO_2 20 mmHg, HCO_3^- 4 mmol/L. Thus, the patient had severe hyperkalemia and metabolic acidosis with an appropriate respiratory compensation.

To assess renal K^+ handling, we measured $urine_K$, $plasma_K$, and $urine_{Osmolarity}$ in a spot sample and estimated $plasma_{Osmolarity}$ from $2xNa^+$ + blood glucose + urea (all mmol/L). With these parameters we calculated the transtubular K^+ gradient (TTKG) using the following equation:

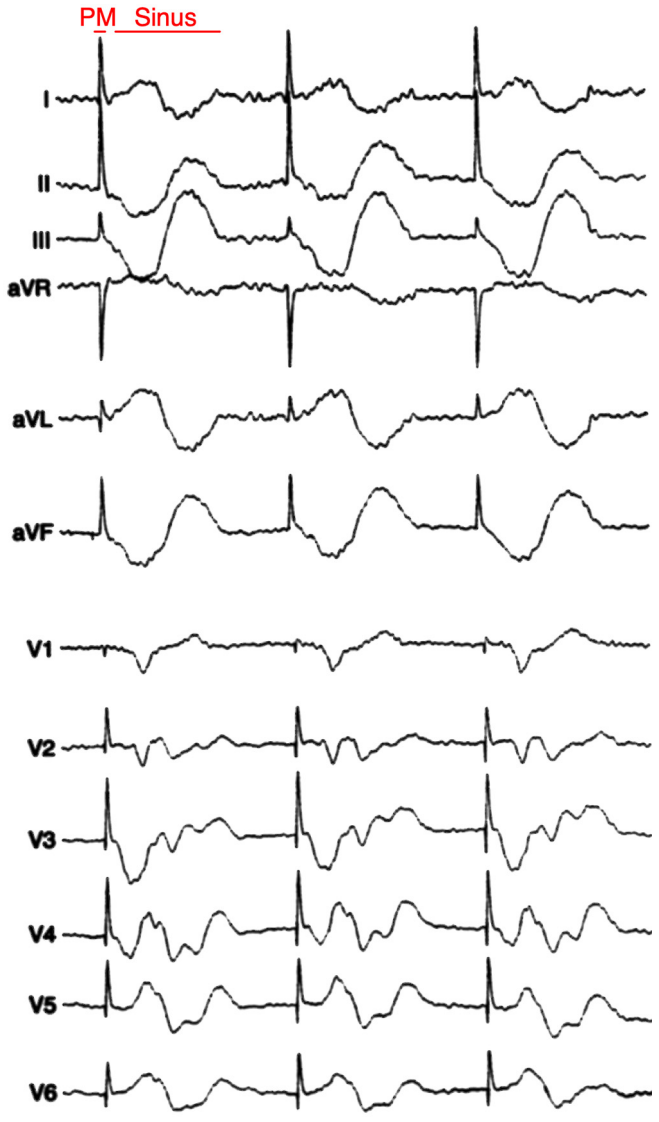

Fig. 5. An electrocardiogram with 50 mm/s at serum K^+ 10.8 mmol/L shows regular pacemaker spikes (PM) followed by a widened and deformed QRS complex with a degenerated sinus wave conformation (Sinus).

$$TTKG = UK \times POsm/PK \times UOsmo$$

The expectation would be that the kidneys secrete ample potassium amounts in the face of a serum K^+ of 10.8 mmol/L. However, a TTKG of 1.9 indicated that this was not the case. An appropriate TTKG would be certainly above 6. As an alternative, we could have used the $urine_K$/$urine_{Creatinine}$ ratio that should be high (>20 mmol/mmol or >200 mmol/g) in a hyperkalemic patient. Important shortcomings of both estimates need to be considered but they nevertheless give clinicians a rough estimate at the bedside (Choi & Ziyadeh, 2008; Kamel & Halperin, 2021). Since K^+ secretion is achieved in an aldosterone-dependent manner in the distal nephron, we realized that this mechanism was compromised in our patient. The reason was his medication that blocked renal renin generation (Cox-inhibitor and β-blocker), angiotensin I to angiotensin II conversion (ACEi), and the mineralocorticoid receptor (steroidal mineralocorticoid receptor antagonist). The condition is called hyporeninemic hypoaldesteronism or RTA type IV providing probably the most common hyperkalemia cause that we see in clinic, particularly in patients with diabetic nephropathy and CKD. Thus, our patient had severe life-threatening hyperkalemia with profound metabolic acidosis. We paused all inflicting medications mentioned above and immediately administered calcium gluconate to electrically stabilize cell membranes. Note, that this measure does not lower serum K^+. In addition, we used insulin to shift potassium into cells, infused sodium bicarbonate because of severe metabolic acidosis, and, given the severe AKI, ordered hemodialysis. Subsequently, serum K^+ fell and the ECG showed a regular sinus rhythm. Nevertheless, in this acute hypokalemic situation, the pacemaker possibly saved the patient's life. This clinical example demonstrates that understanding the pathophysiology of potassium (patho) physiology helps clinicians to diagnose and treat potassium disorders.

7.2. Case 2

A 26-year-old lady presented to the ER with profound muscle weakness, dizziness, and a syncope after standing up. She was 170 cm tall, weighted 46 kg and had lost 6 kg of body weight within the last 4 weeks. She had a blood pressure of 90/60 mmHg in supine position that dropped to 70/55 mmHg when getting up. No peripheral edema was present. Her electrocardiogram is depicted in Fig. 6. The serum concentration was 114 for Na^+, 1.8 for K^+, 50 for Cl^- (all mmol/L), and 134 μmol/L for creatinine. Arterial blood gases showed pH 7.61, pO2 51 mmHg, pCO2 58 mmol/L, and HCO_3^- 59 mmol/L.

Thus, we encountered a patient with hypochloremic hypokalemia and severe metabolic alkalosis. This is a very complex condition that we can resolve by applying renal physiology. An important task in these patients is the assessment of the extracellular volume status because this condition occurs with either volume expansion or contraction. Our patient was clearly volume contracted, but the question was why? Major suspects under these circumstances are vomiting, diuretics, laxatives, and various tubulopathies. Urine electrolytes can help to distinguish these causes (Grams, Hoenig, & Hoorn, 2021). Our patient had low urine Na^+ and Cl^- and it turned out that she suffered from self-induced vomiting. The loss of HCl caused hypochloremic metabolic alkalosis and the loss of ample amounts of gastric fluid (ECF) volume contraction. The latter maximally stimulated the RAAS that in turn induced metabolic alkalosis via aldosterone-induced H^+ secretion by type A intercalated cells. In addition, low urine Cl^- reduced HCO_3^- secretion in type B intercalated cells further contributing to metabolic alkalosis. The next question was how do we explain the hypokalemia in this patient? We determined the TTKG that was 32 - even in the face of low urine Na^+ that limited the aldosterone-mediated K^+ secretion by principal cells! The TTKG should have been less than two to preserve potassium in the kidneys. Thus, renal K^+ loss was the major

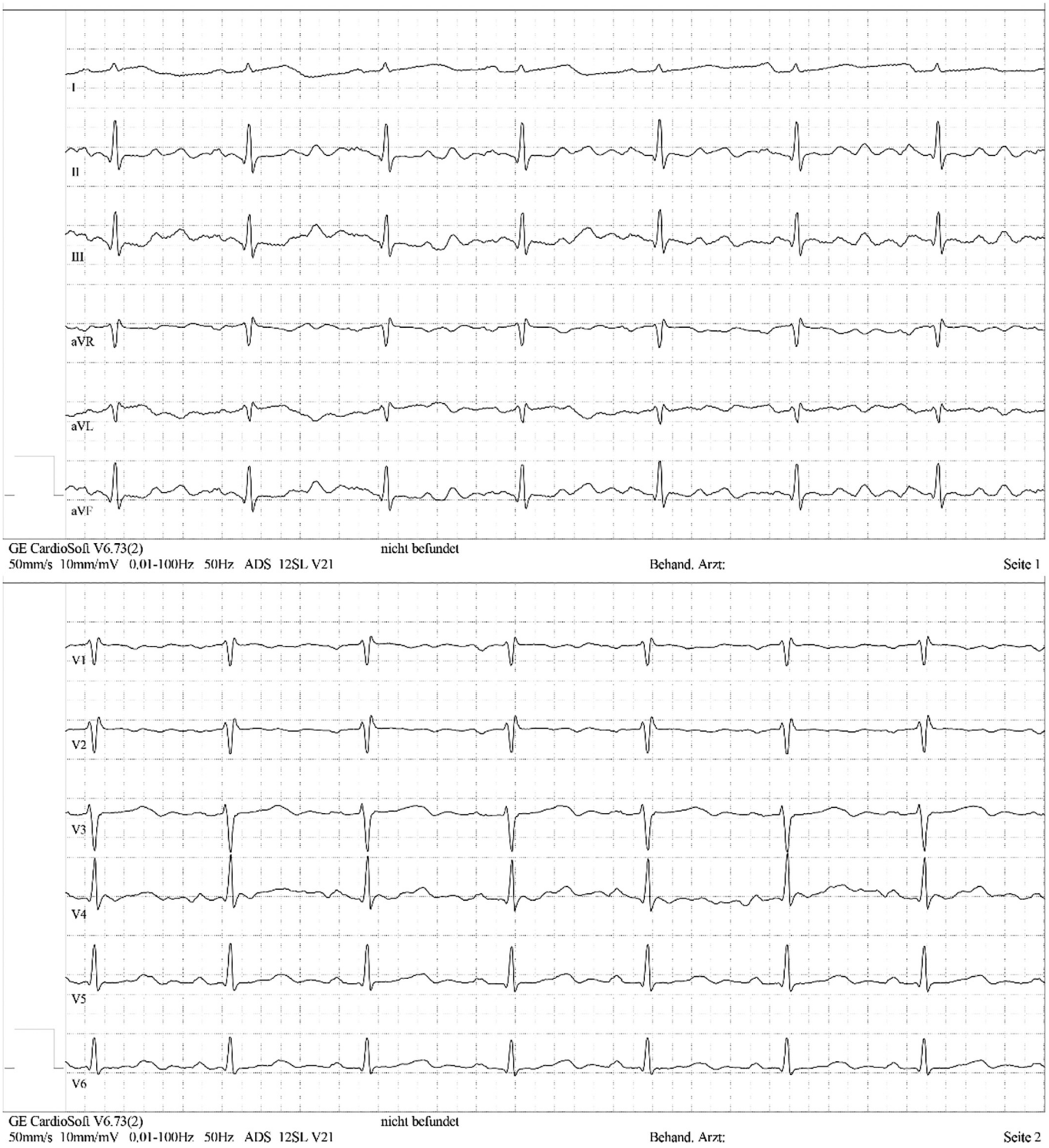

Fig. 6. The patient's electrocardiogram (50 mm/s) at serum K^+ 1.8 mmol/L shows the typical prolonged QT interval with U-waves during repolarization.

contributor to the hypokalemia in this patient, presumably more than the alkalosis-mediated intracellular potassium shift.

Treatment had to address the different clinical aspects of this complex acid-base and electrolyte disorder. Priority had the substitution of the ECF deficit to prevent circulatory shock and to diminish RAAS stimulation. We administered several liters of 0.9% NaCl solution, and, to substitute the potassium deficit, added KCl to the infusions. We are aware of the ongoing discussion on the use if 0.9% saline versus balanced solutions favoring the latter in some but not all studies. However, we intentionally used the 0.9% NaCl to address the profound Cl^- deficit that would further maintain the metabolic alkalosis. Filtered Na^+ needs to be effectively reabsorbed in a volume-depleted patient in order to reconstitute the contracted extracellular compartment. In our hypochloremic patient, Na^+ was reabsorbed together with Cl^- along the nephron until all Cl^- was used up in this process and she produced basically a Cl-free urine. With a serum HCO_3^- value of 59 mmol/L,

huge HCO_3^- amounts were filtered and available as a corresponding anion for reabsorption with Na^+. However, not only the Cl^- but also the K^+ deficit maintains metabolic alkalosis because hypokalemia stimulates H^+ secretion by upregulating the α-subunits of the apical H^+-K^+ ATPase of the type A intercalated collecting duct cells and, in addition, stimulates ammonium generation and secretion. Both effects will maintain the metabolic alkalosis in our patient until the vast Cl^- and K^+ deficits are substituted by NaCl and KCl infusions. When intravenous K^+ substitution is switched to oral medication, it is important to realize that oral K^+ formulations come with two different corresponding ions, either chloride or citrate. The latter contain 20 or even 40 mmol K^+ per dose, whereas the former contain only 8 mmol. Nevertheless, the educated clinician understands that K^+-citrate is not appropriate in a hypokalemic patient with metabolic alkalosis because citrate is metabolized to bicarbonate. Our young lady recovered and left the hospital after being confronted with her bulimia nervosa eating disorder. Because electrolyte and acid-base disorders frequently complicate eating disorders, a questionnaire may assist clinicians in diagnosing these patients (Uniacke & Walsh, 2022).

8. Summary and conclusion

Potassium homeostasis is achieved by adjusting cellular distribution and excretion of potassium to dietary potassium intake. Detailed understanding how these processes are regulated in health and disease, and how potassium interacts with other ions, is important for several medical disciplines, such as epidemiologist, physiologists, pharmacologist, and clinicians. Dyskalemic patients are frequently encountered in clinical medicine and are potentially life-threatening. It is mandatory to identify the underlying cause in each patient. Knowledge of physiological potassium regulation provides the basis for understanding how genetic and acquired diseases, but also pharmacologic interventions lead to dyskalemia. With this knowledge clinicians will derive appropriate strategies to either prevent or treat potassium disorders.

Declaration of Competing Interest

None.

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References

Aburto, N. J., Hanson, S., Gutierrez, H., Hooper, L., Elliott, P., & Cappuccio, F. P. (2013). Effect of increased potassium intake on cardiovascular risk factors and disease: Systematic review and meta-analyses. *BMJ 346*, Article f1378.

Achanti, A., & Szerlip, H. M. (2023). Acid-Base disorders in the critically ill patient. *Clinical Journal of the American Society of Nephrology 18*, 102–112.

Ackermann, D., Gresko, N., Carrel, M., Loffing-Cueni, D., Habermehl, D., Gomez-Sanchez, C. , ... Loffing, J. (2010). In vivo nuclear translocation of mineralocorticoid and glucocorticoid receptors in rat kidney: Differential effect of corticosteroids along the distal tubule. *American Journal of Physiology. Renal Physiology 299*, F1473–F1485.

Agarwal, A. K., Ahlawat, S. K., Gupta, S., Singh, B., Singh, C. P., Wadhwa, S., & Kumar, A. (1995). Hypokalaemic paralysis secondary to acute barium carbonate toxicity. *Tropical Doctor 25*, 101–103.

Agarwal, R., Rossignol, P., Romero, A., Garza, D., Mayo, M. R., Warren, S., ... Williams, B. (2019). Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): A phase 2, randomised, double-blind, placebo-controlled trial. *Lancet 394*, 1540–1550.

Allon, M., Dunlay, R., & Copkney, C. (1989). Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Annals of Internal Medicine 110*, 426–429.

Allon, M., & Shanklin, N. (1996). Effect of bicarbonate administration on plasma potassium in dialysis patients: Interactions with insulin and albuterol. *American Journal of Kidney Diseases 28*, 508–514.

Al-Qusairi, L., Basquin, D., Roy, A., Rajaram, R. D., Maillard, M. P., Subramanya, A. R., & Staub, O. (2017). Renal tubular ubiquitin-protein ligase NEDD4-2 is required for renal adaptation during long-term potassium depletion. *J Am Soc Nephrol 28*, 2431–2442.

Anker, S. D., Kosiborod, M., Zannad, F., Pina, I. L., McCullough, P. A., Filippatos, G., ... Deedwania, P. (2015). Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: Results from a phase 3 randomized, double-blind, placebo-controlled trial. *European Journal of Heart Failure 17*, 1050–1056.

Apel, J., Reutrakul, S., & Baldwin, D. (2014). Hypoglycemia in the treatment of hyperkalemia with insulin in patients with end-stage renal disease. *Clinical Kidney Journal 7*, 248–250.

Aperia, A., Fryckstedt, J., Holtback, U., Belusa, R., Cheng, X. J., Eklof, A. C., ... Ohtomo, Y. (1996). Cellular mechanisms for bi-directional regulation of tubular sodium reabsorption. *Kidney International 49*, 1743–1747.

Aronson, P. S., & Giebisch, G. (2011). Effects of pH on potassium: New explanations for old observations. *J Am Soc Nephrol 22*, 1981–1989.

Bachmann, S., Bostanjoglo, M., Schmitt, R., & Ellison, D. H. (1999). Sodium transport-related proteins in the mammalian distal nephron - distribution, ontogeny and functional aspects. *Anatomy and Embryology (Berlin) 200*, 447–468.

Bailey, M. A., Cantone, A., Yan, Q., MacGregor, G. G., Leng, Q., Amorim, J. B., ... Malnic, G. (2006). Maxi-K channels contribute to urinary potassium excretion in the ROMK-deficient mouse model of Type II Bartter's syndrome and in adaptation to a high-K diet. *Kidney International 70*, 51–59.

Baker, P. F., & Rink, T. J. (1975). Catecholamine release from bovine adrenal medulla in response to maintained depolarization. *The Journal of Physiology 253*, 593–620.

Bakris, G. L., Pitt, B., Weir, M. R., Freeman, M. W., Mayo, M. R., Garza, D., ... Investigators, A. -D. (2015). Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. *JAMA 314*, 151–161.

Banki, E., Fisi, V., Moser, S., Wengi, A., Carrel, M., Loffing-Cueni, D., ... Loffing, J. (2021). Specific disruption of calcineurin-signaling in the distal convoluted tubule impacts the transcriptome and proteome, and causes hypomagnesemia and metabolic acidosis. *Kidney International 100*, 850–869.

Bankir, L., Bouby, N., Blondeau, B., & Crambert, G. (2016). Glucagon actions on the kidney revisited: Possible role in potassium homeostasis. *American Journal of Physiology. Renal Physiology 311*, F469–F486.

Barroso-Sousa, R., Barry, W. T., Garrido-Castro, A. C., Hodi, F. S., Min, L., Krop, I. E., & Tolaney, S. M. (2018). Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *JAMA Oncology 4*, 173–182.

Batuman, V. (2013). Salt and hypertension: Why is there still a debate? *Kidney International. Supplement 2011*(3), 316–320.

Beck, K. R., Telisman, L., van Koppen, C. J., Thompson, G. R., 3rd, & Odermatt, A. (2020). Molecular mechanisms of posaconazole- and itraconazole-induced pseudohyperaldosteronism and assessment of other systemically used azole antifungals. *The Journal of Steroid Biochemistry and Molecular Biology 199*, Article 105605.

Benitez, L. L., & Carver, P. L. (2019). Adverse effects associated with long-term administration of azole antifungal agents. *Drugs 79*, 833–853.

Berber, M., Leng, S., Wengi, A., Winter, D.V., Odermatt, A., Beuschlein, F., … Penton, D. (2023). Calcineurin regulates aldosterone production via dephosphorylation of NFATc4. JCI Insight.Jun 13;e157027, online ahead of print

Bernabe-Ortiz, A., Sal, Y. R. V. G., Ponce-Lucero, V., Cardenas, M. K., Carrillo-Larco, R. M., Diez-Canseco, F., ... Miranda, J. J. (2020). Effect of salt substitution on community-wide blood pressure and hypertension incidence. *Nature Medicine 26*, 374–378.

Beusekamp, J. C., Tromp, J., Cleland, J. G. F., Givertz, M. M., Metra, M., O'Connor, C. M., ... van der Meer, P. (2019). Hyperkalemia and treatment with RAAS inhibitors during acute heart failure hospitalizations and their association with mortality. *JACC Heart Failure 7*, 970–979.

Blanchard, A. (2023). Pathophysiologic approach in genetic hypokalemia: An update. *Annales d'Endocrinologie 84*, 298–307.

Blanchard, A., Bockenhauer, D., Bolignano, D., Calo, L. A., Cosyns, E., Devuyst, O., ... Vargas-Poussou, R. (2017). Gitelman syndrome: Consensus and guidance from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney International 91*, 24–33.

Blumberg, A., Weidmann, P., Shaw, S., & Gnadinger, M. (1988). Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *The American Journal of Medicine 85*, 507–512.

Bockenhauer, D., Feather, S., Stanescu, H. C., Bandulik, S., Zdebik, A. A., Reichold, M., ... Kleta, R. (2009). Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *The New England Journal of Medicine 360*, 1960–1970.

Bockenhauer, D., & Kleta, R. (2021). Tubulopathy meets Sherlock Holmes: Biochemical fingerprinting of disorders of altered kidney tubular salt handling. *Pediatric Nephrology 36*, 2553–2561.

Borschewski, A., Himmerkus, N., Boldt, C., Blankenstein, K. I., McCormick, J. A., Lazelle, R., ... Mutig, K. (2016). Calcineurin and sorting-related receptor with A-type repeats interact to regulate the renal Na(+)-K(+)-2Cl(−) cotransporter. *J Am Soc Nephrol 27*, 107–119.

Brandi, S. L., Feltoft, C. L., Serup, J., & Eldrup, E. (2021). Pseudohyperaldosteroism during itraconazole treatment: A hitherto neglected clinically significant side effect. *BML Case Reports 14*.

Brown, D., Lydon, J., McLaughlin, M., Stuart-Tilley, A., Tyszkowski, R., & Alper, S. (1996). Antigen retrieval in cryostat tissue sections and cultured cells by treatment with sodium dodecyl sulfate (SDS). *Histochemistry and Cell Biology 105*, 261–267.

van Buren, M., Rabelink, T. J., van Rijn, H. J., & Koomans, H. A. (1992). Effects of acute NaCl, KCl and KHCO3 loads on renal electrolyte excretion in humans. *Clinical Science (London, England) 83*, 567–574.

Bushinsky, D. A., Spiegel, D. M., Gross, C., Benton, W. W., Fogli, J., Hill Gallant, K. M., ... Pitt, B. (2016). Effect of patiromer on urinary ion excretion in healthy adults. *Clinical Journal of the American Society of Nephrology 11*, 1769–1776.
Cannon, S. C. (2018). Sodium channelopathies of skeletal muscle. *Handbook of Experimental Pharmacology 246*, 309–330.
Canonica, J., Sergi, C., Maillard, M., Klusonova, P., Odermatt, A., Koesters, R., ... Hummler, E. (2016). Adult nephron-specific MR-deficient mice develop a severe renal PHA-1 phenotype. *Pflügers Archiv 468*, 895–908.
Cappuccio, F. P., Campbell, N. R. C., He, F. J., Jacobson, M. F., MacGregor, G. A., Antman, E., ... Willett, W. (2022). Sodium and health: Old myths and a controversy based on denial. *Current Nutrition Reports 11*, 172–184.
Carrisoza-Gaytan, R., Ray, E. C., Flores, D., Marciszyn, A. L., Wu, P., Liu, L., ... Kleyman, T. R. (2020). Intercalated cell BKalpha subunit is required for flow-induced K+ secretion. *JCI Insight*, 5.
Castaneda-Bueno, M., Ellison, D. H., & Gamba, G. (2022). Molecular mechanisms for the modulation of blood pressure and potassium homeostasis by the distal convoluted tubule. *EMBO Molecular Medicine 14*, Article e14273.
Castro, H., & Raij, L. (2013). Potassium in hypertension and cardiovascular disease. *Seminars in Nephrology 33*, 277–289.
Castrop, H., & Schiessl, I. M. (2014). Physiology and pathophysiology of the renal Na-K-2Cl cotransporter (NKCC2). *American Journal of Physiology. Renal Physiology 307*, F991–F1002.
Chambrey, R., Kurth, I., Peti-Peterdi, J., Houillier, P., Purkerson, J. M., Leviel, F., ... Eladari, D. (2013). Renal intercalated cells are rather energized by a proton than a sodium pump. *Proceedings of the National Academy of Sciences of the United States of America 110*, 7928–7933.
Chambrey, R., & Trepiccione, F. (2015). Relative roles of principal and intercalated cells in the regulation of sodium balance and blood pressure. *Current Hypertension Reports 17*, 538.
Chan, W. Y., Clark, A. B., Wilson, A. M., Loke, Y. K., & investigators, T. (2017). The effect of co-trimoxazole on serum potassium concentration: Safety evaluation of a randomized controlled trial. *British Journal of Clinical Pharmacology 83*, 1808–1814.
Chang, A. R., Sang, Y., Leddy, J., Yahya, T., Kirchner, H. L., Inker, L. A., ... Grams, M. E. (2016). Antihypertensive medications and the prevalence of hyperkalemia in a large health system. *Hypertension 67*, 1181–1188.
Chang, H. Y., Hu, Y. W., Yue, C. S., Wen, Y. W., Yeh, W. T., Hsu, L. S., ... Pan, W. H. (2006). Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *The American Journal of Clinical Nutrition 83*, 1289–1296.
Chapman, F. A., Dickerson, J. E., Daly, C., Clancy, M., & Geddes, C. (2019). Impact of increased duration of trimethoprim-sulfamethoxazole prophylaxis for pneumocystis pneumonia after renal transplant. *Annals of Transplantation 24*, 625–630.
Cheng, C. J., Kuo, E., & Huang, C. L. (2013). Extracellular potassium homeostasis: Insights from hypokalemic periodic paralysis. *Seminars in Nephrology 33*, 237–247.
Choi, M. J., & Ziyadeh, F. N. (2008). The utility of the transtubular potassium gradient in the evaluation of hyperkalemia. *J Am Soc Nephrol 19*, 424–426.
Clase, C. M., Carrero, J. J., Ellison, D. H., Grams, M. E., Hemmelgarn, B. R., Jardine, M. J., ... Conference, P. (2020). Potassium homeostasis and management of dyskalemia in kidney diseases: Conclusions from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney International 97*, 42–61.
Clausen, T. (2008). Role of Na+,K+-pumps and transmembrane Na+,K+-distribution in muscle function. The FEPS lecture - Bratislava 2007. *Acta Physiologica (Oxford, England) 192*, 339–349.
Conen, K., Scanni, R., Gombert, M. T., Hulter, H. N., & Krapf, R. (2016). Effects of potassium citrate or potassium chloride in patients with combined glucose intolerance: A placebo-controlled pilot study. *Journal of Diabetes and its Complications 30*, 1158–1161.
Creamer, T. P. (2020). Calcineurin. *Cell Communication and Signaling: CCS 18*, 137.
Cuevas, C. A., Su, X. T., Wang, M. X., Terker, A. S., Lin, D. H., McCormick, J. A., ... Wang, W. H. (2017). Potassium sensing by renal distal tubules requires Kir4.1. *J Am Soc Nephrol 28*, 1814–1825.
DeFronzo, R. A., Felig, P., Ferrannini, E., & Wahren, J. (1980). Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *The American Journal of Physiology 238*, E421–E427.
Di Palo, K. E., Sinnett, M. J., & Goriacko, P. (2022). Assessment of patiromer monotherapy for hyperkalemia in an acute care setting. *JAMA Network Open 5*, Article e2145236.
Dimke, H., & Schnermann, J. (2018). Axial and cellular heterogeneity in electrolyte transport pathways along the thick ascending limb. *Acta Physiologica (Oxford, England) 223*, Article e13057.
Drueke, T. B. (2016). Salt and health: Time to revisit the recommendations. *Kidney International 89*, 259–260.
EFSA NDA Panel (EFSA Panel on Dietetic Products, N. a. A, Turck, D., Bresson, J. -L., Burlingame, B., Dean, T., Fairweather-Tait, S., ... Naska, A. (2016). Scientific opinion on dietary reference values for potassium. *EFSA Journal 14*, 1831–4732.
Einhorn, L. M., Zhan, M., Hsu, V. D., Walker, L. D., Moen, M. F., Seliger, S. L., ... Fink, J. C. (2009). The frequency of hyperkalemia and its significance in chronic kidney disease. *Archives of Internal Medicine 169*, 1156–1162.
El Moghrabi, S., Houillier, P., Picard, N., Sohet, F., Wootla, B., Bloch-Faure, M., ... Chambrey, R. (2010). Tissue kallikrein permits early renal adaptation to potassium load. *Proceedings of the National Academy of Sciences of the United States of America 107*, 13526–13531.
Elabida, B., Edwards, A., Salhi, A., Azroyan, A., Fodstad, H., Meneton, P., ... Crambert, G. (2011). Chronic potassium depletion increases adrenal progesterone production that is necessary for efficient renal retention of potassium. *Kidney International 80*, 256–262.
Ellison, D. H. (2019). Clinical pharmacology in diuretic use. *Clinical Journal of the American Society of Nephrology 14*, 1248–1257.
Ellison, D. H., Terker, A. S., & Gamba, G. (2016). Potassium and its discontents: New insight, new treatments. *J Am Soc Nephrol 27*, 981–989.
Ellison, D. H., & Welling, P. (2021). Insights into salt handling and blood pressure. *The New England Journal of Medicine 385*, 1981–1993.
Emmett, M., Hootkins, R. E., Fine, K. D., Santa Ana, C. A., Porter, J. L., & Fordtran, J. S. (1995). Effect of three laxatives and a cation exchange resin on fecal sodium and potassium excretion. *Gastroenterology 108*, 752–760.
Emmett, M., & Mehta, A. (2016). Patiromer-an oral calcium-loaded potassium binder: Kalirrhea with calciuresis. *Clinical Journal of the American Society of Nephrology 11*, 1723–1725.
Ergonul, Z., Frindt, G., & Palmer, L. G. (2006). Regulation of maturation and processing of ENaC subunits in the rat kidney. *American Journal of Physiology. Renal Physiology 291*, F683–F693.
Estilo, G., Liu, W., Pastor-Soler, N., Mitchell, P., Carattino, M. D., Kleyman, T. R., & Satlin, L. M. (2008). Effect of aldosterone on BK channel expression in mammalian cortical collecting duct. *American Journal of Physiology. Renal Physiology 295*, F780–F788.
Evans, B. M., Jones, N. C., Milne, M. D., & Yellowlees, H. (1953). Ion-exchange resins in the treatment of anuria. *Lancet 265*, 791–795.
Fava, C., Montagnana, M., Rosberg, L., Burri, P., Almgren, P., Jonsson, A., ... Melander, O. (2008). Subjects heterozygous for genetic loss of function of the thiazide-sensitive cotransporter have reduced blood pressure. *Human Molecular Genetics 17*, 413–418.
Ferdaus, M., Terker, A., Koumangoye, R., Wall, S. M., & Delpire, E. (2023). Bicarbonate is the primary inducer of KCC3a expression in renal cortical B-type intercalated cells. *American Journal of Physiology. Cell Physiology. 324*, C1171–C1178.
Ferraro, P. M., Mandel, E. I., Curhan, G. C., Gambaro, G., & Taylor, E. N. (2016). Dietary protein and potassium, diet-dependent net acid load, and risk of incident kidney stones. *Clinical Journal of the American Society of Nephrology 11*, 1834–1844.
Field, M. J., Stanton, B. A., & Giebisch, G. H. (1984). Differential acute effects of aldosterone, dexamethasone, and hyperkalemia on distal tubular potassium secretion in the rat kidney. *The Journal of Clinical Investigation 74*, 1792–1802.
Flinn, R. B., Merrill, J. P., & Welzant, W. R. (1961). Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. *The New England Journal of Medicine 264*, 111–115.
Flucher, B. E. (2020). Skeletal muscle ca(V)1.1 channelopathies. *Pflügers Archiv 472*, 739–754.
Fordjour, K. N., Walton, T., & Doran, J. J. (2014). Management of hyperkalemia in hospitalized patients. *The American Journal of the Medical Sciences 347*, 93–100.
Frindt, G., Houde, V., & Palmer, L. G. (2011). Conservation of Na+ vs. K+ by the rat cortical collecting duct. *American Journal of Physiology. Renal Physiology 301*, F14–F20.
Frindt, G., & Palmer, L. G. (2010). Effects of dietary K on cell-surface expression of renal ion channels and transporters. *American Journal of Physiology. Renal Physiology 299*, F890–F897.
Fujita, T., & Sato, Y. (1983). Natriuretic and antihypertensive effects of potassium in DOCA-salt hypertensive rats. *Kidney International 24*, 731–739.
Fujita, T., & Sato, Y. (1984). Changes in renal and central noradrenergic activity with potassium in DOCA-salt rats. *The American Journal of Physiology 246*, F670–F675.
Funder, J. W. (2017). Apparent mineralocorticoid excess. *The Journal of Steroid Biochemistry and Molecular Biology 165*, 151–153.
Furgeson, S. B., & Linas, S. (2010). Mechanisms of type I and type II pseudohypoaldosteronism. *J Am Soc Nephrol 21*, 1842–1845.
Geller, D. S., Farhi, A., Pinkerton, N., Fradley, M., Moritz, M., Spitzer, A., ... Lifton, R. P. (2000). Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science 289*, 119–123.
Gerstman, B. B., Kirkman, R., & Platt, R. (1992). Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *American Journal of Kidney Diseases 20*, 159–161.
Giebisch, G. (2004). Challenges to potassium metabolism: Internal distribution and external balance. *Wiener Klinische Wochenschrift 116*, 353–366.
Giebisch, G. (2009). Transport of potassium. In B. E. Boron (Ed.), *Medical physiology* (pp. 821–834) (2 ed.). Philadelphia: Saunders Elsevier.
Giebisch, G. H. (2002). A trail of research on potassium. *Kidney International 62*, 1498–1512.
Gradon, J. D., & Sepkowitz, D. V. (1991). Fluconazole-associated acute adrenal insufficiency. *Postgraduate Medical Journal 67*, 1084–1085.
Grahammer, F., Nesterov, V., Ahmed, A., Steinhardt, F., Sandner, L., Arnold, F., ... Huber, T. B. (2016). mTORC2 critically regulates renal potassium handling. *The Journal of Clinical Investigation 126*, 1773–1782.
Grams, M. E., Hoenig, M. P., & Hoorn, E. J. (2021). Evaluation of hypokalemia. *JAMA 325*, 1216–1217.
Greenlee, M. M., Lynch, I. J., Gumz, M. L., Cain, B. D., & Wingo, C. S. (2010). The renal H,K-ATPases. *Current Opinion in Nephrology and Hypertension 19*, 478–482.
Grimm, P. R., Lazo-Fernandez, Y., Delpire, E., Wall, S. M., Dorsey, S. G., Weinman, E. J., ... Welling, P. A. (2015). Integrated compensatory network is activated in the absence of NCC phosphorylation. *The Journal of Clinical Investigation 125*, 2136–2150.
Grodsky, G. M., & Bennett, L. L. (1966). Cation requirements for insulin secretion in the isolated perfused pancreas. *Diabetes 15*, 910–913.
Grouthier, V., Lebrun-Vignes, B., Moey, M., Johnson, D. B., Moslehi, J. J., Salem, J. E., & Bachelot, A. (2020). Immune checkpoint inhibitor-associated primary adrenal insufficiency: WHO VigiBase report analysis. *Oncologist 25*, 696–701.
Harel, Z., Harel, S., Shah, P. S., Wald, R., Perl, J., & Bell, C. M. (2013). Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: A systematic review. *The American Journal of Medicine 126*(264) e269–224.
Hayes, C. P., Jr., & Robinson, R. R. (1965). Fecal potassium excretion in patients on chronic intermittent Hemodialysis. *Transactions of the American Society for Artificial Internal Organs 11*, 242–246.

He, F. J., & MacGregor, G. A. (2008). Beneficial effects of potassium on human health. *Physiologia Plantarum 133*, 725–735.

Herrmann, S. M., Alexander, M. P., Romero, M. F., & Zand, L. (2020). Renal tubular acidosis and immune checkpoint inhibitor therapy: An immune-related adverse event of PD-1 inhibitor-A report of 3 cases. *Kidney Medicine 2*, 657–662.

Higgins, R., Ramaiyan, K., Dasgupta, T., Kanji, H., Fletcher, S., Lam, F., & Kashi, H. (2004). Hyponatraemia and hyperkalaemia are more frequent in renal transplant recipients treated with tacrolimus than with cyclosporin. Further evidence for differences between cyclosporin and tacrolimus nephrotoxicities. *Nephrology, Dialysis, Transplantation 19*, 444–450.

Hoffmann, W. J., McHardy, I., & Thompson, G. R., 3rd. (2018). Itraconazole induced hypertension and hypokalemia: Mechanistic evaluation. *Mycoses 61*, 337–339.

Hoorn, E. J., Gritter, M., Cuevas, C. A., & Fenton, R. A. (2020). Regulation of the renal NaCl cotransporter and its role in potassium homeostasis. *Physiological Reviews 100*, 321–356.

Hoorn, E. J., Walsh, S. B., McCormick, J. A., Furstenberg, A., Yang, C. L., Roeschel, T., ... Ellison, D. H. (2011). The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. *Nature Medicine 17*, 1304–1309.

Hoorn, E. J., Walsh, S. B., McCormick, J. A., Zietse, R., Unwin, R. J., & Ellison, D. H. (2012). Pathogenesis of calcineurin inhibitor-induced hypertension. *Journal of Nephrology 25*, 269–275.

Huang, C. L., & Kuo, E. (2007). Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol 18*, 2649–2652.

Hundemer, G. L., Talarico, R., Tangri, N., Leon, S. J., Bota, S. E., Rhodes, E., ... Sood, M. M. (2021). Ambulatory treatments for RAAS inhibitor-related hyperkalemia and the 1-year risk of recurrence. *Clinical Journal of the American Society of Nephrology 16*, 365–373.

Intersalt-Cooperative-Research-Group (1988). Intersalt: An international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ 297*, 319–328.

Ishizawa, K., Wang, Q., Li, J., Yamazaki, O., Tamura, Y., Fujigaki, Y., ... Shibata, S. (2019). Calcineurin dephosphorylates Kelch-like 3, reversing phosphorylation by angiotensin II and regulating renal electrolyte handling. *Proceedings of the National Academy of Sciences of the United States of America 116*, 3155–3160.

Ishizawa, K., Xu, N., Loffing, J., Lifton, R. P., Fujita, T., Uchida, S., & Shibata, S. (2016). Potassium depletion stimulates Na-Cl cotransporter via phosphorylation and inactivation of the ubiquitin ligase Kelch-like 3. *Biochemical and Biophysical Research Communications 480*, 745–751.

Ito, R., Morita, M., Nakano, T., Sato, I., Yokoyama, A., & Sugawara, A. (2021). The establishment of a novel high-throughput screening system using RNA-guided genome editing to identify chemicals that suppress aldosterone synthase expression. *Biochemical and Biophysical Research Communications 534*, 672–679.

Jablonski, K. L., & Kendrick, J. B. (2014). Renal outcomes and dietary potassium: The overshadowed electrolyte? *Kidney International 86*, 1077–1078.

Jaffey, L., & Martin, A. (1981). Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. *Lancet 1*, 1272.

Jamison, R. L., Work, J., & Schafer, J. A. (1982). New pathways for potassium transport in the kidney. *The American Journal of Physiology 242*, F297–F312.

Jehle, S., Hulter, H. N., & Krapf, R. (2013). Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: A randomized controlled trial. *The Journal of Clinical Endocrinology and Metabolism 98*, 207–217.

Jensen, I. S., Larsen, C. K., Leipziger, J., & Sorensen, M. V. (2016). Na(+) dependence of K(+)-induced natriuresis, kaliuresis and Na(+)/Cl(−) cotransporter dephosphorylation. *Acta Physiologica (Oxford, England) 218*, 49–61.

Ji, W., Foo, J. N., O'Roak, B. J., Zhao, H., Larson, M. G., Simon, D. B., ... Lifton, R. P. (2008). Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nature Genetics 40*, 592–599.

Juel, C. (1997). Lactate-proton cotransport in skeletal muscle. *Physiological Reviews 77*, 321–358.

Juel, C. (1998). Skeletal muscle Na+/H+ exchange in rats: pH dependency and the effect of training. *Acta Physiologica Scandinavica 164*, 135–140.

Jung, J. Y., Kim, S., Lee, J. W., Jung, E. S., Heo, N. J., Son, M. J., ... Joo, K. W. (2011). Effects of potassium on expression of renal sodium transporters in salt-sensitive hypertensive rats induced by uninephrectomy. *American Journal of Physiology. Renal Physiology 300*, F1422–F1430.

Kamel, K. S., & Halperin, M. L. (2021). Use of urine electrolytes and urine osmolality in the clinical diagnosis of fluid, electrolytes, and acid-base disorders. *Kidney International Reports 6*, 1211–1224.

Kamel, K. S., & Schreiber, M. (2012). Asking the question again: Are cation exchange resins effective for the treatment of hyperkalemia? *Nephrology, Dialysis, Transplantation 27*, 4294–4297.

Kamel, K. S., Schreiber, M., & Halperin, M. L. (2014). Integration of the response to a dietary potassium load: A paleolithic perspective. *Nephrology, Dialysis, Transplantation 29*, 982–989.

Kaplan, J. L., Braitman, L. E., Dalsey, W. C., Montgomery, M., & Mangione, A. (1997). Alkalinization is ineffective for severe hyperkalemia in nonnephrectomized dogs. Hyperkalemia Research Group. *Academic Emergency Medicine 4*, 93–99.

Kermond, R., Mallett, A., & McCarthy, H. (2023). A clinical approach to tubulopathies in children and young adults. *Pediatric Nephrology 38*, 651–662.

Kleophas, W., Bieber, B., Robinson, B. M., Duttlinger, J., Fliser, D., Lonnemann, G., ... group, F. s (2013). Implementation and first results of a German chronic kidney disease registry. *Clinical Nephrology 79*, 184–191.

Knochel, J. P. (1984). Diuretic-induced hypokalemia. *The American Journal of Medicine 77*, 18–27.

Komhoff, M., & Laghmani, K. (2018). MAGED2: A novel form of antenatal Bartter's syndrome. *Current Opinion in Nephrology and Hypertension 27*, 323–328.

Konrad, M., Nijenhuis, T., Ariceta, G., Bertholet-Thomas, A., Calo, L. A., Capasso, G., ... Bockenhauer, D. (2021). Diagnosis and management of Bartter syndrome: Executive summary of the consensus and recommendations from the European rare kidney disease reference network working group for tubular disorders. *Kidney International 99*, 324–335.

Kosiborod, M., Peacock, W. F., & Packham, D. K. (2015). Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. *The New England Journal of Medicine 372*, 1577–1578.

Kovesdy, C. P. (2014). Management of hyperkalaemia in chronic kidney disease. *Nature Reviews. Nephrology 10*, 653–662.

Kovesdy, C. P., Matsushita, K., Sang, Y., Brunskill, N. J., Carrero, J. J., Chodick, G., ... Consortium, C. K. D. P (2018). Serum potassium and adverse outcomes across the range of kidney function: A CKD prognosis consortium meta-analysis. *European Heart Journal 39*, 1535–1542.

Krishna, G. G., & Kapoor, S. C. (1991). Potassium depletion exacerbates essential hypertension. *Annals of Internal Medicine 115*, 77–83.

Kuriakose, K., Nesbitt, W. J., Greene, M., & Harris, B. (2018). Posaconazole-Induced Pseudohyperaldosteronism. *Antimicrobial Agents and Chemotherapy 62*.

Laghmani, K., Beck, B. B., Yang, S. S., Seaayfan, E., Wenzel, A., Reusch, B., ... Komhoff, M. (2016). Polyhydramnios, transient antenatal Bartter's syndrome, and MAGED2 mutations. *The New England Journal of Medicine 374*, 1853–1863.

Larivee, N. L., Michaud, J. B., More, K. M., Wilson, J. A., & Tennankore, K. K. (2023). Hyperkalemia: Prevalence, predictors and emerging treatments. *Cardiology and Therapy 12*, 35–63.

Lee Hamm, L., Hering-Smith, K. S., & Nakhoul, N. L. (2013). Acid-base and potassium homeostasis. *Seminars in Nephrology 33*, 257–264.

Lehmann-Horn, F., & Jurkat-Rott, K. (1999). Voltage-gated ion channels and hereditary disease. *Physiological Reviews 79*, 1317–1372.

Lehnhardt, A., & Kemper, M. J. (2011). Pathogenesis, diagnosis and management of hyperkalemia. *Pediatric Nephrology 26*, 377–384.

Lemann, J., Jr., Pleuss, J. A., Gray, R. W., & Hoffmann, R. G. (1991). Potassium administration reduces and potassium deprivation increases urinary calcium excretion in healthy adults [corrected]. *Kidney International 39*, 973–983.

Lepage, L., Dufour, A. C., Doiron, J., Handfield, K., Desforges, K., Bell, R., ... Lafrance, J. P. (2015). Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clinical Journal of the American Society of Nephrology 10*, 2136–2142.

Lesko, L. J., Offman, E., Brew, C. T., Garza, D., Benton, W., Mayo, M. R., ... Weir, M. R. (2017). Evaluation of the potential for drug interactions with patiromer in healthy volunteers. *Journal of Cardiovascular Pharmacology and Therapeutics 22*, 434–446.

Li, K. X., & Sperelakis, N. (1993). Isoproterenol- and insulin-induced hyperpolarization in rat skeletal muscle. *Journal of Cellular Physiology 157*, 631–636.

Lijnen, P., Hespel, P., Fagard, R., Goris, M., Lysens, R., Vanden Eynde, E., & Amery, A. (1989). Effect of prolonged physical exercise on intra-erythrocyte and plasma potassium. *European Journal of Applied Physiology and Occupational Physiology 59*, 296–302.

Lin, D., Sterling, H., Lerea, K. M., Giebisch, G., & Wang, W. H. (2002). Protein kinase C (PKC)-induced phosphorylation of ROMK1 is essential for the surface expression of ROMK1 channels. *The Journal of Biological Chemistry 277*, 44278–44284.

Lin, D. H., Duan, X. P., Zheng, J. Y., & Wang, W. H. (2022). Role of inwardly rectifying K+ channel 5.1 (Kir5.1) in the regulation of renal membrane transport. *Current Opinion in Nephrology and Hypertension 31*, 479–485.

Lin, S. H., & Huang, C. L. (2012). Mechanism of thyrotoxic periodic paralysis. *J Am Soc Nephrol 23*, 985–988.

Lin, Z., Wong, L. Y. F., & Cheung, B. M. Y. (2022). Diuretic-induced hypokalaemia: An updated review. *Postgraduate Medical Journal 98*, 477–482.

Lindinger, M. I., & Cairns, S. P. (2021). Regulation of muscle potassium: Exercise performance, fatigue and health implications. *European Journal of Applied Physiology 121*, 721–748.

Little, R., Murali, S. K., Poulsen, S. B., Grimm, P. R., Assmus, A., Cheng, L., ... Fenton, R. A. (2023). Dissociation of sodium-chloride cotransporter expression and blood pressure during chronic high dietary potassium supplementation. *JCI Insight 8*.

Liu, W., Morimoto, T., Woda, C., Kleyman, T. R., & Satlin, L. M. (2007). Ca2+ dependence of flow-stimulated K secretion in the mammalian cortical collecting duct. *American Journal of Physiology. Renal Physiology 293*, F227–F235.

Liu, W., Schreck, C., Coleman, R. A., Wade, J. B., Hernandez, Y., Zavilowitz, B., ... Satlin, L. M. (2011). Role of NKCC in BK channel-mediated net K(+) secretion in the CCD. *American Journal of Physiology. Renal Physiology 301*, F1088–F1097.

Lo, J., Forst, A. L., Warth, R., & Zdebik, A. A. (2022). EAST/SeSAME syndrome and beyond: The spectrum of Kir4.1- and Kir5.1-associated channelopathies. *Frontiers in Physiology 13*, Article 852674.

Loffing, J. (2014). Renale Kontrolle der Kaliumhomöostase. *Nephrologe 9*, 473–476.

Loffing, J., & Kaissling, B. (2003). Sodium and calcium transport pathways along the mammalian distal nephron: From rabbit to human. *American Journal of Physiology. Renal Physiology 284*, F628–F643.

Loffing, J., Zecevic, M., Feraille, E., Kaissling, B., Asher, C., Rossier, B. C., ... Verrey, F. (2001). Aldosterone induces rapid apical translocation of ENaC in early portion of renal collecting system: Possible role of SGK. *American Journal of Physiology. Renal Physiology 280*, F675–F682.

van der Lubbe, N., Lugtenburg, P. J., & Hoorn, E. J. (2021). Electrolyte disorders secondary to venetoclax. *Clinical Kidney Journal 14*, 1272–1274.

van der Lubbe, N., Moes, A. D., Rosenbaek, L. L., Schoep, S., Meima, M. E., Danser, A. H., ... Hoorn, E. J. (2013). K+-induced natriuresis is preserved during Na+ depletion and accompanied by inhibition of the Na+-Cl- cotransporter. *American Journal of Physiology. Renal Physiology 305*, F1177–F1188.

Maddox, R. W., Arnold, W. S., & Dewell, W. M., Jr. (1985). Extreme hyperkalemia associated with amiloride. *Southern Medical Journal 78*, 365.
Maeoka, Y., Cornelius, R. J., & McCormick, J. A. (2023). Cullin 3 and blood pressure regulation: Insights from familial hyperkalemic hypertension. *Hypertension 80*, 912–923.
Maertens, J. A., Rahav, G., Lee, D. G., Ponce-de-Leon, A., Ramirez Sanchez, I. C., Klimko, N., ... study, i. (2021). Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: A phase 3, randomised, controlled, non-inferiority trial. *Lancet 397*, 499–509.
Makoff, D. L., da Silva, J. A., Rosenbaum, B. J., Levy, S. E., & Maxwell, M. H. (1970). Hypertonic expansion: Acid-base and electrolyte changes. *The American Journal of Physiology 218*, 1201–1207.
Malnic, G., Berliner, R. W., & Giebisch, G. (1989). Flow dependence of K+ secretion in cortical distal tubules of the rat. *The American Journal of Physiology 256*, F932–F941.
Malnic, G., Klose, R. M., & Giebisch, G. (1964). Micropuncture study of renal potassium excretion in the rat. *The American Journal of Physiology 206*, 674–686.
Marklund, M., Tullu, F., Raj Thout, S., Yu, J., Brady, T. M., Appel, L. J., ... Gupta, R. (2022). Estimated benefits and risks of using a reduced-sodium, potassium-enriched salt substitute in India: A modeling study. *Hypertension 79*, 2188–2198.
Marlicz, K., & Chrzanowska, K. (1988). Determining chymotrypsin level in stools in the diagnosis of chronic pancreatitis. *Wiadomości Lekarskie 41*, 704–707.
Matsuura, Y., Nomura, N., Shoda, W., Mori, T., Isobe, K., Susa, K., ... Uchida, S. (2019). Tacrolimus ameliorates the phenotypes of type 4 Bartter syndrome model mice through activation of sodium-potassium-2 chloride cotransporter and sodium-chloride cotransporter. *Biochemical and Biophysical Research Communications 517*, 364–368.
McCance, D. R., Ritchie, C. M., Sheridan, B., & Atkinson, A. B. (1987). Acute hypoadrenalism and hepatotoxicity after treatment with ketoconazole. *Lancet 1*, 573.
McCormick, J. A., & Ellison, D. H. (2015). Distal convoluted tubule. *Comprehensive Physiology 5*, 45–98.
McDonough, A. A., & Fenton, R. A. (2022). Potassium homeostasis: Sensors, mediators, and targets. *Pflügers Archiv 474*, 853–867.
McDonough, A. A., & Youn, J. H. (2013). Need to quickly excrete K(+)? Turn off NCC. *Kidney International 83*, 779–782.
McDonough, A. A., & Youn, J. H. (2017). Potassium homeostasis: The knowns, the unknowns, and the health benefits. *Physiology (Bethesda) 32*, 100–111.
Melnikov, S., Mayan, H., Uchida, S., Holtzman, E. J., & Farfel, Z. (2011). Cyclosporine metabolic side effects: Association with the WNK4 system. *European Journal of Clinical Investigation 41*, 1113–1120.
Meneton, P., Loffing, J., & Warnock, D. G. (2004). Sodium and potassium handling by the aldosterone-sensitive distal nephron: The pivotal role of the distal and connecting tubule. *American Journal of Physiology. Renal Physiology 287*, F593–F601.
Mennitt, P. A., Wade, J. B., Ecelbarger, C. A., Palmer, L. G., & Frindt, G. (1997). Localization of ROMK channels in the rat kidney. *Journal of the American Society of Nephrology 8*, 1823–1830.
Mente, A., O'Donnell, M., Rangarajan, S., McQueen, M., Dagenais, G., Wielgosz, A., ... Yusuf, S. (2018). Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: A community-level prospective epidemiological cohort study. *Lancet 392*, 496–506.
Mente, A., O'Donnell, M. J., Rangarajan, S., McQueen, M. J., Poirier, P., Wielgosz, A., ... Investigators, P. (2014). Association of urinary sodium and potassium excretion with blood pressure. *The New England Journal of Medicine 371*, 601–611.
Messerli, F. H., Hofstetter, L., & Bangalore, S. (2018). Salt and heart disease: A second round of "bad science"? *Lancet 392*, 456–458.
Metcalfe, M. J., & Entrican, J. H. (1987). Carbenoxolone and hypokalaemia. *Lancet 2*, 1525–1526.
Monteiro, J. S., Blanchard, A., Curis, E., Chambrey, R., Jeunemaitre, X., & Azizi, M. (2013). Partial genetic deficiency in tissue kallikrein impairs adaptation to high potassium intake in humans. *Kidney International 84*, 1271–1277.
Moreno, M., Murphy, C., & Goldsmith, C. (1969). Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. *The Journal of Laboratory and Clinical Medicine 73*, 291–298.
Mukherjee, A., Yang, C. L., McCormick, J. A., Martz, K., Sharma, A., & Ellison, D. H. (2021). Roles of WNK4 and SPAK in K(+)-mediated dephosphorylation of the NaCl cotransporter. *American Journal of Physiology. Renal Physiology 320*, F719–F733.
Murillo-de-Ozores, A. R., Carbajal-Contreras, H., Magana-Avila, G. R., Valdes, R., Grajeda-Medina, L. I., Vazquez, N., ... Castaneda-Bueno, M. (2022). Multiple molecular mechanisms are involved in the activation of the kidney sodium-chloride cotransporter by hypokalemia. *Kidney International 102*, 1030–1041.
Mutig, K., & Bachmann, S. (2019). Hyperkalemia and blood pressure regulation. *Nephrology, Dialysis, Transplantation 34* iii26-iii35.
Najjar, F., Zhou, H., Morimoto, T., Bruns, J. B., Li, H. S., Liu, W., ... Satlin, L. M. (2005). Dietary K+ regulates apical membrane expression of maxi-K channels in rabbit cortical collecting duct. *American Journal of Physiology. Renal Physiology 289*, F922–F932.
Neal, B., Wu, Y., Feng, X., Zhang, R., Zhang, Y., Shi, J., ... Elliott, P. (2021). Effect of salt substitution on cardiovascular events and death. *The New England Journal of Medicine 385*, 1067–1077.
Nesterov, V., Bertog, M., & Korbmacher, C. (2022). High baseline ROMK activity in the mouse late distal convoluted and early connecting tubule probably contributes to aldosterone-independent K(+) secretion. *American Journal of Physiology. Renal Physiology 322*, F42–F54.
Nguyen, T. Q., Maalouf, N. M., Sakhaee, K., & Moe, O. W. (2011). Comparison of insulin action on glucose versus potassium uptake in humans. *Clinical Journal of the American Society of Nephrology 6*, 1533–1539.
Noel, J. A., Bota, S. E., Petrcich, W., Garg, A. X., Carrero, J. J., Harel, Z., ... Sood, M. M. (2019). Risk of hospitalization for serious adverse gastrointestinal events associated with sodium polystyrene sulfonate use in patients of advanced age. *JAMA Internal Medicine 179*, 1025–1033.
Nomura, N., Shoda, W., & Uchida, S. (2019). Clinical importance of potassium intake and molecular mechanism of potassium regulation. *Clinical and Experimental Nephrology 23*, 1175–1180.
Oberleithner, H., Callies, C., Kusche-Vihrog, K., Schillers, H., Shahin, V., Riethmuller, C., ... de Wardener, H. E. (2009). Potassium softens vascular endothelium and increases nitric oxide release. *Proceedings of the National Academy of Sciences of the United States of America 106*, 2829–2834.
O'Donnell, M., Mente, A., Rangarajan, S., McQueen, M. J., Wang, X., Liu, L., ... Investigators, P. (2014). Urinary sodium and potassium excretion, mortality, and cardiovascular events. *The New England Journal of Medicine 371*, 612–623.
Oster, J. R., Perez, G. O., & Vaamonde, C. A. (1978). Relationship between blood pH and potassium and phosphorus during acute metabolic acidosis. *The American Journal of Physiology 235*, F345–F351.
Overwyk, K. J., Pfeiffer, C. M., Storandt, R. J., Zhao, L., Zhang, Z., Campbell, N. R. C., ... Cogswell, M. E. (2021). Serum sodium and potassium distribution and characteristics in the US population, National Health and nutrition examination survey 2009-2016. *The Journal of Applied Labaratory Medicine 6*, 63–78.
Packham, D. K., Rasmussen, H. S., Lavin, P. T., El-Shahawy, M. A., Roger, S. D., Block, G., ... Singh, B. (2015). Sodium zirconium cyclosilicate in hyperkalemia. *The New England Journal of Medicine 372*, 222–231.
Palmer, B. F. (2015). Regulation of potassium homeostasis. *Clinical Journal of the American Society of Nephrology 10*, 1050–1060.
Palmer, B. F., & Clegg, D. J. (2016). Achieving the benefits of a high-potassium, paleolithic diet, without the toxicity. *Mayo Clinic Proceedings 91*, 496–508.
Palmer, B. F., & Clegg, D. J. (2019). Physiology and pathophysiology of potassium homeostasis: Core curriculum 2019. *American Journal of Kidney Diseases 74*, 682–695.
Palmer, B. F., & Clegg, D. J. (2022). Extrarenal effects of aldosterone on potassium homeostasis. *Kidney 360*(3), 561–568.
Palmer, L. G., Antonian, L., & Frindt, G. (1994). Regulation of apical K and Na channels and Na/K pumps in rat cortical collecting tubule by dietary K. *The Journal of General Physiology 104*, 693–710.
Palmer, L. G., & Frindt, G. (1999). Regulation of apical K channels in rat cortical collecting tubule during changes in dietary K intake. *The American Journal of Physiology 277*, F805–F812.
Palmer, L. G., & Frindt, G. (2007). High-conductance K channels in intercalated cells of the rat distal nephron. *American Journal of Physiology. Renal Physiology 292*, F966–F973.
Palygin, O., Pochynyuk, O., & Staruschenko, A. (2018). Distal tubule basolateral potassium channels: Cellular and molecular mechanisms of regulation. *Current Opinion in Nephrology and Hypertension 27*, 373–378.
Pana, Z. D., Kourti, M., Vikelouda, K., Vlahou, A., Katzilakis, N., Papageorgiou, M., ... Roilides, E. (2018). Voriconazole antifungal prophylaxis in children with malignancies: A Nationwide study. *Journal of Pediatric Hematology/Oncology 40*, 22–26.
Pearce, D., Manis, A. D., Nesterov, V., & Korbmacher, C. (2022). Regulation of distal tubule sodium transport: Mechanisms and roles in homeostasis and pathophysiology. *Pflügers Archiv 474*, 869–884.
Penton, D., Czogalla, J., & Loffing, J. (2015). Dietary potassium and the renal control of salt balance and blood pressure. *Pflügers Archiv 467*, 513–530.
Penton, D., Czogalla, J., Wengi, A., Himmerkus, N., Loffing-Cueni, D., Carrel, M., ... Loffing, J. (2016). Extracellular K(+) rapidly controls NaCl cotransporter phosphorylation in the native distal convoluted tubule by Cl(−) -dependent and independent mechanisms. *The Journal of Physiology 594*, 6319–6331.
Penton, D., Vohra, T., Banki, E., Wengi, A., Weigert, M., Forst, A. L., ... Loffing, J. (2020). Collecting system-specific deletion of Kcnj10 predisposes for thiazide- and low-potassium diet-induced hypokalemia. *Kidney International 97*, 1208–1218.
Pham, T. D., Verlander, J. W., Wang, Y., Romero, C. A., Yue, Q., Chen, C., ... Wall, S. M. (2020). Aldosterone regulates pendrin and epithelial sodium channel activity through intercalated cell mineralocorticoid receptor-dependent and -independent mechanisms over a wide range in serum potassium. *J Am Soc Nephrol 31*, 483–499.
Pilegaard, H., Terzis, G., Halestrap, A., & Juel, C. (1999). Distribution of the lactate/H+ transporter isoforms MCT1 and MCT4 in human skeletal muscle. *The American Journal of Physiology 276*, E843–E848.
Pitt, B., Anker, S. D., Bushinsky, D. A., Kitzman, D. W., Zannad, F., Huang, I. Z., & Investigators, P. -H. (2011). Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *European Heart Journal 32*, 820–828.
Pitt, B., Bakris, G. L., Weir, M. R., Freeman, M. W., Lainscak, M., Mayo, M. R., ... Bushinsky, D. A. (2018). Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: Results from AMETHYST-DN. *ESC Heart Failure 5*, 592–602.
Poortmans, J. R. (1984). Exercise and renal function. *Sports Medicine 1*, 125–153.
Postow, M. A., Sidlow, R., & Hellmann, M. D. (2018). Immune-related adverse events associated with immune checkpoint blockade. *The New England Journal of Medicine 378*, 158–168.
Powles, J., Fahimi, S., Micha, R., Khatibzadeh, S., Shi, P., Ezzati, M., ... Global Burden of Diseases, N., & Chronic Diseases Expert, G (2013). Global, regional and national sodium intakes in 1990 and 2010: A systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open 3*, Article e003733.
Rabinowitz, L., Green, D. M., Sarason, R. L., & Yamauchi, H. (1988). Homeostatic potassium excretion in fed and fasted sheep. *The American Journal of Physiology 254*, R357–R380.
Rafferty, K., Davies, K. M., & Heaney, R. P. (2005). Potassium intake and the calcium economy. *Journal of the American College of Nutrition 24*, 99–106.
Ransick, A., Lindstrom, N. O., Liu, J., Zhu, Q., Guo, J. J., Alvarado, G. F., ... McMahon, A. P. (2019). Single-cell profiling reveals sex, lineage, and regional diversity in the mouse kidney. *Developmental Cell 51*(399–413), Article e397.

Rao, R., Bhalla, V., & Pastor-Soler, N. M. (2019). Intercalated cells of the kidney collecting duct in kidney physiology. *Seminars in Nephrology 39*, 353–367.

Ray, E. C., Carrisoza-Gaytan, R., Al-Bataineh, M., Marciszyn, A. L., Nkashama, L. J., Chen, J., ... Satlin, L. M. (2021). L-WNK1 is required for BK channel activation in intercalated cells. *American Journal of Physiology. Renal Physiology 321*, F245–F254.

Reddin, C., Ferguson, J., Murphy, R., Clarke, A., Judge, C., Griffith, V., ... O'Donnell, M. J. (2023). Global mean potassium intake: A systematic review and Bayesian meta-analysis. *European Journal of Nutrition 62*, 2027–2037.

Rieg, T., Vallon, V., Sausbier, M., Sausbier, U., Kaissling, B., Ruth, P., & Osswald, H. (2007). The role of the BK channel in potassium homeostasis and flow-induced renal potassium excretion. *Kidney International 72*, 566–573.

Rizzo, F., & Staub, O. (2015). NEDD4-2 and salt-sensitive hypertension. *Current Opinion in Nephrology and Hypertension 24*, 111–116.

Robert, T., Vanelle, P., Brunet, P., Martin, N., Burtey, S., & Curti, C. (2021). Impact of insulin adsorption in various containers during hyperkalaemia treatment. *Clinical Kidney Journal 14*, 2255–2260.

Roger, S. D., Lavin, P. T., Lerma, E. V., McCullough, P. A., Butler, J., Spinowitz, B. S., ... Packham, D. K. (2021). Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalaemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: Comparative results from an open-label, phase 3 study. *Nephrology, Dialysis, Transplantation 36*, 137–150.

Roger, S. D., Spinowitz, B. S., Lerma, E. V., Fishbane, S., Ash, S. R., Martins, J. G., ... Packham, D. K. (2021). Sodium zirconium cyclosilicate increases serum bicarbonate concentrations among patients with hyperkalaemia: Exploratory analyses from three randomized, multi-dose, placebo-controlled trials. *Nephrology, Dialysis, Transplantation 36*, 871–883.

Rosa, R. M., Silva, P., Young, J. B., Landsberg, L., Brown, R. S., Rowe, J. W., & Epstein, F. H. (1980). Adrenergic modulation of extrarenal potassium disposal. *The New England Journal of Medicine 302*, 431–434.

Rosner, M. H., & Perazella, M. A. (2017). Acute kidney injury in patients with cancer. *The New England Journal of Medicine 376*, 1770–1781.

Rossier, B. C., Bochud, M., & Devuyst, O. (2017). The hypertension pandemic: An evolutionary perspective. *Physiology (Bethesda) 32*, 112–125.

Ryan, D. P., da Silva, M. R., Soong, T. W., Fontaine, B., Donaldson, M. R., Kung, A. W., ... Ptacek, L. J. (2010). Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. *Cell 140*, 88–98.

Sacks, F. M., Svetkey, L. P., Vollmer, W. M., Appel, L. J., Bray, G. A., Harsha, D., ... Group, D. A.-S. C. R (2001). Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. DASH-sodium collaborative research group. *The New England Journal of Medicine 344*, 3–10.

Saha, B., Leite-Dellova, D. C. A., Demko, J., Sorensen, M. V., Takagi, E., Gleason, C. E., ... Pearce, D. (2022). WNK1 is a chloride-stimulated scaffold that regulates mTORC2 activity and ion transport. *Journal of Cell Science 135*.

Saha, B., Shabbir, W., Takagi, E., Duan, X. P., Almeida Leite Dellova, D. C., Demko, J., ... Pearce, D. (2023). Potassium activates mTORC2-dependent SGK1 phosphorylation to stimulate ENaC: Role in rapid renal responses to dietary potassium. *J Am Soc Nephrol..34,1019-1038.*.

Santeusanio, F., Faloona, G. R., Knochel, J. P., & Unger, R. H. (1973). Evidence for a role of endogenous insulin and glucagon in the regulation of potassium homeostasis. *The Journal of Laboratory and Clinical Medicine 81*, 809–817.

Saw, H. P., Chiu, C. D., Chiu, Y. P., Ji, H. R., & Chen, J. Y. (2019). Nebulized salbutamol diminish the blood glucose fluctuation in the treatment of non-oliguric hyperkalemia of premature infants. *Journal of the Chinese Medical Association 82*, 55–59.

Scherr, L., Ogden, D. A., Mead, A. W., Spritz, N., & Rubin, A. L. (1961). Management of hyperkalemia with a cation-exchange resin. *The New England Journal of Medicine 264*, 115–119.

Scholl, U. I., Choi, M., Liu, T., Ramaekers, V. T., Hausler, M. G., Grimmer, J., ... Lifton, R. P. (2009). Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. *Proceedings of the National Academy of Sciences of the United States of America 106*, 5842–5847.

Schott, G. D., & McArdle, B. (1974). Barium-induced skeletal muscle paralysis in the rat, and its relationship to human familial periodic paralysis. *Journal of Neurology, Neurosurgery, and Psychiatry 37*, 32–39.

Sejersted, O. M., & Sjogaard, G. (2000). Dynamics and consequences of potassium shifts in skeletal muscle and heart during exercise. *Physiological Reviews 80*, 1411–1481.

Sennels, H. P., Jorgensen, H. L., Goetze, J. P., & Fahrenkrug, J. (2012). Rhythmic 24-hour variations of frequently used clinical biochemical parameters in healthy young males–the Bispebjerg study of diurnal variations. *Scandinavian Journal of Clinical and Laboratory Investigation 72*, 287–295.

Shibata, S. (2016). Context-dependent mechanisms modulating aldosterone signaling in the kidney. *Clinical and Experimental Nephrology 20*, 663–670.

Shibata, S., Ishizawa, K., Wang, Q., Xu, N., Fujita, T., Uchida, S., & Lifton, R. P. (2018). ULK1 phosphorylates and regulates mineralocorticoid receptor. *Cell Reports 24*, 569–576.

Shibata, S., Rinehart, J., Zhang, J., Moeckel, G., Castaneda-Bueno, M., Stiegler, A. L., ... Lifton, R. P. (2013). Mineralocorticoid receptor phosphorylation regulates ligand binding and renal response to volume depletion and hyperkalemia. *Cell Metabolism 18*, 660–671.

Shoda, W., Nomura, N., Ando, F., Mori, Y., Mori, T., Sohara, E., ... Uchida, S. (2017). Calcineurin inhibitors block sodium-chloride cotransporter dephosphorylation in response to high potassium intake. *Kidney International 91*, 402–411.

Shoda, W., Nomura, N., Ando, F., Tagashira, H., Iwamoto, T., Ohta, A., Isobe, K., Mori, T., Susa, K., Sohara, E., Rai, T., & Uchida, S. (2020). Sodium-calcium exchanger 1 is the key molecule for urinary potassium excretion against acute hyperkalemia. *PLoS One 15*, Article e0235360.

Smyth, A., Dunkler, D., Gao, P., Teo, K. K., Yusuf, S., O'Donnell, M. J., ... Ontarget, & investigators, T (2014). The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. *Kidney International 86*, 1205–1212.

Sorensen, M. V., Grossmann, S., Roesinger, M., Gresko, N., Todkar, A. P., Barmettler, G., ... Loffing, J. (2013). Rapid dephosphorylation of the renal sodium chloride cotransporter in response to oral potassium intake in mice. *Kidney International 83*, 811–824.

Sorensen, M. V., Saha, B., Jensen, I. S., Wu, P., Ayasse, N., Gleason, C. E., ... Pearce, D. (2019). Potassium acts through mTOR to regulate its own secretion. *JCI Insight 5*.

de Souza, M. C., Santos, A. G., & Reis, A. M. (2016). Adverse drug reactions in patients receiving systemic antifungal therapy at a high-complexity hospital. *Journal of Clinical Pharmacology 56*, 1507–1515.

Spinowitz, B. S., Fishbane, S., Pergola, P. E., Roger, S. D., Lerma, E. V., Butler, J., ... Investigators, Z. S. S. (2019). Sodium zirconium cyclosilicate among individuals with hyperkalemia: A 12-month phase 3 study. *Clinical Journal of the American Society of Nephrology 14*, 798–809.

Stanton, B., Giebisch, G., Klein-Robbenhaar, G., Wade, J., & DeFronzo, R. A. (1985). Effects of adrenalectomy and chronic adrenal corticosteroid replacement on potassium transport in rat kidney. *The Journal of Clinical Investigation 75*, 1317–1326.

Stanton, B., Pan, L., Deetjen, H., Guckian, V., & Giebisch, G. (1987). Independent effects of aldosterone and potassium on induction of potassium adaptation in rat kidney. *The Journal of Clinical Investigation 79*, 198–206.

Stanton, B. A. (2010). Renal potassium transport: The pioneering studies of Gerhard Giebisch. *American Journal of Physiology. Renal Physiology 298*, F233–F234.

Stauber, T., Weinert, S., & Jentsch, T. J. (2012). Cell biology and physiology of CLC chloride channels and transporters. *Comprehensive Physiology 2*, 1701–1744.

Stavniichuk, A., Pyrshev, K., Zaika, O., Tomilin, V. N., Kordysh, M., Lakk, M., ... Pochynyuk, O. (2023). TRPV4 expression in the renal tubule is necessary for maintaining whole body K(+) homeostasis. *American Journal of Physiology. Renal Physiology, 324, F603-F616*.

Stavros, F., Yang, A., Leon, A., Nuttall, M., & Rasmussen, H. S. (2014). Characterization of structure and function of ZS-9, a K+ selective ion trap. *PLoS One 9*, Article e114686.

Sterns, R. H., Rojas, M., Bernstein, P., & Chennupati, S. (2010). Ion-exchange resins for the treatment of hyperkalemia: Are they safe and effective? *J Am Soc Nephrol 21*, 733–735.

Su, X. T., Ellison, D. H., & Wang, W. H. (2019). Kir4.1/Kir5.1 in the DCT plays a role in the regulation of renal K(+) excretion. *American Journal of Physiology. Renal Physiology 316*, F582–F586.

Su, X. T., Klett, N. J., Sharma, A., Allen, C. N., Wang, W. H., Yang, C. L., & Ellison, D. H. (2020). Distal convoluted tubule Cl(−) concentration is modulated via K(+) channels and transporters. *American Journal of Physiology. Renal Physiology 319*, F534–F540.

Sumida, K., Dashputre, A. A., Potukuchi, P. K., Thomas, F., Obi, Y., Molnar, M. Z., ... Kovesdy, C. P. (2021). Laxative use and risk of dyskalemia in patients with advanced CKD transitioning to dialysis. *Journal of the American Society of Nephrology 32*, 950–959.

Svendsen, S. L., Kornvig, S., Berg, P., Jensen, I. S., de Araujo, I., Larsen, C. K., ... Sorensen, M. V. (2022). Dietary K(+) acts as a genuine diuretic. *Acta Physiologica (Oxford, England) 234*, Article e13762.

Tabibzadeh, N., & Crambert, G. (2023). Mechanistic insights into the primary and secondary alterations of renal ion and water transport in the distal nephron. *Journal of Internal Medicine 293*, 4–22.

Tannen, R. L., Wedell, E., & Moore, R. (1973). Renal adaptation to a high potassium intake. The role of hydrogen ion. *The Journal of Clinical Investigation 52*, 2089–2101.

Terker, A. S., Yarbrough, B., Ferdaus, M. Z., Lazelle, R. A., Erspamer, K. J., Meermeier, N. P., ... Ellison, D. H. (2016). Direct and indirect mineralocorticoid effects determine distal salt transport. *J Am Soc Nephrol 27*, 2436–2445.

Terker, A. S., Zhang, C., Erspamer, K. J., Gamba, G., Yang, C. L., & Ellison, D. H. (2016). Unique chloride-sensing properties of WNK4 permit the distal nephron to modulate potassium homeostasis. *Kidney International 89*, 127–134.

Terker, A. S., Zhang, C., McCormick, J. A., Lazelle, R. A., Zhang, C., Meermeier, N. P., ... Ellison, D. H. (2015). Potassium modulates electrolyte balance and blood pressure through effects on distal cell voltage and chloride. *Cell Metabolism 21*, 39–50.

Thomson, M. N., Cuevas, C. A., Bewarder, T. M., Dittmayer, C., Miller, L. N., Si, J., ... Mutig, K. (2020). WNK bodies cluster WNK4 and SPAK/OSR1 to promote NCC activation in hypokalemia. *American Journal of Physiology. Renal Physiology 318*, F216–F228.

Todkar, A., Picard, N., Loffing-Cueni, D., Sorensen, M. V., Mihailova, M., Nesterov, V., ... Loffing, J. (2015). Mechanisms of renal control of potassium homeostasis in complete aldosterone deficiency. *J Am Soc Nephrol 26*, 425–438.

Torpy, D. J., Mullen, N., Ilias, I., & Nieman, L. K. (2002). Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: A series of 58 cases. *Annals of the New York Academy of Sciences 970*, 134–144.

Tran, C. T., Atanasovska, T., Graff, C., Melgaard, J., Kanters, J. K., Smith, R., ... McKenna, M. J. (2022). Plasma potassium concentration and cardiac repolarisation markers, T (peak)-T(end) and T(peak)-T(end)/QT, during and after exercise in healthy participants and in end-stage renal disease. *European Journal of Applied Physiology 122*, 691–702.

Tran, C. T., Bundgaard, H., Ladefoged, S. D., Haunso, S., & Kjeldsen, K. (2013). Potassium dynamics are attenuated in hyperkalemia and a determinant of QT adaptation in exercising hemodialysis patients. *Journal of Applied Physiology 1985*(115), 498–504.

Trulls, J. C., Morales-Rull, J. L., Casado, J., Carrera-Izquierdo, M., Snchez-Marteles, M., Conde-Martel, A., ... investigators, C. t (2023). Combining loop with thiazide diuretics for decompensated heart failure: The CLOROTIC trial. *European Heart Journal 44*, 411–421.

Tucker, K. L., Hannan, M. T., Chen, H., Cupples, L. A., Wilson, P. W., & Kiel, D. P. (1999). Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *The American Journal of Clinical Nutrition 69*, 727–736.

Uniacke, B., & Walsh, B. T. (2022). Eating disorders. *Annals of Internal Medicine 175* ITC113-ITC128.
Uyehara, C. F., & Sarkar, J. (2013). Role of vasopressin in maintenance of potassium homeostasis in severe hemorrhage. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology 305*, R101–R103.
Verzicco, I., Regolisti, G., Quaini, F., Bocchi, P., Brusasco, I., Ferrari, M., ... Cabassi, A. (2020). Electrolyte disorders induced by antineoplastic drugs. *Frontiers in Oncology 10*, 779.
Virvidakis, C., Loukas, A., Mayopoulou-Symvoulidou, D., & Mountokalakis, T. (1986). Renal responses to bicycle exercise in trained athletes: Influence of exercise intensity. *International Journal of Sports Medicine 7*, 86–88.
Vivekanandam, V., Mannikko, R., Matthews, E., & Hanna, M. G. (2020). Improving genetic diagnostics of skeletal muscle channelopathies. *Expert Review of Molecular Diagnostics 20*, 725–736.
Wade, J. B., Fang, L., Coleman, R. A., Liu, J., Grimm, P. R., Wang, T., & Welling, P. A. (2011). Differential regulation of ROMK (Kir1.1) in distal nephron segments by dietary potassium. *American Journal of Physiology. Renal Physiology 300*, F1385–F1393.
Wagner, C. A., Finberg, K. E., Breton, S., Marshansky, V., Brown, D., & Geibel, J. P. (2004). Renal vacuolar H+-ATPase. *Physiological Reviews 84*, 1263–1314.
Wall, S. M., Verlander, J. W., & Romero, C. A. (2020). The renal physiology of pendrin-positive intercalated cells. *Physiological Reviews 100*, 1119–1147.
Walter, C., Tanfous, M. B., Igoudjil, K., Salhi, A., Escher, G., & Crambert, G. (2016). H,K-ATPase type 2 contributes to salt-sensitive hypertension induced by K(+) restriction. *Pflügers Archiv 468*, 1673–1683.
Wan, X., Perry, J., Zhang, H., Jin, F., Ryan, K. A., Van Hout, C., ... Regeneron Genetics, C. (2021). Heterozygosity for a pathogenic variant in SLC12A3 that causes autosomal recessive Gitelman syndrome is associated with lower serum potassium. *J Am Soc Nephrol 32*, 756–765.
Wanchoo, R., Jhaveri, K. D., Deray, G., & Launay-Vacher, V. (2016). Renal effects of BRAF inhibitors: A systematic review by the cancer and the kidney international network. *Clinical Kidney Journal 9*, 245–251.
Wanchoo, R., Sakhiya, V., & Jhaveri, K. D. (2021). Immune checkpoint inhibitor-associated electrolyte disorders: Query of the Food and Drug Administration adverse event reporting system. *Kidney International 100*, 945–947.
Wang, B., & Sansom, S. C. (2019). Potassium-sparing effects of furosemide in mice on high-potassium diets. *American Journal of Physiology. Renal Physiology 316*, F970–F973.
Wang, Q., Qi, Y., Zhang, D., Gong, C., Yao, A., Xiao, Y., ... Zhou, Y. (2015). Electrolyte disorders assessment in solid tumor patients treated with anti-EGFR monoclonal antibodies: A pooled analysis of 25 randomized clinical trials. *Tumour Biology 36*, 3471–3482.
Wang, W. H., & Lin, D. H. (2022). Inwardly rectifying K(+) channels 4.1 and 5.1 (Kir4.1/Kir5.1) in the renal distal nephron. *American Journal of Physiology. Cell Physiology 323*, C277–C288.
Watson, M., Abbott, K. C., & Yuan, C. M. (2010). Damned if you do, damned if you don't: Potassium binding resins in hyperkalemia. *Clinical Journal of the American Society of Nephrology 5*, 1723–1726.
Watson, M. A., Baker, T. P., Nguyen, A., Sebastianelli, M. E., Stewart, H. L., Oliver, D. K., ... Yuan, C. M. (2012). Association of prescription of oral sodium polystyrene sulfonate with sorbitol in an inpatient setting with colonic necrosis: A retrospective cohort study. *American Journal of Kidney Diseases 60*, 409–416.
Wei, K. Y., Gritter, M., Vogt, L., de Borst, M. H., Rotmans, J. I., & Hoorn, E. J. (2020). Dietary potassium and the kidney: Lifesaving physiology. *Clinical Kidney Journal 13*, 952–968.
Weinstein, A. M. (2022). A mathematical model of the rat kidney. IV. Whole kidney response to hyperkalemia. *American Journal of Physiology. Renal Physiology 322*, F225–F244.
Weir, M. R., Bakris, G. L., Bushinsky, D. A., Mayo, M. R., Garza, D., Stasiv, Y., ... Investigators, O. -H. (2015). Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England Journal of Medicine 372*, 211–221.
Welling, P. A. (2013). Regulation of renal potassium secretion: Molecular mechanisms. *Seminars in Nephrology 33*, 215–228.
Welling, P. A. (2016). Roles and regulation of renal K channels. *Annual Review of Physiology 78*, 415–435.
Wen, D., Cornelius, R. J., Rivero-Hernandez, D., Yuan, Y., Li, H., Weinstein, A. M., & Sansom, S. C. (2014). Relation between BK-alpha/beta4-mediated potassium secretion and ENaC-mediated sodium reabsorption. *Kidney International 86*, 139–145.
Wen, D., Cornelius, R. J., & Sansom, S. C. (2014). Interacting influence of diuretics and diet on BK channel-regulated K homeostasis. *Current Opinion in Pharmacology 15*, 28–32.
Wetli, C. V., & Davis, J. H. (1978). Fatal hyperkalemia from accidental overdose of potassium chloride. *JAMA 240*, 1339.
WHO (2012a). *Guideline: Potassium intake for adults and children*. Geneva: World Health Organization.
WHO (2012b). *Guideline: Sodium intake for adults and children*. Geneva: World Health Organization.
van der Wijst, J., Tutakhel, O. A. Z., Bos, C., Danser, A. H. J., Hoorn, E. J., Hoenderop, J. G. J., & Bindels, R. J. M. (2018). Effects of a high-sodium/low-potassium diet on renal calcium, magnesium, and phosphate handling. *American Journal of Physiology. Renal Physiology 315*, F110–F122.
Williams, M. E., Gervino, E. V., Rosa, R. M., Landsberg, L., Young, J. B., Silva, P., & Epstein, F. H. (1985). Catecholamine modulation of rapid potassium shifts during exercise. *The New England Journal of Medicine 312*, 823–827.
Woda, C. B., Bragin, A., Kleyman, T. R., & Satlin, L. M. (2001). Flow-dependent K+ secretion in the cortical collecting duct is mediated by a maxi-K channel. *American Journal of Physiology. Renal Physiology 280*, F786–F793.
Xu, J. Z., Hall, A. E., Peterson, L. N., Bienkowski, M. J., Eessalu, T. E., & Hebert, S. C. (1997). Localization of the ROMK protein on apical membranes of rat kidney nephron segments. *The American Journal of Physiology 273*, F739–F748.
Yang, L., Frindt, G., Xu, Y., Uchida, S., & Palmer, L. G. (2020). Aldosterone-dependent and -independent regulation of Na(+) and K(+) excretion and ENaC in mouse kidneys. *American Journal of Physiology. Renal Physiology 319*, F323–F334.
Yang, L., Xu, S., Guo, X., Uchida, S., Weinstein, A. M., Wang, T., & Palmer, L. G. (2018). Regulation of renal Na transporters in response to dietary K. *American Journal of Physiology. Renal Physiology 315*, F1032–F1041.
Yang, L., Xu, Y., Gravotta, D., Frindt, G., Weinstein, A. M., & Palmer, L. G. (2021). ENaC and ROMK channels in the connecting tubule regulate renal K+ secretion. *The Journal of General Physiology 153*.
Yoshino, T., Shimada, S., Homma, M., Makino, T., Mimura, M., & Watanabe, K. (2021). Clinical risk factors of licorice-induced pseudoaldosteronism based on glycyrrhizin-metabolite concentrations: A narrative review. *Frontiers in Nutrition 8*, Article 719197.
Youn, J. H., & McDonough, A. A. (2009). Recent advances in understanding integrative control of potassium homeostasis. *Annual Review of Physiology 71*, 381–401.
Young, D. B. (1982). Relationship between plasma potassium concentration and renal potassium excretion. *The American Journal of Physiology 242*, F599–F603.
Young, D. B., McCaa, R. E., Pan, Y. J., & Guyton, A. C. (1976). The natriuretic and hypotensive effects of potassium. *Circulation Research 38*, 84–89.
Yuan, Y., Jin, A., Neal, B., Feng, X., Qiao, Q., Wang, H., ... Wu, Y. (2023). Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: A cluster-randomized trial. *Nature Medicine 29*, 973–981.
Zhang, C., Wang, L., Zhang, J., Su, X. T., Lin, D. H., Scholl, U. I., ... Wang, W. H. (2014). KCNJ10 determines the expression of the apical Na-Cl cotransporter (NCC) in the early distal convoluted tubule (DCT1). *Proceedings of the National Academy of Sciences of the United States of America 111*, 11864–11869.
Zollinger, R. M., Jr., Van DeWater, J. M., Maletskos, C. J., & Moore, F. D. (1970). Exchangeable potassium in man using a new radioisotope 43K. *Surgical Forum 21*, 213–215.