Potassium homeostasis and dyskalemias: the respective roles of renal, extrarenal, and gut sensors in potassium handling

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Integrated mechanisms controlling the maintenance of potassium homeostasis are well established and are defined by the classic "feedback control" of potassium balance. Recently, increasing investigative attention has focused on novel physiological paradigms that increase the complexity and precision of homeostasis. This review briefly considers the classic and well-established feedback control of potassium and then considers subsequent investigations that inform on an intriguing and not widely recognized complementary paradigm: the "feed-forward control of potassium balance." Feed-forward control refers to a pathway in a homeostatic system that responds to a signal in the environment in a predetermined manner, without responding to how the system subsequently reacts (i.e., without responding to feedback). Studies in several animal species, and recently in humans, have confirmed the presence of a feed-forward control mechanism that is capable of mediating potassium excretion independent of changes in serum potassium concentration and aldosterone. Knowledge imparted by this update of potassium homeostasis hopefully will facilitate the clinical management of hyperkalemia in patients with chronic and recurrent hyperkalemia. Awareness of this updated integrative control mechanism for potassium homeostasis is more relevant today when the medical community is increasingly focused on leveraging and expanding established renin-angiotensin-aldosterone system inhibitor treatment regimens and on successfully coping with the challenges of managing hyperkalemia provoked by renin-angiotensin-aldosterone system inhibitors. These new insights are relevant to the future design of clinical trials delineating renal potassium handling.

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The integrated mechanisms controlling the maintenance of potassium homeostasis are well established and are defined by the classic "feedback control" of potassium balance. In recent years, increasing investigative attention has focused on novel physiological paradigms that increase the complexity as well as the precision of homeostasis. In this review, we briefly consider the classic and well-established feedback control of potassium and then consider subsequent investigations that inform on an intriguing and not widely recognized complementary paradigm: the "feed-forward control of potassium balance." Awareness of this updated integrative control mechanism for potassium homeostasis is more relevant today when the medical community is increasingly focused on the challenges of managing the hyperkalemia provoked by renin-angiotensin-aldosterone system inhibitors (RAASi).[1–11]

As detailed elsewhere in this supplement (Epstein[12]), it is well established that RAASi confer substantive benefits, such as reducing cardiovascular events and retarding the progression of renal disease in several disease states, including congestive heart failure, chronic kidney disease, and diabetes.[13–24] Regretfully, treatment with RAASi is complicated by hyperkalemia, which is a frequent side effect of RAASi therapy.[1–4,9–11] Indeed, the problem will only become increasingly prominent and frequent, because hyperkalemia will remain an issue with newly introduced drugs such as neprilysin inhibitors (LCZ-696, now known as valsartan/sacubitril, brand name Entresto; Novartis Pharmaceuticals Corporation, East Hanover, NJ), as reported in PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial).[25] Furthermore, as detailed by Epstein,[12] the wide gap between RAASi prescribing guidelines and reality is widely thought to be attributable to hyperkalemia.[1–4,9–11] Consequently, we require a greater knowledge of the complexities of the regulatory mechanisms that subserve potassium homeostasis. Finally, as detailed in Weir[26] in this supplement, with the recent approval of a potassium-binding polymer and the imminent approval of another potassium binder,[2,4–7,9] it is essential to understand how these binders mediate their effects. A thorough understanding of potassium homeostasis is a requirement if we are to avail ourselves of the maximum benefits from these newly available agents.

Normal potassium balance and renal potassium excretion

To establish the context and foundation for considering newer—albeit poorly recognized—adaptive mechanisms for subserving potassium homeostasis, we will first summarize key concepts of steady-state potassium handling. Normal persons who consume a typical Western diet ingest approximately 70–80 mmol of potassium per day.[27,28] The intestine absorbs virtually all of the ingested potassium and delivers it to the liver by means of the hepatoportal circulation, where the ingested potassium is extracted by the liver. In normal circumstances, minimal amounts of potassium are excreted in the feces.

The principal defense against chronic potassium imbalances is renal potassium excretion, which depends on free filtration at the glomerulus, extensive proximal tubule reabsorption, and a highly regulated secretory process in the distal convoluted tubule and segments of the collecting duct in the cortex and outer medulla (the cortical collecting duct and the outer medullary collecting duct, respectively). The more predominant of the 2 types of collecting duct cells are the principal cells, which comprise approximately 75% of collecting duct cells. They mediate sodium reabsorption and potassium secretion and also constitute targets for angiotensin II,[29–31] aldosterone, mineralocorticoid receptor antagonists, and potassium-sparing diuretics (Figure 1).

Principal cells exploit the electrochemical gradient established by sodium entry into the cell through a sodium channel at the luminal membrane (the molecular target of amiloride) and the basolateral membrane sodium-potassium adenosine triphosphatase (Na-K-ATPase) to drive potassium secretion through 2 classes of luminal membrane potassium channels.[32] One class, the renal outer medullary potassium (also termed ROMK) channels, secretes potassium under normal tubular fluid flow conditions and is inserted into or internalized from the luminal membrane, depending on the demand for potassium secretion. The other class of potassium channels is the "big" conductance channels (known as BK channels), which are relatively inactive under normal conditions but exhibit increased activity during high tubular flow or high-potassium conditions.[32] The factors that regulate principal cell potassium secretion include previous potassium intake; intracellular potassium level; sodium delivery to the cells; urine flow rate; and hormones, such as aldosterone and catecholamines.[33] The other of the 2 collecting duct cell types, intercalated cells,