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The expanding role of aldosterone in the regulation of body Na content

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Maintenance of body Na content and thereby of extracellular fluid volume is one of the most important prerequisites for optimum organ perfusion, the ultimate purpose of the cardiovascular system. While absolute constancy of extracellular fluid volume is not necessarily the homeostatic target, it is critical to keep it in a range compatible with normal arterial perfusion pressures, a range that is flanked by arterial hypertension on the one side and circulatory collapse on the other. Entrance into these unhealthy fringes requires uncorrected deviations in body salt content, and in the absence of extrarenal Na losses these can only result from abnormal Na reabsorption by the kidneys. It is therefore not surprising that the major adjustments that take place when body salt content increases or decreases are all targeted towards altering renal tubular Na reabsorption.

The crucial role of the kidneys in controlling body Na content has been appreciated ever since Guyton's seminal work [1]. However, the recent evidence from genetic alterations of genes coding for transport proteins, mostly loss-of-function alterations, has provided direct and convincing proof that chronic derangements of extracellular fluid volume in general have a renal cause. Furthermore, studies of the consequences of singular and complete Na transporter deficiencies have yielded sometimes unexpected insights into the net contribution of various transporters to body Na content or its derangements. Reaffirming the central role of aldosterone in control of body salt content, it has become evident that perturbations in salt reabsorption along the collecting ducts cause unmanageable alterations in body salt balance with permanent derailment of the circulatory system into the hypertensive or hypotensive fringes. Na traverses the apical membrane of collecting duct cells through the aldosterone-regulated Na channel ENaC, and knockout mutations of each of the three ENaC subunits are associated with early postnatal death, at least in part due to extracellular volume depletion [2]. Autosomal recessive pseudohypoaldosteronism, the human disease caused by ENaC mutations, is likewise associated with severe Na wasting, failure to thrive, and sometimes death in infancy [3]. Since salt reabsorption in the collecting duct is primarily regulated by aldosterone, it is not surprising that a genetic ablation of mineralocorticoid receptors causes the same Na-wasting phenotype [4]. Conversely, a constitutively active ENaC protein causes unregulated salt reabsorption along the collecting duct with the result of the development of early and malignant arterial hypertension [5].

The conclusion from these studies is that a major role in body Na homeostasis is assigned to a tubular segment that reabsorbs no more than 5% of filtered Na, and that has a comparatively low transport capacity under all conditions. One may therefore argue that the regulation of glomerular filtration rate and of tubular reabsorption in all segments prior to the collecting duct serves the purpose of ascertaining that Na delivery to the terminal segment is kept within its limited regulatory range. A system in which early renal tubule and late renal tubule reabsorption capacities are at least partly coupled by the same mechanism would seem an ideal solution.

The work by Krug et al. published in this issue of *Pflügers Archiv* seems to provide an example for such a mechanism [6]. While aldosterone is commonly seen as a stimulator of Na reabsorption in the collecting duct, Krug and his collaborators demonstrate that proximal tubule fluid reabsorption increased when adrenalectomized rats were substituted with aldosterone. Using the amiloride sensitivity as a measure of NHE_3-dependent fluid reabsorption, the authors detected an approximately 10% increase in NHE_3 activity and subsequent fluid reabsorption in adrenalectomized rats receiving aldosterone at a rate that returned plasma levels to the high physiological range. Thus, in contrast to the collecting duct where aldosterone regulates the activity and abundance of

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ENaC, the mechanism of action of aldosterone in the proximal tubule consists of an increase in the activity of NHE_3, the most important Na uptake promoter in this part of the nephron. Upregulation of NHE_3 activity by aldosterone is achieved by the integration of preformed transporter protein into the apical membrane. Exactly how aldosterone is involved in the trafficking of NHE_3 is unclear, but the speculation by the authors that cytoskeletal proteins are induced by aldosterone seems the most likely mechanism.

In the overall scheme of volume homeostasis, the work of Krug and colleagues suggests a hierarchy of volume-conserving mechanisms [6]. When Na supply is normal and Na reabsorption along the collecting duct must be incomplete to achieve Na balance, plasma aldosterone levels are in a concentration range where ENaC-mediated Na reabsorption is undersaturated, and the proximal NHE_3-dependent mechanism is probably not engaged. When a chronically low Na intake or a loss of blood have caused volume depletion, plasma aldosterone levels are driven into a range where proximal Na reabsorption is stimulated. An enhanced proximal reabsorption of Na is predicted to augment the release of renin through the macula densa mechanism by further reducing NaCl concentration at the macula densa. Under these chronic conditions the incremental activation of the renin–angiotensin system promotes a reduction of glomerular filtration rate (GFR) by enhanced tubuloglomerular feedback activity. A combination of the effects of high aldosterone levels to increase proximal reabsorption and to reduce the filtered Na load permits the activated ENaC and Na/K ATPase along the collecting duct to generate the Na-free urine characteristic for states of volume depletion.

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