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Review

Intracellular sodium sensing: SIK1 network, hormone action and high blood pressure☆

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ABSTRACT

Sodium is the main determinant of body fluid distribution. Sodium accumulation causes water retention and, often, high blood pressure. At the cellular level, the concentration and active transport of sodium is handled by the enzyme Na^+,K^+-ATPase, whose appearance enabled evolving primitive cells to cope with osmotic stress and contributed to the complexity of mammalian organisms. Na^+,K^+-ATPase is a platform at the hub of many cellular signaling pathways related to sensing intracellular sodium and dealing with its detrimental excess. One of these pathways relies on an intracellular sodium-sensor network with the salt-inducible kinase 1 (SIK1) at its core. When intracellular sodium levels rise, and after the activation of calcium-related signals, this network activates the Na^+,K^+-ATPase and expel the excess of sodium from the cytosol. The SIK1 network also mediates sodium-independent signals that modulate the activity of the Na^+,K^+-ATPase, like dopamine and angiotensin, which are relevant *per se* in the development of high blood pressure. Animal models of high blood pressure, with identified mutations in components of multiple pathways, also have alterations in the SIK1 network. The introduction of some of these mutants into normal cells causes changes in SIK1 activity as well. Some cellular processes related to the metabolic syndrome, such as insulin effects on the kidney and other tissues, also appear to involve the SIK1. Therefore, it is likely that this protein, by modulating active sodium transport and numerous hormonal responses, represents a "crossroad" in the development and adaptation to high blood pressure and associated diseases.

1. Sodium—a double-edged sword

Sodium, the most important determinant of extracellular osmolarity, plays a crucial role in the homeostasis and compartmental distribution of body fluids. In fact, water – the main intracorporeal solvent – is dragged across membranes by the osmolar differences between body compartments. No energy is spent *directly* to move water; instead, pumps and transporters move sodium ions across membranes, changing and balancing the osmolar composition of body compartments, thus *indirectly* affecting the distribution of water [1].

Frequently, the sodium concentration in blood, or *natremia*, reflects the water distribution status rather than the net sodium content. Most patients with hypernatremia are dehydrated, and similarly many of those with hyponatremia are over hydrated (dilutional hyponatremia). Indeed, patients with edema can show normal sodium concentrations in plasma but nonetheless have a total excess of sodium contained in the excess water in the form of edema [2]. Alterations of sodium homeostasis can cause water to accumulate abnormally in the intravascular compartment leading to blood pressure elevations, as occurs in patients with sodium-sensitive high blood pressure [3]. Most of these patients are instructed to limit their intake of sodium, but not of water, and are frequently given natriuretic drugs to control the blood intravascular volume and so the blood pressure [3]. In patients with heart failure, similarly, ingestion of free water scarcely affects their extracellular volume status, as opposed to sodium excess, which causes volume overload and eventually anasarca (disseminated edemas) and pulmonary edema [4]. Sodium restriction is the paramount measure to prevent abnormal accumulation of water in these patients [4]. Patients with liver cirrhosis and portal hypertension who consume too much sodium accumulate water in the peritoneal cavity and develop ascites; if this happens, they are requested to limit their sodium intake and take natriuretic drugs to correct the water excess [5]. Under ischemic conditions such as acute stroke, the amount of energy supplied to cells may be inadequate to maintain active sodium transport across the plasma membrane. Sodium then accumulates in the intracellular compartment [6]. This new status causes intracellular edema and cellular swelling which, because of the non-compliant nature of the skull, leads to intracranial hypertension and further exacerbates the injury. In fact, a common strategy to prevent intracranial injury is to

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administer hypertonic solutions to render the extracellular compartment relatively hyperosmolar and, as a consequence, to shrink cells back [7]. In critically ill patients, inflammatory injury to the lung renders the pulmonary epithelium incapable of handling water reabsorption, which causes accumulation of fluid in interstitial and alveolar space [8]. This situation is resolved when the alveolar epithelial cells recover their capacity to transport sodium back from the alveolar space to the blood [9]. Given that the resolution of pulmonary edema is associated with decrease of mortality of critically ill patients [10], there have been many attempts to manipulate sodium transport in order to hasten the reversion of lung edema. The use of diuretics [11], sodium restriction [12], delivery of sodium transporters to the air space by using aerosolized viral vectors [13] and other measures [14] have been proposed to hasten the resolution of pulmonary edema.

It has also been suggested that sodium can jeopardize the homeostasis not only through its effect on water but also on its own. Indeed, the "normal saline" solution commonly used in clinical settings (that contains 154 mmol of sodium per liter of water as opposed to the ~140 mmol/l in plasma), might be relatively harmful compared with other formulas such as Ringer's, which has a lower sodium content [15].

In summary, sodium is the primary determinant of water content in the body compartments and its misdistribution can cause intra- and extracellular edema, excess of intravascular water, and hypervolemia. In addition, independently of its osmotic properties, sodium excess can be deleterious by affecting the ionic composition of body fluids, pH, etc. Finally, as described in the next sections, intracellular sodium *per se* can influence the actions of hormones and also trigger activation of numerous signal transduction pathways, affecting multiples cellular processes.

2. Sodium sensing—a matter of cell survival

As primitive organisms originated in the salty oceanic medium, cells had to deal with the potential osmotic insult caused by entrance of sodium [22]. Indeed, given that sodium is potentially toxic for many biologically relevant components [16], cells had to develop mechanisms to cope with this challenge. The adaptations that have evolved over millions of years are both complex and extremely diverse. Some cells, such as those in plants, have a semi-rigid wall that prevents significant volume changes that might be detrimental to cellular functions. The disadvantage of that "solution" is that as multicellular organisms, plants with semi-rigid cell walls are sessile, confined to relatively fixed locations, which limits their ability to escape from adverse environmental conditions [17]. Although bacteria also have a semi-rigid cell wall, they can migrate long distances; yet their unicellular nature limits their complexity [17]. Mammalian cells, despite being "extremely modern" in evolutionary terms, cannot survive without proper control of intracellular sodium. Indeed, the aqueous environment in which most mammalian cells are embedded poses a threat of *death by flooding* due to the Donnan effect. The water-attracting power of this effect is related to the number of intracellular molecules, which in turn is proportional to the structural complexity of the cytosol [18]. Animal cells compensate this "sucking force from inside" by pumping sodium towards the extracellular milieu through the Na^+,K^+-ATPase located in the plasma membrane [19]: when Na^+ is actively ejected from the cell, water passively follows. In some tissues the cost of this process corresponds to as much as 40% of the total ATP produced. Without the Na^+,K^+-ATPase, evolutionarily advanced cells are defenseless against the sodium insult [20].

The Na^+,K^+-ATPase belongs to a superfamily of proteins known as P-type ATPases, whose evolutionary links have been traced through cloning and sequencing efforts [21]. It is accepted that the Na^+,K^+-ATPase appeared only once in evolution and developed from a proton ATPase that constituted the primary cell volume regulator at the time life evolved in the oceans [22]. Some have suggested that plants originated in fresh water and for that reason were not challenged with the sodium stress, an event that presumably resulted in the development of the semi-rigid wall [17]. These observations are significant because they suggest that Na^+,K^+-ATPase-mediated transport is not a dispensable function but an essential *requirement* for evolution of animal cells. Many of the critical properties of animal cells – not to mention the cells themselves – might never have developed without the appearance of the Na^+,K^+-ATPase. Some of these properties are indirectly yet fundamentally affected by the Na^+,K^+-ATPase activity. As indicated, the lack of the "straitjacket" represented by a semi-rigid wall allows animal cells to integrate themselves in a complex way that makes possible the stereotyped development pattern observed in advanced species. That complexity also demands a diverse array of proteins to guide the construction of sophisticated cellular networks. Indeed, that intracellular complexity in turn contributes to the cytosolic osmolarity that parallels the evolutionary level of living organisms. Not surprisingly, genes related to both cell adhesion and signaling, and genes encoding DNA-binding proteins, which are critical for the development of multicellular eukaryotes, are significantly more abundant in the highly evolved organisms such as *Homo sapiens* [23].

The Na^+,K^+-ATPase constitutes a highly versatile membrane transport system, as the same Na^+ gradient drives the transport of H^+, HCO_3^- and glucose. In other words, cells make use of their strategy for coping with sodium to perform other critical functions as well, such as nutrient uptake and pH regulation [24]. In some tissues, epithelia for example, the localization of the Na^+,K^+-ATPase to the basolateral domain of the plasma membrane is critical to vectorial transport (i.e. from one particular place to another) of water and solutes. In fact, loss of the pump's polarized localization is characteristic of the renal acute tubular necrosis and causes oliguria secondary to the inability to transport water and sodium across the tubular epithelium [25].

Due to its exchange stoechiometry of 3 Na^+ against 2 K^+, the sodium pump is, in contrast to the other P-type ATPases, *electrogenic* and thereby contributes by its pumping activity directly to the membrane potential. Many functions like ion channels' opening and closure in excitable and nonexcitable cells would not be possible without the activity of the Na^+,K^+-ATPase that establishes the Na^+ gradient across plasma membranes. It has been suggested that a single residue is responsible for the electrogenic property [26] and that mutation in this position can abolish such property. Conversely, the incorporation of this residue into the highly homologous, but non-electrogenic H^+,K^+ gastric ATPase can render it electrogenic, which suggests a high degree of evolutionary refinement in the development of this property [26]. Interestingly, both Na^+,K^+-ATPase and H^+,K^+-ATPase (gastric) belong to the same branch of the P-type ATPases' phylogenetic tree, so this subtle change seems to have occurred over a short evolutionary time span and enabled the diversification of tissues [27,28]. In summary, sodium challenge appears to have caused organisms to develop very sophisticated mechanisms that rendered them able to perform functions of which primitive and simpler cells were incapable.

As one delves deeper into the complexity of maintaining cell sodium and water homeostasis, it becomes clear that the presence of Na^+,K^+-ATPase in the plasma membrane provides a crucial platform that enables various specialized mechanisms to work in a concerted manner. Because so much depends on its function it is reasonable to think that cells might be better "armed" if they have in place a sodium-dependent signaling network controlling key mechanisms (active transport via the Na^+,K^+-ATPase) responsible for its cellular- and many other secondary-derived homeostatic processes. Because of the chaotic nature of the behavior of ions in solution, it is inferred,