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An emerging concept of vascular salt sensitivity

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Abstract

Excessive amounts of salt in food, as usually consumed worldwide, affect the vascular system, leading to high blood pressure and premature disabilities. Salt entering the vascular bed after a salty meal is transiently bound to the endothelial glycocalyx, a negatively charged biopolymer lining the inner surface of the blood vessels. This barrier protects the endothelium against salt overload. A poorly-developed glycocalyx increases the salt permeability of the vascular system and the amount of salt being deposited in the body, which affects organ function. A simple test system is now available that evaluates vascular salt sensitivity in humans and identifies individuals who are at risk of salt-induced hypertension. This short review aims to discuss how the underlying basic research can be translated into medical practice and, thus, meaningful health outcomes.

Introduction

For millions of years, daily salt (sodium chloride) intake in man was about 1g. Then recently, about 10,000 years ago, salt intake increased by about ten-fold [1,2] because of the practice of using salt as a food preservative. It allowed former nomads to settle, grow grain and preserve food-stuffs over long periods. Over the last few millennia, humans got used to the taste of salt and enjoyed the benefits of non-perishable food [3]. However, the human genome could not adapt so quickly. Genetically, humans are well-equipped with mechanisms that retain even tiny amounts of salt, a prerequisite for survival at those times when salt was scarce and intake was low. In keeping with this background, humans have less efficient excretory mechanisms when challenged with large salt loads, and the limiting factor is the rate of renal salt excretion [4]. If salt intake exceeds the kidneys' ability for salt excretion, then salt is deposited in the body, which, in synergy with aldosterone, affects heart [5], blood vessels [6] and kidneys [7]. Arterial hypertension, stroke and cardiac infarction are often the end result.

A paradigm shift

Not everybody is sensitive to salt. It is estimated that at least 30% of the world's population develop hypertension (elevated blood pressure) when exposed to a high salt diet [8]. In the past, salt sensitivity was thought to be the result of kidney malfunction, i.e. on the imbalance between salt input and salt output [9]. However, recent observations suggest that the vascular system may also play an important role in this imbalance [10]. More than 20 years ago, it was shown that the vascular endothelium expresses sodium channels similar to those in renal epithelia [11]. Some years later, it was demonstrated that sodium channel function in endothelium was regulated, much as it is in the kidney, by the mineralocorticoid hormone aldosterone [12]. The fact that the vascular system is also a potential target for aldosterone led to a paradigm shift in so far as the attention was no longer directed solely to the kidney but also to the vascular system [13-20].

Endothelium senses salt

Currently, there are far more data on the pathophysiology of aldosterone affecting vascular function than on the "normal" vascular physiology of this steroid hormone [21-33]. Sodium and aldosterone synergistically act on the endothelium. At cellular level, small changes in plasma sodium concentration can have a large impact on endothelial function as long as aldosterone (or aldosterone receptor function) is available [34]. Even a 5% increase in

plasma sodium concentration mechanically stiffens endothelial cells by about 25%, leading to cellular dysfunction (decreased nitric oxide release/increased vascular smooth muscle tone). A major component of this high sodium sensitivity is the sodium channel in the endothelial plasma membrane [11,12,35], which is identical to the epithelial sodium channel cloned from renal tissue [36]. This channel allows sodium to enter the endothelial cells [37] and, by yet unknown mechanisms, turn off endothelial nitric oxide synthase activity [38].

Do these *in vitro* experiments translate into the *in vivo* setting and explain how plasma sodium *as such* affects blood pressure? This question is not easy to answer since changes in plasma sodium are usually accompanied by changes in osmolality, which may mask any direct action of sodium. However, a recent study properly corrected for any changes in osmolality, shows that there is indeed a marked alteration in blood pressure observable when plasma sodium is manipulated [39]. Similarly, blood pressure in dialysis patients is known to decrease when sodium concentration in the dialysate is lowered [40]. Furthermore, small but significant changes in plasma sodium, paralleled by concomitant changes in blood pressure, are known to occur in humans during acute or chronic salt intake [41,42]. Finally, there is experimental evidence that the brain may be involved in the sodium-triggered increase of blood pressure [41,43]. Blaustein and colleagues postulated an interesting hypothesis, namely that high sodium in the cerebrospinal fluid triggers the secretion of endogenous ouabain in the hypothalamus and suprarenal glands [44]. Endogenous ouabain acts in the brain, increasing sympathetic nerve activity, but also acts on blood vessels. Both endogenous ouabain actions lead to vasoconstriction and increase in blood pressure [45]. For obvious reasons, this more complex mechanism, involving different organs, cannot be used to explain the *in vitro* effect of sodium.

Endothelial glycocalyx, sodium buffer and barrier

Most recently, the endothelial surface layer facing the blood stream has become a focus of interest [46-54]. This soft layer, termed endothelial glycocalyx, is a negatively charged biopolymer known to preferentially bind sodium [55]. It has been calculated that about 700 mg of sodium can be transiently bound to the endothelial glycocalyx in the human body, which is about the amount contained in a single meal [10]. Interestingly, the sodium buffering capacity of the endothelial glycocalyx is severely damaged by excessive sodium intake over time, leading to a significant reduction of the negatively charged heparan sulphate residues in the endothelial glycocalyx [56].

These observations led to a new concept of vascular sodium permeability, namely that two (more or less) permeable barriers determine the rate of sodium elimination after a salty meal [10]. One barrier is the endothelial plasma membrane, with a variable sodium permeability depending on the abundance of epithelial sodium channels. The other barrier, located on the surface of the endothelium, is the endothelial glycocalyx that transiently buffers ingested sodium [55,57,58] and, thus, controls access to the epithelial sodium channels (Figure 1). Sodium channel activity and glycocalyx function are inversely related to each other. A plasma sodium concentration in the high-physiological range (>140 mM) reduces the negatively charged heparan sulphate residues of the endothelial glycocalyx [56], increasing the amount of sodium reaching the endothelial sodium channels, which in turn makes the channels more active [34,37]. The overall effect is that the barrier against sodium entry fails under these conditions and the endothelium becomes more permeable to sodium (Figure 2).

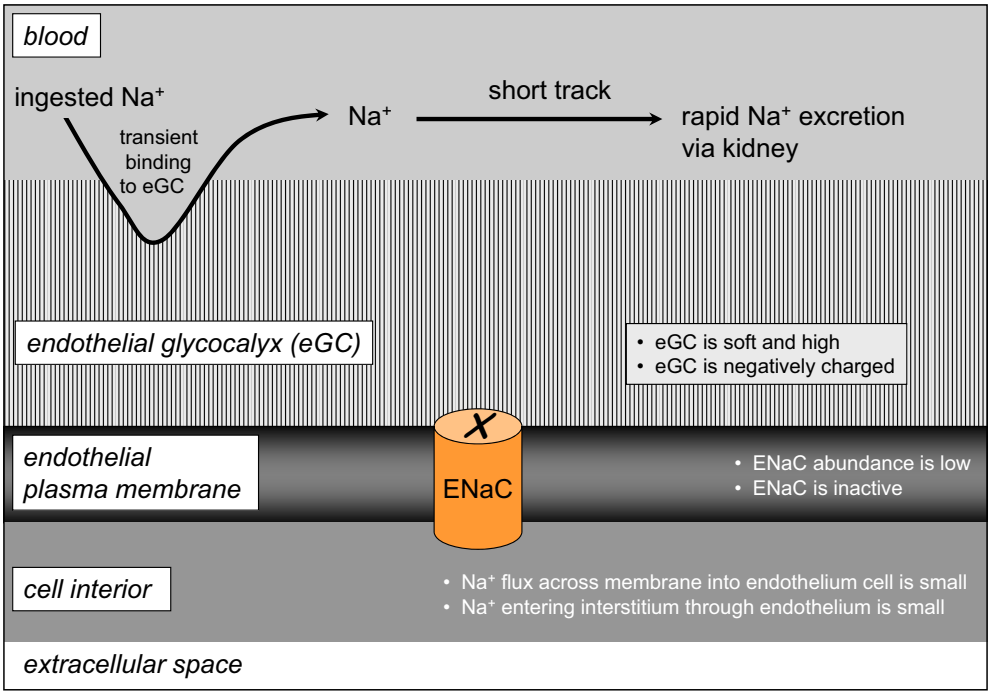
As indicated above, evidence for a salt-sensitive endothelial glycocalyx and its relationship to endothelial epithelial sodium channels is based on *in vitro* experiments and, at best, on *ex vivo* studies in human tissue (e.g. human umbilical veins). To our knowledge, there are no direct studies in humans. However, if aldosterone is viewed as a hormone that facilitates sodium retention and epithelial sodium channel expression in the vascular endothelium [14], then a link between salt and glycocalyx, albeit indirect, becomes visible. Clinical research often describes potentially important phenomena in the human without a mechanistic model. In this case, a mechanistic model based on *in vitro* experiments is available first, and it will be up to clinical research to test it in the human.

Salty food and sodium balance

After a salty meal, the translocation of sodium from the blood into the interstitium is delayed by the significant buffering capacity of the endothelial glycocalyx. Sodium will reversibly bind to/dissociate from the endothelial glycocalyx binding sites and, thus, can be readily excreted via the kidneys. Excessive sodium intake over time will damage the endothelial glycocalyx and lead to a decrease in its sodium buffering capacity because of the loss of negatively charged heparan sulphate residues. Following that, sodium gains direct access to the "unprotected" epithelial sodium channels. Thus, in addition to the paracellular transport route (i.e. sodium transport between endothelial cells along its chemical gradient), sodium uses the transcellular pathway for entering the large extracellular space (about 30% of body weight). There, sodium is bound reversibly to the extracellular matrix [59-63].

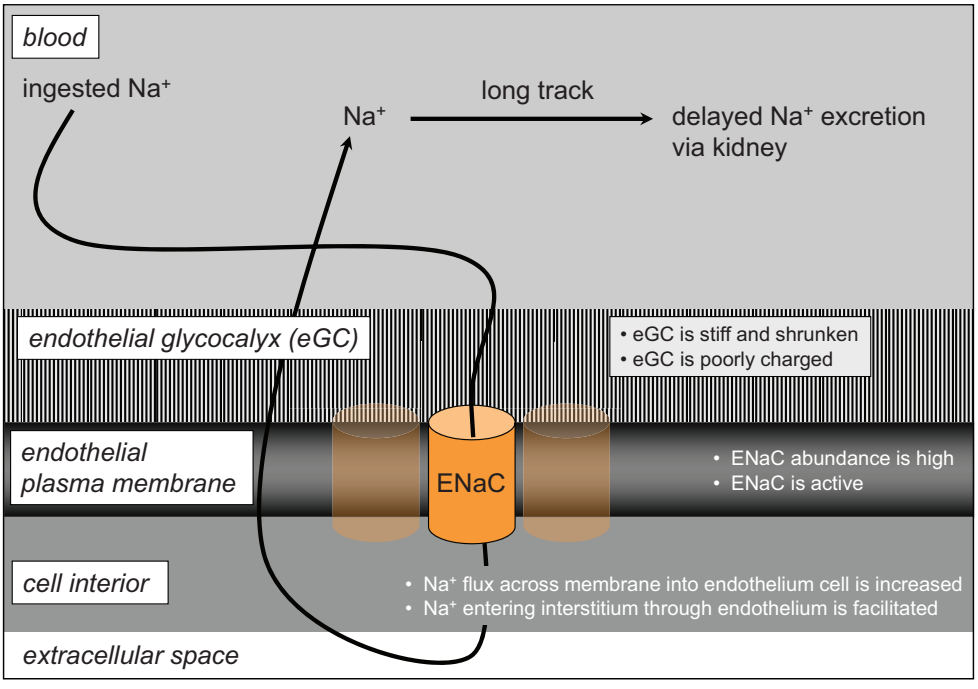
After the ingested sodium has spread throughout the body, the plasma sodium concentration decreases.

Figure 1. Model explaining *low* vascular sodium sensitivity



This state of vascular function is associated with low daily sodium intake, and/or low aldosterone and/or favorable genetics. Abbreviations: ENaC, epithelial sodium channel.

Figure 2. Model explaining *high* vascular sodium sensitivity



This state of vascular function is associated with high daily sodium intake, and/or high aldosterone and/or unfavorable genetics. Abbreviations: ENaC, epithelial sodium channel.

Now, sodium starts diffusing back into the vascular bed (along its chemical gradient directed from interstitium to blood) and will finally be excreted by the kidneys (Figure 2). This "detour of sodium" through the whole organism delays renal sodium excretion significantly. In the meantime, a sodium load from the next salty meal may arrive and so on, leading over time to sodium accumulation in the organism.

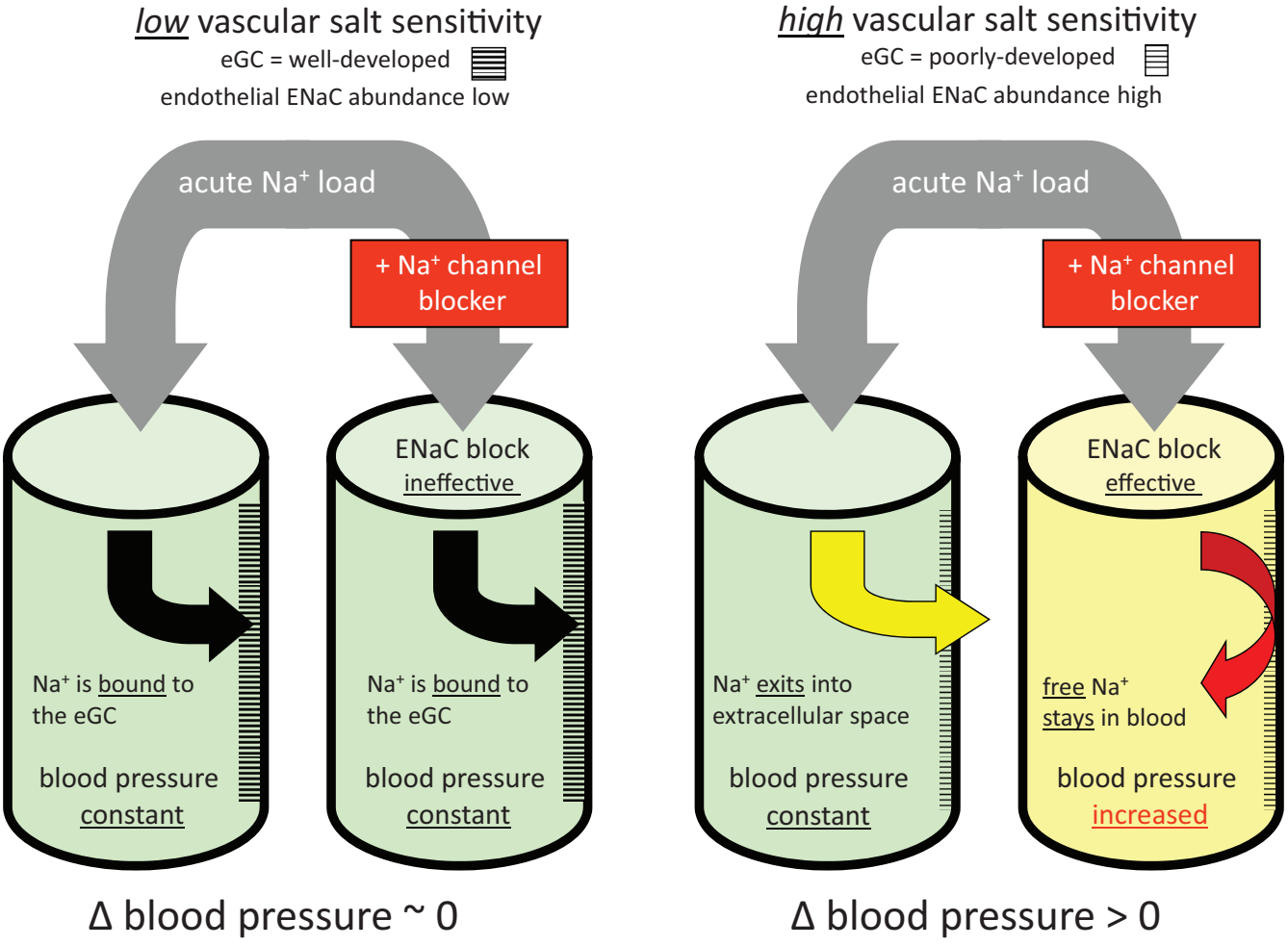
Salt provocation test

Vascular salt sensitivity can be defined as the ratio of "endothelial sodium channel activity over endothelial glycocalyx sodium buffer capacity". It should be noted that vascular salt sensitivity is not thought to be exclusively "congenital" [8,64-66] but could most likely be influenced (among other yet-unknown factors) by the amount of ingested salt and by endogenous aldosterone [67]. As salt sensitivity correlates positively with sodium channel activity in the endothelium, the blockade of these channels by amiloride analogues should help in identifying individuals with a high sensitivity to salt. Based on this concept, a *salt provocation test* has recently been published [68]. This test evaluates salt sensitivity in human subjects in quantitative terms. The test is described in general terms in Figure 3 (see figure legend and, for more details, see [68]).

Conclusions

The endothelial glycocalyx appears to be a key structure for regulating body sodium. *In vitro* studies show that the quality of this biopolymer layer is determined by the

Figure 3. Salt provocation test



The four cylinders symbolize the vascular system. After an acute Na^+ load (5 g NaCl orally), with and without addition of an epithelial sodium channel blocker (two separate sessions), blood pressure is measured over a period of one hour. The difference between these two measurements (Δ blood pressure) is evaluated. Low vascular sensitivity is indicated by a Δ ~ zero, high vascular sensitivity is indicated by a Δ > zero. Abbreviations: eGC, endothelial glycocalyx; ENaC, epithelial sodium channel.

abundance of its electrical negative charges. Loss of these surface charges renders the endothelial surface vulnerable to unwanted intruders, among them excessive sodium. We look forward to clinical research that will hopefully confirm these results *in vivo* in humans and substantiate the mechanism behind the protective effect of a low salt diet on the cardiovascular system.

Competing interests

The authors declare that they have no competing interests. The salt provocation test is covered by the authors pending patent number EP12154853.

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