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REVIEW ARTICLE

Properties of circulating blood cell membranes regarding sodium content in individuals suffering from essential hypertension

Charalabopoulos K

Department of Physiology, Clinical Unit, Medical Faculty, University of Ioannina, Ioannina, Greece

The aim of the present review article is to present a global view on perturbations of blood cells membranes which are observed in human essential hypertension. Especially, we are focused on erythrocytes and leukocytes sodium content, since the hypothesis that an increase in cell sodium is regarded to be a leading event in the hypertension process. Of course, essential hypertension is a multifactorial disease and exist several possible confounding factors that could be present in hypertensive patients affecting the erythrocyte and leukocyte sodium content. The major role of sodium pump in controlling the concentration of intracellular sodium, passive sodium permeability, sodium-potassium-chloride cotransport, sodium-hydrogene exchange, as well as some points on sodium intake, are also discussed.
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Erythrocyte sodium content

The term essential, primary or idiopathic hypertension is given for patients with arterial hypertension and definable cause. Essential hypertension appears a prevalence of 92-94% in general population (Table 1). One of the most widely popularized hypotheses relating cell ions to hypertension has been proposed by Blaustein, in which an increase in cell sodium was proposed as a leading event in the process[1]. Since the proposed increase in cell sodium was ascribed to inhibition of sodium pumps by a non-specific mechanism, investigators argued that the increase in cell sodium would be generalized and should affect blood cells. These were important experiments since if cell sodium was not increased then the hypothesis must fail irrespective of any changes in ion fluxes. In essential hypertension a different behavior of the membrane dynamic properties in the circulating blood cells is evident[2].

Erythrocytes as the most accessible cells in the body received most attention, and many studies of erythrocyte sodium in essential hypertension were reported. Studies that were performed up until the mid-1980s, have been reviewed by Hilton, who analyzed the results overall and suggested that there was a tension towards an increase in erythrocyte sodium content[3]. Nonetheless, individual studies have reported increases, decreases and no difference in erythrocyte sodium in essential hypertension compared with normal controls[4-12]. Some problems may have been due to some groups of patients that were too small or to subject variation as suggested by Hilton[3]. This is certainly a recipe for type 2 statistical errors. However, some studies showed quite marked elevations in erythrocyte sodium in essential hypertensives, whereas others found significantly lower values. Hilton affirmed that this phenomenon could not be explained by random variation. This suggests that the patients studied, or the methods used, or both, were causing important differences between studies.

It is usually said that essential hypertension is a multifactorial disease, so that it may not be surprising that different ways of approaching patients could unwittingly give rise to different subgroups. There are several possible confounding factors that could be present in hypertensive patients and may affect erythrocyte sodium. A high-salt intake appears to have little effect on erythrocyte sodium[11,13-15]. However, it is possible that there is a salt-sensitive subgroup which would be analogous to the Dahl salt-sensitive and -resistant rats where it is reported that only the former have increased erythrocyte sodium[16]. Increased dietary magnesium may decrease blood pressure and erythrocyte sodium, and increase sodium pump activity, but there is no evidence that the effect on blood pressure is via the effect on cell sodium[17]. Increased dietary calcium has also been reported to reduce both erythrocyte sodium and blood pressure in rats[18]. There may also be a sex difference, and one large study found that increased erythrocyte sodium was associated with hypertension in women but not in men[19]. Another question is whether the increased erythrocyte sodium is functionally related to the rise in blood pressure or whether it is a marker of susceptibility. There is good evidence of a strong genetic effect on erythrocyte sodium and evidence that alterations in sodium intake that affect blood pressure, have no effect on erythrocyte sodium[11,13-15,20,21]. Erythrocyte sodium has also been reported to be increased in hypertensives only if they have a family his-

Table 1. *Prevalence of various forms of hypertension in the general population.*

Diagnosis	General population (%)
Essential hypertension	92-94
Renal hypertension	3-5
Endocrine hypertension	~1
Miscellaneous	0.2

tory, and regardless of their blood pressure, which would suggest a marker of predisposition to hypertension[22].

Since sodium has so often been linked with hypertension in the popular view, the effects of sodium intake on cellular sodium metabolism has frequently been investigated. The majority of such studies have been unable to find an effect on erythrocyte sodium content, but several have nonetheless reported various alterations in sodium fluxes that may or may not depend on a family history of hypertension[11-15,23,24]. Some of these changes in the absence of a change in sodium content are at best difficult to rationalize. The rate constant for ouabain-insensitive sodium isotope flux is occasionally found to be altered, but this quantity is virtually uninterpretable and may well be no more than isotopic exchange with no net sodium movement. In support of a functional relationship there are several reports of a correlation between erythrocyte sodium and blood pressure with sodium chloride diet[25-27].

The possible effects of differences in methodology have also been discussed[28]. Sodium may accumulate in erythrocytes during the preparation time prior to measurement of sodium content. If the erythrocyte membrane in hypertension is different from that in normals then a more rapid accumulation of sodium could result. Normal unidirectional sodium flux is around 1,5-2mmol/h so that it could only take 3 or 4 min for a 0.1mmol increase in erythrocyte sodium content during preparation. Studies in which a very rapid erythrocyte separation technique has been used have in fact found a lower erythrocyte sodium content in essential hypertensives[5]. Changes in erythrocyte water occur very rapidly (seconds) with changes in osmolality or pH of the suspending medium, and this will cause apparent changes in ion content based on volume or weight of cells. It is well known that erythrocyte sodium content increases with cell age, so that in a mixed sample of erythrocytes, as has almost always been used in studies of hypertension, an older cell age distribution will give higher erythrocyte sodium contents. The increase in sodium content with cell age may also alter as appears to be the case in elderly subjects[29].

Although among mammalian cells the erythrocyte is relatively simple, it is still a complex mixture of charged molecules and structural lipid and protein components, which account for about a third of its volume and weight. It is the thermodynamic activity of an ion that is the biologically important variable. This may be related to he ion concentration if it is assumed that the activity coefficient is unchanged. However, such considerations have been ignored in studies of erythrocyte sodium. If erythrocyte water is increased, then an increase in sodium content may simply maintain a normal sodium ion concentration activity. There is evidence to suggest that erythrocyte water is increased in pregnancy-induced hypertension[30].

It would therefore appear that studies of erythrocyte sodium in hypertension have yielded little information due to a somewhat naove and simplistic clinical and physiological approach.

Leukocyte sodium content

The motivation for studying the sodium content of leukocytes was that they were considered to be more "typical" cells than erythrocytes. This is obviously true in so far as they have a membrane potential close to the potassium diffusion potential, functional sodium-proton exchange and an aerobic metabolism, all of which erythrocytes lack. However, they also present even greater methodological pitfalls.

To prepare an acceptably pure sample of leukocytes requires considerable manipulation and perturbation from their in vivo condition and the leukocyte plasma membrane is considerably more delicate than the erythrocyte cell membrane. The method almost always used to prepare mixed leukocytes for the study of ion content is first to sediment the bulk of erythrocytes by the addition of dextran of molecular weight about 500.000 to the blood[31]. This leaves a supernatant plasma containing leukocytes, platelets and contaminating erythrocytes. Slow-speed centrifugation at about 250g gives a pellet containing the leukocytes and erythrocytes. The leukocyte membrane is very sensitive to g-force and only slightly greater speeds will induce a sodium leak that will increase cell sodium content[32]. The contaminating erythrocytes are removed by hypotonic lysis of the cell pellet using a 10-s exposure to distilled water and restoration of osmolality with an equal volume of double-strength tissue culture medium. If the erythrocytes are not completely destroyed then the fragments will reseal containing tissue culture medium, and the sodium content of the leukocyte pellet, even after exhaustive washing, will be proportional to the volume of erythrocyte ghosts in the pellet[33].

The hypotonic exposure considerably disturbs the leukocytes, and their sodium content rises sharply on addition of the culture medium to anything up to 10 times the basal level. However, with careful handling the cells remain fit enough to recover during a 40-60min incubation to restore and then maintain their basal sodium content. The ability to do this must be demonstrated if the results are to be considered reliable. Even mechanical agitation of the cells in suspension can cause a significant increase in their sodium content[32].

Some studies of leukocytes have reported sodium contents in the region of 2.5nmol per million cells, with sodium: potassium ratios around 0.08-0.12. Unfortunately, most of the work on leukocyte sodium content in essential hypertension was done before cell-handling techniques had been refined, and the results must be treated with some caution. The sodium: potassium ratios for leukocytes from normal subjects were around 0.3, which would now be considered to be a non-viable cell preparation[34]. Even with severe uremia such values are now rarely observed[35]. These early studies in essential hypertension did in fact show a more uniformly increased level of sodium in leukocytes than was reported for erythrocytes, but it is quite possible that they are uniformly wrong due to a consistent methodological artifact. There were also many more studies of erythrocytes than leukocytes, so that the scope for disagreement was much less. A recent study could only find leukocyte sodium content to be increased in relation to obesity in hypertensives[36]. Leukocyte sodium in lean hypertensives was normal. As with erythrocyte sodium, so with leukocyte sodium the questions whether there is an effect of sodium intake, whether there is a mechanistic association with the rise in blood pressure or whether it is a marker of predisposition have attracted interest. Unfortunately there are few reports of leukocyte sodium content and more of isotopic sodium fluxes, although the latter can not be interpreted reliably without knowing the sodium content. Lymphocyte sodium was reported to be increased in some normotensive relatives of essential hypertensives, and 31% of such subjects were hypertensive on 5-year follow-up, whereas those with a normal lymphocyte sodium remained normotensive[37]. This would suggest a marker of predisposition, and agrees with some studies on sodium fluxes.

The ion content of leukocytes has generally been expressed in relation to either the dry weight of cells or the number of cells. As discussed above, the biologically important quantity is the activity of the ion, or at least its concentration in the cell water. This has not been measured in essential hypertension. In early studies on leukocytes an attempt was made to measure the cell water content, but this did not persist, probably because the method guess at the value[31]. The rapidly evolving fluorescent dye technology for measuring ion activities may be applicable to leukocytes.

However, the relation of in vivo measurements to in vivo values still needs to be resolved. Until relatively recently measurements of leukocyte ion content were made after the cells had spent some time in tissue culture medium. It is now clear that in the presence of homologous plasma the sodium content of leukocytes is greatly increased due to activation of sodium influx pathways, possibly sodium-proton exchange[38]. It is therefore difficult to evaluate the studies of leukocyte sodium in essential hypertension, but it seems likely that the cells as measured had suffered disruption to the extent of causing a substantial increase in their sodium content.

Sodium pump

The sodium pump has a major role in controlling the concentration of intra cellular sodium, and it was a center of interest as a possible cause of an increase in intracellular sodium as proposed by the original hypothesis. Figure 1 shows schematically the possible mechanism of sodium pump function. The most popular way of measuring sodium (usually ^{22}Na) or rubidium-86, the radioactive analogue of potassium. The technique gives a rate constant for sodium efflux or rubidium influx, and the ouabain-sensitive component is used as a measure of the sodium pump. However, the terminology has become rather loose and the rate constant (units of h^{-1}) is often referred to as an activity, which it is not. The activity (units of mmol of sodium or potassium transported/unit time/unit of cells) requires knowledge of the specific activity of the radioisotope in the compartment from which it is transported. This is rarely done, but is very important to allow interpretation of the results, because the proper function of the sodium pump is to pump out of the cell as much sodium as enters it at normal sodium content. If the rate of influx is low, then it would be appropriate for the rate of efflux and the rate constant to be low. A knowledge of the cell sodium content during isotope efflux experiments is important form another point of view. It is assumed that the decline in specific activity in the cell compartment from which it is transported is due to the rate of efflux. If there is net uptake of sodium from the medium then this will additionally reduce the specific activity of the isotope, which will therefore be less rapidly removed from the cell, leading to a possible underestimate of sodium pump activity. In view of the suggestion that cells from hypertensives are more susceptible to induced sodium leak, this possibility can not be dismissed lightly[28]. The measurement of sodium pump activity at a single non-saturating ion concentration has also been criticized[39]. Under such conditions theoretically a change in either the Michaelis constant (Km) or maximum velocity (Vmax) of the pump

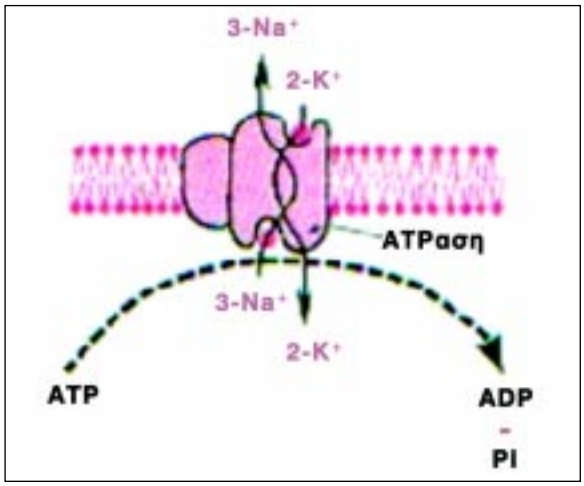

Fig. 1. *Mechanism of the Na^+-K^+ pump function*

could affect activity. More importantly a change in both Km and Vmax could occur in a way that has little effect on the activity at an arbitrary ion concentration. A comparison in erythrocytes has suggested that the rate constant is a reasonable estimate of available sodium pump activity, but that the relative contribution of Km and Vmax varies between subjects[40]. Since it is the purpose of the sodium pump to maintain a normal cell sodium concentration, it is surprising that so many studies have neglected to estimate the level of cell sodium. A reduced rate constant of the sodium pump has been reported in both erythrocytes and leucocytes in hypertensives, but other investigators have failed to find a difference[4,7,9-11,34,41-43].

The sodium pump has been measured on cells that have been washed repeatedly during the course of preparation for flux measurement. This would suggest that only defect found was intrinsic to the cell membrane, whereas the original hypothesis proposed a humoral factor that inhibited the sodium pump.

An analogy of the sodium pump inhibitor hypothesis of hypertension is the treatment of patients with the sodium pump inhibitor digoxin. Studies of such patients have shown that on commencement of digoxin treatment there is a sharp rise in erythrocyte sodium content due to inhibition of the sodium pump, but that after a few weeks of continuing treatment the erythrocyte sodium content has returned to normal, due to the recruitment of additional sodium pumps.[44] There seems to be no reason to believe from this, that a circulating sodium pump inhibitor would do more, than cause a transient rise in cell sodium unless other defects were present. Nonetheless correlation of sodium pump inhibition with blood pressure has been reported, and an acute saline infusion to increase blood pressure may also increase sodium pump inhibitor activity in the subject's plasma[45,46]. However, suggestions of a causal relationship between the changes in cell sodium and blood pressure should be treated with caution. The case for a plasma-borne inhibitor of the sodium pump has been discussed[47]. There are many qualitative data but the inhibitor remains elusive[48-52]. There is even evidence from leukocyte studies that non-esterified fatty acids can act as a sodium pump inhibitor[53]. This returns to the question of whether differences in cell sodium metabolism are markers of a predisposition or related to the mechanism of blood pressure elevation. One study of the leukocyte sodium pump reported that the sodium pump rate constant in essential hypertensives was low, but that it was also low in first degree relatives of the hypertensives[54]. This would suggest an intrinsic defect in the sodium pump, but not causally related to the development of hypertension. However, whether such a low sodium pump rate constant can be regarded as a defect can only be judged in relation to whether a normal cell sodium was maintained, and this was not reported.

It is surprising how many ways sodium intake can be varied, and the results interpreted to aid the confusion of the reader. In one study sodium restriction had no effect on leukocyte sodium or blood pressure in normal controls, but in essential hypertensives blood pressure was reduced and a low total sodium isotope efflux rate constant (i.e. including passive isotope exchange, etc) was increased towards normal. This was interpreted in favor of a circulating sodium pump inhibitor[55]. In another study in normotensive relatives of hypertensives sodium restriction reduced blood pressure and increased the ouabain-sensitive sodium efflux rate constant (i.e. sodium pump). This was interpreted against a circulating sodium pump inhibitor and in favor of genetic predisposition[21,56-58]. It seems unlikely that sodium diet affects sodium pump activity, although a decrease in sodium pump rate constant, from an elevated value towards normal, with increased sodium intake has been observed in hypertensives[11,13,14,24]. In leukocytes a decreased rate constant with sodium depletion has been found, but this is opposite to the change expected by the original hypothesis[23]. Alterations in sodium diet may also modify sodium pump inhibitor activity in plasma in relation to the change in blood pressure[59]. Differences in the erythrocyte sodium pump or its response to changes in sodium diet in hypertensives have also been reported to be dependent on or independent of the presence of a family history.[15,45]

Hyperinsulinemia and insulin resistance have been implicated by some investigators as having a possible role in the development of hypertension. Erythrocyte sodium and blood pressure were higher in a group of hyperinsulinemic subjects, but in another study the increased plasma insulin in essential hypertensives had no relation to increased erythrocyte sodium[44,60]. It has also been shown that insulin stimulates leukocyte sodium pump activity in vivo and in vitro, so that a causative link between insulin and hypertension via raised cell sodium due to sodium pump inhibition is difficult to envisage[61,62].

It is difficult to escape the conclusion that hypertension is really no more than a clinical sign, perhaps at best it can, as suggested by some, claim the status of a syndrome[63]. It hyperglycemia was treated in the same way it may well be decided that insulin had nothing to do with it, since it is increased in some and decreased in others. The most comprehensive attempt to classify hypertensives by their sodium fluxes had the uncomfortable feeling of a self-fulfilling prophesy in that hypertensives selected for having a low sodium pump activity would of course have a low sodium pump activity[64]. The modulating/non-modulating subgroups do not appear to have differences in sodium pump activity[65].

Somewhat at variance with the original hypothesis, there have been several studies where sodium pump activity was increased in hypertensive patients[12,66] A hypothesis has been proposed suggesting how this could give rise to hypertension[67]. In addition, a genotype of high sodium pump numbers in the cell membrane has been reported and women identified with this genotype had an earlier hypertension[68].

Therefore, despite much data, the sodium pump has provided no answers. Perhaps a component that is fundamentally linked to the most basic survival function of the cell is unlikely to alter drastically unless as an appropriate response to maintain cell function. The suggestion that a sodium pump inhibitor could modulate sodium reabsorption in the renal tubule may also be flawed, rather like supposing that the speed of a car can be controlled by the amount of petrol placed in its fuel tank.

Passive sodium permeability

Several authors have demonstrated increase passive sodium flux in erythrocytes from patients with essential hypertension, although very few attempts have been made to determine the mechanism of this increased flux[69-73]. Fitzgibbon et al detected increased total sodium efflux from erythrocytes of hypertensive patients compared to normotensive controls only when cells were incubated in their own plasma[69]. Etkin et al reported increased sodium influx into ouabain-treated cells in white but not black essential hypertensive patients[70]. Similar findings have been reported by Mahoney et al and Postonov et al[71,73]. Wessels and Zumkley reported that a rise in passive sodium permeability was predominantly responsible for increased sodium flux seen in hypertensive patients with a contribution from increased sodium countertransport[74].

Sodium – potasium – chloride cotransport (COT)

The sodium-potassium cotransporter mediates passive flux of Na^+-K^+-$2Cl^-$ ions across the erythrocyte membrane in a bidirectional fashion depending on the prevailing concentration gradients and is inhibited by the loop diuretics furosemide and bumetanide[75]. Whilst this transporter may contribute to net changes in sodium or potassium the effects are normally equal in each direction under physiological conditions[76]. Cotransport activity is very low at normal erythrocyte sodium concentrations. Therefore, activity is measured after raising erythrocyte internal sodium to supra-physiological levels by exposure to parachloromercuribenzene sulphate (20h) or nystatin (20 min) to enhance membrane permeability during the loading procedure. The furosemide – sensitive actward flux of sodium and potassium into sodium –and potassium free media is then measured. The literature is controversial regarding the activity of the contransporter in essential hypertension. Initially, Garay et al reported reduced cotransport activity in hypertensive subjects compared to normal controls, with very little overlap between the normotensive and hypertensive groups[75,77]. Garay et al also reported reduced cotransport activity in normotensive subjects with a family history of hypertension, and suggested an inherited component[78]. However, subsequent studies have failed to demonstrate this clear distinction between normotensive and hypertensive groups, and other investigators have reported normal and elevated cotransport activities in hypertensive patients[79-82]. Scrutiny of the literature reveals differences in methodology which provide some explanation for the discrepancy in reported findings. Authors have quoted only the transport rate or the rate constant assuming linear relation of rate to sodium concentration and not the kinetic characteristics of the cotransport, i.e. Vmax and Km. Variations in the loading procedure between studies led to large variation in the intracellular sodium concentration, i.e. Garay et al internal sodium concentration 20-30mmol/l and Adragna et al 50mmol/l[75,82]. The Km for sodium efflux is around 13mmol/l for the contransporter[39]. Thus, in the experiments of Adragna et al which reported elevated contrasport activity in hypertensives the cotransporter was approximately 80% saturated, i.e. close to Vmax, whereas in the study of Garay et al the cotransporter was only 60% saturated, which helps to explain the discrepant results if there was a change in Km in hypertension[75,82]. Another methodological factor which may influence the contrasport activity is the composition of the external medium; magnesium (75mmol/l) is commonly used, and inhibits the cotransporter by 50-70%[83]. Despite methodological problems genetic and environmental factors have been found to influence the activity of the cotransporter. Several studies have investigated the influence of race on the cotransport activity. The majority of studies reported reduced furosemide-sensitive sodium efflux in black hypertensive patients, and in some studies also in black normotensive subjects[84-87]. Canessa et al reported reduced potassium contransport in blacks, which was positively correlated with increased body wieght[88]. A twin study similarly supported the influence of genetic factors on cotransport activity[85]. Environmental factors found to influence cotransport activity include hypokalaemia and alterations in membrane lipid composition[89]. Duhm and Behr reported reduced cotransport activity in the presence of increased erythrocyte membrane cholesterol content[89].

Sodium – hydrogen exchange

The sodium-hydrogen exchanger is a ubiquitous transport system which has been suggested to be involved in the regulation of intracellular pH, cell growth and proliferation, control of cell volume and sodium reabsorption in the renal proximal tubule (Figure 2). This transporter exchanges one sodium with one hydrogen ion, and is inhibited by amiloride and its analogues. Energy for sodium-hydrogen exchange is derived from the inwardly directed sodium gradient maintained by sodium-potassium ATPase activity[90,91]. The sodium-hydrogen exchanger can operate in several exchange modes, for example accepting a sodium lithium or amonium ion instead of a hydrogen ion[90,92,93]. Altered activity of the sodium-hydrogen exchanger has been implicated in the development of hypertension and in patients with essential hypertension[94]. Several mecha-

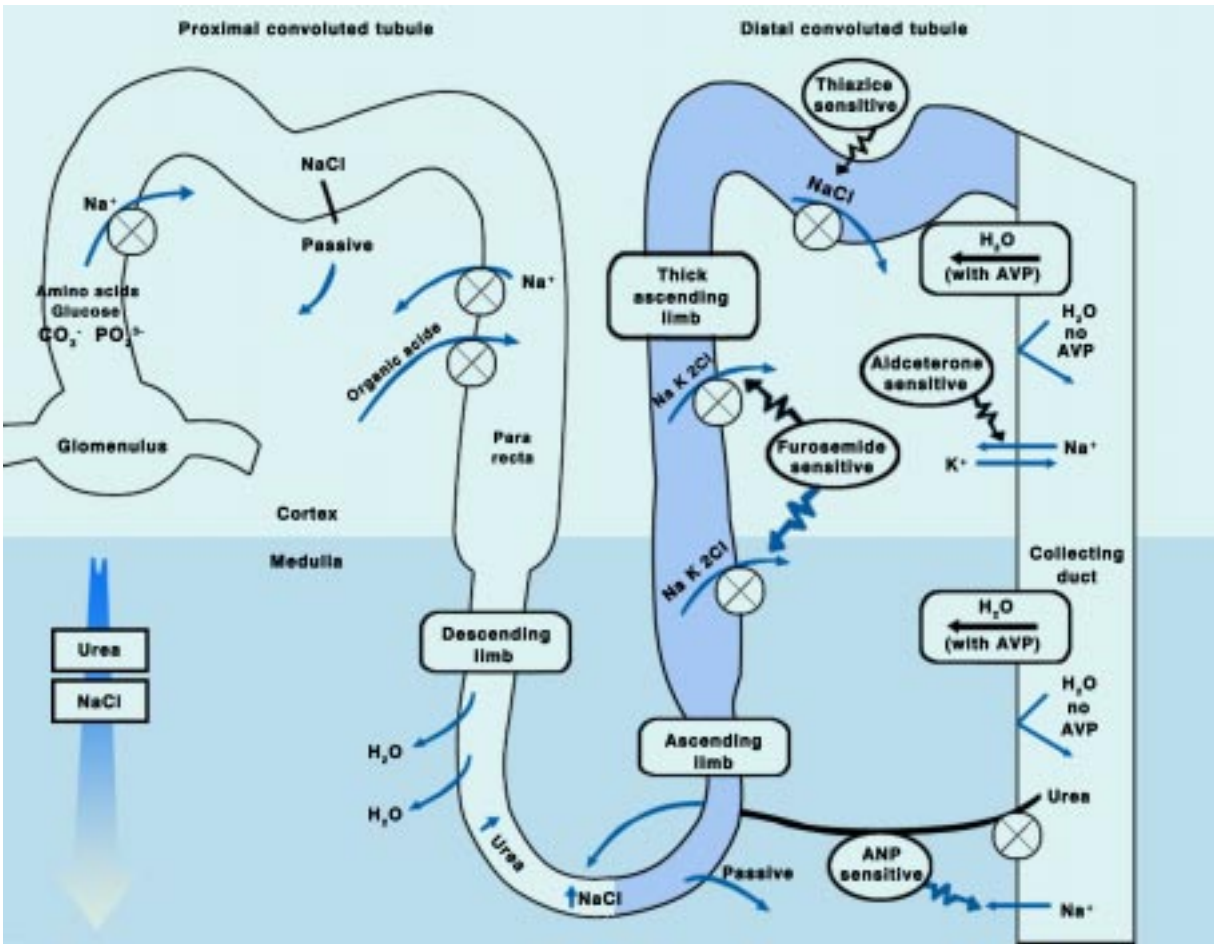

Figure 2. *Transport functions of the various segments of the nephron in humans*

nisms have been proposed by which increased activity of the plasma membrane sodium-hydrogen exchanger in cells other than blood cells could play a pathophysiological role in the development of hypertension:

i. Increased sodium-protein exchange in vascular smooth muscle cells may lead to elevated intracellular sodium concentration (if the sodium pump in inhibited) and thereby elevated intracellular calcium concentration via the sodium-calcium exchanger. This increase in intracellular calcium may lead to increased vascular tone, vasoconstriction and elevated peripheral vascular resistance[1,90,91,95].

ii. Elevated intracellular pH (in bicarbonate- free medium) may facilitate cell proliferation in vascular smooth muscle cells leading to vascular hypertophy[90,91].

iii. Increased sodium-hydrogen exchange in renal proximal tubule could lead to net increase in sodium reabsorption and thus volume expansion[90,96,97].

Several studies have reported elevated sodium-hydrogen exchange activity in patients with essential hypertension. Livine et al demonstrated increased sodium-hydrogen exchange (measuring amiloride-sensitive sodium –dependent volume gain in the presence of sodium proprionate) in platelets from patients with essential hypertension compared to normotensive controls[98]. Ng et al similarly reported elevated amiloride-(and bumetanide)-sensitive influx of radiolabelled sodium in leukocytes from essential hypertensive patients compared to controls[99]. This group also demonstrated a lower resting intracellular pH and reduced suffering capacity in leukocytes of hypertensive patients[100]. Some studies report similar findings in platelets and leukocytes[101-103]. Schmander and Weder detected elevated sodium-hydrogen antiport activity in platelets from hypertensive subjects, and reported a correlation with diastolic blood pressure. In this study there were no racial differences in sodium-hydrogen antiport activity[101].

The sodium-lithium countertransport activity in a subgroup of hypertensive patients showed no correlation to the sodium-hydrogen antiport activity. Since Canessa reported elevated sodium-lithium countertransport activity in essential hypertension the pathophysiological role of the sodium-lithium countertransporter has been difficult to see, and several authors suggested it to be a mode of operation of the sodium-hydrogen exchanger[81,104,105]. In the presence review article we are not focused on this point in further detail.

Περίληψη

Κ. Χαραλαμπόπουλος. **Ιδιότητες των κυτταρικών μεμβρανών των κυκλοφορούντων κυττάρων του αίμα-**

τος σχετικά με το περιεχόμενο νάτριο, σε ασθενείς με ιδιοπαθή υπέρταση. ***Ιπποκράτεια 7 (4): 159-167***

Σκοπός του παρόντος άρθρου ανασκόπησης είναι να παρουσιάσει μια σφαιρική όψη επί του θέματος των διαταραχών της κυτταρικής μεμβράνης των ερυθρών αιμοσφαιρίων και των λευκοκυττάρων, που παρατηρούνται σε ασθενείς πάσχοντες από ιδιοπαθή υπέρταση. Στο όλο θέμα γίνεται επικέντρωση στο περιεχόμενο νάτριο των ερυθροκυττάρων και των λευκοκυττάρων καθώς είναι πολύ διαδεδομένη η θεωρία ότι τα αυξημένα ενδοκυτταρικά επίπεδα νατρίου, αποτελούν κυρίαρχο χαρακτηριστικό στην όλη υπόθεση της υπέρτασης. Βεβαίως, η ιδιοπαθής υπέρταση είναι μια πολυπαραγοντική νόσος καθώς υφίστανται διάφοροι πιθανοί συνεισφέροντες παράγοντες που δυνατόν να επηρεάσουν το περιεχόμενο νάτριο των ερυθροκυττάρων και των λευκοκυττάρων. Ο μείζων ρόλος της αντλίας νατρίου στον έλεγχο των σταθμών του ενδοκυτταρικού νατρίου, η παθητική διαβατότητα, η συμμεταφορά νατρίου-καλίου-χλωρίου, η ανταλλαγή νατρίου-υδρογόνου καθώς και μερικά σημεία επί του θέματος της διαιτητικής πρόληψης νατρίου, αναφέρονται στην παρούσα εργασία.

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Corresponding author: Charalabopoulos K.A - 13, Solomou street - 452 21 Ioannina, Greece
Υπεύθυνος αλληλογραφίας: Κ.Α. Χαραλαμπόπουλος - Σολωμού 13, 452 21 Ιωάννινα