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REVIEW ARTICLE

Dietary potassium intake and blood pressure: possible beneficial effect of Paleolithic diet.

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ABSTRACT

Potassium is one of the most important elements of human organism. Its main distribution in the intracellular space makes it an essential component of intracellular volume regulation on the other hand extracellular/ intracellular potassium ratio determines the resting membrane potential. This later capability of potassium makes essential the necessity of maintaining extracellular potassium levels in a narrow range limit between 3.5 and 5.5 mEq/L in order to avoid dangerous dysfunction of excitable cells such as myocardium, neuronal cells and muscle cells. Because of asymmetric potassium distribution between intracellular and extracellular space there is a continuous need to excrete the excess of potassium ingested by food in a diurnal basis. The main site of potassium excretion is the distal nephron and it is coupled directly with the amount of sodium and solute delivered to this segment of the nephron. Although the very early segment of distal convoluted tubule has no ability to excrete potassium it is capable to regulate the amount of sodium chloride delivered downstream the nephron and by this way is implicated indirectly in potassium excretion. Newer data suggest that this segment of the nephron responds to increased extracellular levels of potassium by reducing sodium chloride cotransporter activity and so increases sodium delivery to distal nephron for exchange with potassium and leads to kaliuresis as well as natriuresis. It is believed that this mechanism is responsible for the beneficial effect of increased potassium intake in ameliorating hypertension even in cases of increased salt intake. In this review article, under the light of recent discoveries, we try to elucidate the complex underlying mechanisms of increased potassium intake and blood pressure regulation as well as the possible beneficial effect of Paleolithic diet upon hypertension.

Keywords: potassium intake, extracellular potassium, intracellular chloride, blood pressure, paleolithic diet.

Introduction

Potassium is one of the most interesting minerals in human organism. Its main distribution in the intracellular space renders it one of the most important regulators of cell volume whereas the ratio of extracellular/ intracellular potassium concentration is the main regulator of resting membrane potential. These fundamental potassium capabilities make it an essential component of normal cell function and survival[1].

It is estimated that the total amount of potassium content of a normal human adult is about 3,500 mEq. The vast majority of potassium is distributed in the intracellular space (98 %) and only 2 % (about 70 mEq) is distributed in the extracellular space. This discrepancy needs a continuous and strict regulation of extracellular potassium concentration between 3.5 and 5.5 mEq/L whereas the intracellular potassium concentration is estimated to be between 120 and 140 mEq/L[1].

The main source of potassium for humans is the dietary consumption of plant derived foods. The regulation of potassium balance needs the interplay of gastrointestinal tract and the kidneys. It is estimated that 90 % of daily ingested potassium is excreted by the kidneys and the remaining 10 % is excreted by the feces. Because of the need to keep extracellular potassium levels in a strict narrow normal range human organism, after potassium absorption from gastrointestinal tract, quickly distributes it in the intracellular space, mainly the skeletal muscles, liver, bones and erythrocytes, until the kidneys excrete effectively the positive potassium burden obtained by the food in order to avoid death from hyperkalemia[1].

Very early observations, dated from the 19th century, showed that potassium ingestion leads to increased excretion of potassium as well as sodium by the kidneys. These and subsequent observations showed that the manipulation of sodium by the kidneys is coupled with the amount of potassium ingested[2,3].

From the beginning of 20th century it became evident that the prevalence of hypertension was high among the industrialized communities whereas it was very rare or even absent among underdeveloped or isolated communities. This discrepancy was attributed mainly to the dietary habits of industrialized communities focusing upon the increased amount of salt consumption either as a food preservative or as a spice[4].

In advance it became evident that the anion which accompanies the sodium, namely chloride, plays an important role in the pathogenesis of hypertension because substitution of sodium chloride with equal amount of sodium bicarbonate or sodium citrate failed to increase blood pressure. Furthermore the increased consumption of potassium rich diets was capable to reduce the levels of blood pressure even among individuals with high salt consumption[5,6,7,8].

These findings put ahead the investigational interest the possibility that chloride anion and potassium cation are the mediators of salt sensitivity which characterizes the salt sensitive hypertension and raised a considerable concern about the dramatic change of dietary habits and life style of mankind during the last ten thousand years after the evolution of agriculture and soon thereafter the evolution of livestock[9,10].

It is now believed that the evolution of mankind during the previous 7 million years ensured our ancestors with functional kidneys adapted properly to dietary habits and life style of Paleolithic man. It seems likely that the modern man although changed dramatically his dietary habits continuous to "wear" a Paleolithic kidney[11,12].

In this review article we'll try to elucidate the crucial role of extracellular potassium and intracellular chloride levels in determining the sodium chloride reabsorption and potassium excretion by the distal nephron which in turn determines the blood volume and hence blood pressure regulation. We focus also upon the beneficial effect of potassium rich and sodium deficient diet such as the natural diet of humans during their Paleolithic period of evolution.

1. Potassium homeostasis.

The main potassium sources for humans are the plant derived foods and in a lesser degree dairy products and meets. According to the National Institutes of Health (NIH) the adequate daily intake for potassium is estimated to be 3,400 mg (87.2 mEq) for males and 2,600 mg (66.7 mEq) for females aged 51+ years[13].

After potassium ingestion 90 % is absorbed in small intestine and 10 % is excreted in feces, this percentage is generally unaffected by the amount of potassium ingested. Increased potassium ingestion in humans showed only a slight increase of potassium excretion in feces (5 mEq/day of potassium for each 50 mEq/day of potassium ingested). Studies in animals and humans showed that about 10 mEq of potassium per day are passed from the ileum to the colon. Human colon exhibits a dual capacity to absorb and excrete potassium. It is estimated that human colon absorbs about 5 mEq/day of potassium and excretes an equal amount 5 mEq/day of potassium[14].

There is no definite mechanism for active potassium absorption in small intestine instead it passes in the circulation via a passive mechanism known as solvent drag phenomenon. Conversely there is sufficient evidence to support active potassium absorption in colon via the apical H^+/ K^+ –ATPase and active potassium excretion via the apical big potassium (BK) channel which is up-regulated in case of compromised renal potassium excretion such as chronic kidney disease[14].

After potassium absorption from the intestine human organism quickly redistributes potassium in the intracellular space so that potassium levels variation in serum does not exceed 10 % during the day irrespective of total amount of potassium ingested. This goal is achieved via two distinct potassium homeostasis processes: the external and internal potassium homeostasis[15].

External potassium homeostasis is achieved via the renal potassium excretion in order to balance the amount of potassium ingested minus the extra renal losses of potassium. A circadian rhythm of renal potassium excretion is established with the highest excretion rates in the midday and the lowest in midnight. Internal potassium homeostasis is achieved via the asymmetric potassium distribution between the intracellular space (98 %) and extracellular space (2 %)[15].

1.1. INTERNAL POTASSIUM HOMEOSTASIS.

Internal potassium homeostasis is triggered immediately after potassium absorption because the amount of daily potassium

ingested far exceeds the total amount of extracellular potassium (~65 mEq) and possess the threat of sudden death because of hyperkalemia. The key molecule for internal potassium homeostasis is the Na^+/ K^+-ATPase which moves potassium inside the cell and extrudes sodium outside the cell in a stoichiometry of 2 K^+/3Na^+[15].

Apart from active potassium pumping inside the cell there is also a continuous passive potassium leak outside the cell (leak rate). The sum of these two potassium movements constitutes the internal potassium balance which leads to intracellular potassium accumulation mainly in muscles, about 80 %, and the remainder is distributed in liver, bones and erythrocytes. The activity of Na+/ K+-ATPase, and hence the intracellular potassium movement, is affected by insulin, catecholamines and mineralcorticoids. Absorption of sugars together with potassium contained in the meals increase the secretion of insulin which in turn increases Na+/ K+-ATPase activity and facilitates the intracellular movement of potassium[15].

Recent data suggest that there is a crosstalk between skeletal muscles and kidney and between gut and kidney in order to achieve a better and effective external balance of ingested potassium.

McFarlin et al[16] showed in an experimental study in mice that potassium deprivation of their diet produced a considerable decrease of intracellular potassium concentration in gastrocnemius and soleus muscle with concomitant increase (doubling) of intracellular sodium concentration and a considerable decrease in potassium excretion by the kidneys. These changes were accompanied with an array of changes in the activity of certain transporters and proteins in muscles and kidney. In precise authors found a considerable decrease in the expression of Na^+/K^+-ATPase isoform α2-β2 and increased expression of potassium-chloride cotransporter KCC3 in hindlimp muscle where as they found an increase in phosphorylated sodium chloride cotransporter (pNCC) and ste-20-proline-alanine rich (SPAK) kinase and oxidative-stress responsive kinase-1 (OSR1) kinases in distal nephron. These changes led to a decrease in renal potassium excretion of 98 %. The net result after 10 days of diet with zero potassium content was the shift of ~ 47 μmol of potassium from the intracellular to extracellular space and the loss of ~ 48 μmol of potassium in urine.

In another experimental study in humans Preston et al[17] showed that an acute potassium load in the form of KCl accompanied with or without meal exhibited an acute potassium excretion (in 60 minutes) from the kidneys and this effect of potassium loading persisted after administration of a mineral corticoid receptor blocker (eplerenone) indicating that this kaliuretic effect of potassium is at least part independent of aldosterone. These findings suggest the existence of a feedforward mechanism for renal potassium excretion in parallel to the well-known feedback mechanism, but the signals and effectors of the previous mechanism are still not well known.

1.2. EXTERNAL POTASSIUM HOMEOSTASIS. External potassium homeostasis is achieved mainly via the kidney (90 %) and in a lesser degree by colon (10%). The human kidney effectively excretes the amount of daily

potassium ingested even if it reaches 500-600 mEq/day.

Rabelink et al[18] showed experimentally in humans that acute (72 hours) and chronic (20 days) potassium loading (400 mmol/day divided in four equal meals) are effectively manipulated as follow: during the first 72 hours potassium loading produces a transient rise in serum potassium level, aldosterone levels and increased kaliuresis. Renal potassium excretion equal to 80 % of potassium ingested achieved after the second 24 hours of acute potassium loading and was followed with increased serum potassium levels, aldosterone levels, increased renin activity and increased sodium excretion. After 20 days of potassium loading natriuresis was ceased and renin activity and aldosterone levels returned to baseline values although aldosterone and kaliuresis showed transient increments after each potassium meal. Abrupt discontinuation of potassium loading produced a prolonged potassium loss for the next 24 hours and increased natriuresis for the next 72 hours[18].

The amount of potassium filtered in Bowman's space is mostly reabsorbed in proximal convoluted tubule (65 %) and in a lesser degree (25 %) in the thick ascending limp of Henle's loop (TAL), the remainder 10 % is manipulated in distal nephron, namely distal convoluted tubule (DCT) and cortical collecting duct (CCD), either excreted or reabsorbed according to the needs of potassium status (hyperkalemia or hypokalemia)[19].

Potassium reabsorption in proximal tubule is mainly accomplished through the paracellular way together with sodium and water. This mechanism is known as solvent drag phenomenon and represents the main component of potassium reabsorption in PCT but there is evidence of transcellular potassium reabsorption, although in a lesser degree, by diffusion in this segment of the nephron[19].

The loop of Henle shows a pivotal contribution in potassium transport. The thin descending limp excretes potassium in tubular lumen whereas the thin ascending limp absorbs potassium from the tubular lumen. Both movements are passively accomplished through potassium diffusion. The thick ascending limp drives potassium inside the cell via the apical membrane sodium-potassium-2 chloride cotransporter (NKCC2) and excretes potassium in tubular lumen via the renal outer medullary potassium channel (ROMK) also presented in the apical membrane. This potassium recycling is necessary for the proper function of NKCC2 as well as the generation of positive tubular charge which is necessary for the paracellular reabsorption of positive charged ions such as sodium, calcium and magnesium[19].

Potassium transport in distal nephron is vital for external potassium homeostasis because in this segment of the nephron is accomplished the fine tuning of potassium balance according to the amount of potassium ingested. In case of normal or increased potassium ingestion the excess potassium has to be excreted whereas in case of decreased potassium ingestion potassium balance has to be conserved either by decreasing potassium excretion and/or increasing potassium reabsorption.

The term distal nephron is referred to: early DCT, late DCT, connecting tubule (CNT) and CCD and is also known as aldosterone -

sensitive distal nephron (ASDN) because represents the main site of aldosterone action. For many years it was believed that CCD was the main site of sodium and potassium balance mainly because of technical difficulties in investigating the role of DCT and CNT but newer findings suggest the importance of these two parts of renal tubule and that the CCD is recruited under extraordinary conditions of very low sodium intake and very high potassium intake[20].

The epithelial cells of ASDN exhibit different functional properties and have different embryologic origin. The collecting duct is originated from the ureteric dud whereas the DCT is originated from the metanephric blastema. The CNT is composed from cells of both origins and represents a hybrid epithelium. The epithelial cells of ASDN are composed of two different populations: the principal cells and the intercalated cells. Principal cells are more abundant and represent 60 % of cell population whereas intercalated cells represent 40 % of the population. Early DCT (DCT1) is composed primarily from principal cells whereas intercalated cells appear from the late DCT. Intercalated cells are of two types the alpha (a) and beta (b), a-intercalated cells excretes acid in tubular lumen whereas the b-intercalated cells excrete bicarbonate in tubular lumen. Under circumstances of low potassium intake intercalated cells are capable to absorb potassium and excrete hydrogen via the H^+/K^+-ATPase located at the luminal membrane of both cell types[21].

The main channels which regulate potassium excretion in ASDN are the renal outer medullary potassium channel (ROMK) and the big potassium (BK) channel. Both channels are expressed at the luminal membrane of distal nephron epithelial cells and exhibits different potassium conductance capacity. ROMK in TAL forms a 70 pS potassium conductance channel whereas in CCD forms a 30 pS potassium conductance channel. ROMK is activated by external K^+, phosphatidylinositol 4,5- bisphosphate and protein kinase A (PKA). BK exhibits a higher capacity of potassium excretion and forms a 150-200 pS potassium conductance channel and is expressed in principal as well as intercalated cells. BK is activated by the luminal stretch produced from increased luminal flow of solute as well as by increased intracellular Ca^{++} concentration. Both channels are activated also by aldosterone. Under basal conditions the majority of potassium ingested is excreted via ROMK channel because it exhibits a higher open probability (Po) but in cases of increased potassium ingestion BK is recruited and excretes the excess potassium ingested[22].

Potassium excretion in TAL is coupled with the activity of NKCC2 located at the luminal surface of TAL. Actually ROMK recycles potassium to the lumen of TAL because it is necessary for proper function of NKCC2 and to generate positive transepithelial voltage of about +5 to +10 mV which are necessary for the paracellular absorption of positive cations such as Na^+, Ca^{++} and Mg^{++}. Potassium excretion in ASDN is mainly coupled with sodium reabsorption via the Epithelial Sodium Channel (ENaC) located also in the luminal membrane of epithelial cells. Sodium reabsorption via ENaC is electrogenic and produces depolarization of cell membrane as well as lumen negative transepithelial voltage between -5 and -10 mV which facilitates

potassium excretion via ROMK. The activity of both channels is increased by aldosterone[23].

Although DCT1 has no capacity of excreting potassium it plays a crucial role in potassium excretion in distal nephron because regulates the amount of solute and sodium delivered to the downstream segments of nephron and hence affects indirectly the activity of ENaC and ROMK. The overall process of potassium excretion and sodium reabsorption in ASDN is a complicated procedure with many steps remaining ill-defined until now but there is sufficient evidence suggestive of the crucial role of extracellular potassium and intracellular chloride concentration in the regulation of this process which affects the sodium sensitivity and points to the important role of potassium rich diet in controlling hypertension even in cases of increased salt consumption.

2. Sodium and potassium interplay in distal nephron epithelia.

Distal nephron plays a crucial role in sodium and potassium balance because this segment of the nephron is beyond the regulatory effect of tubuloglomerular feedback and hence the amount of sodium which escapes reabsorption in this segment of the nephron is lost in urine and possesses the threat of extracellular volume depletion. Moreover, as described above, distal nephron is the main site of external potassium balance. It is obvious that this segment of the nephron has to achieve a delicate balance between these two important cations in order to ensure the proper conservation of extracellular volume and extracellular potassium concentration.

Numerous experimental studies in animals and humans have showed unequivocally that potassium excretion in distal nephron is coupled with sodium reabsorption and this process is activated by aldosterone but there is also robust evidence suggesting the important role of DCT1 in mediating potassium homeostasis via the action of NCC which determines the amount of sodium and solute delivered downstream the ASDN. In order to achieve this difficult mission distal nephron epithelial cells have acquired special morphological and functional capacities through the evolutionary adaptation process over the past 7 million years of human kind evolution according to his dietary habits[20,21].

The main sodium and chloride transporter in DCT1 is the sodium-chloride cotransporter (NCC) located at the luminal membrane of the cell and carries sodium and chloride inside the cell in a stoichiometry of 1:1. Expression of NCC is almost exclusively confined in this segment of the nephron and its presence characterizes DCT1. The driving force for sodium and chloride transport is the low intracellular concentration of sodium maintained by the activity of Na^+/K^+-ATPase located in the basolateral membrane of the cell. NCC activity is regulated by salt and potassium consumption: high salt intake suppresses NCC phosphorylation (pNCC) whereas low salt intake increases pNCC on the other hand low potassium intake increases pNCC whereas increased potassium intake dephosphorylates NCC and increases aldosterone secretion. Although aldosterone has implicated in NCC activation it is uncertain if aldosterone exerts any significant effect upon DCT1 because this segment of the nephron exhibits very low expression of mineral corticoid receptors (MR) and is almost devoted of 11-β-hydroxysteroid dehydronase

type 2 (11β-HSD2) and hence MR are occupied mainly by cortisol[20].

Downstream organization of distal nephron is as follow: in the early segment of DCT2 there is co-expression of NCC and ENaC in the tubular cell membrane and after that only ENaC is expressed accompanied by ROMK. In connecting tubule and cortical collecting duct are expressed ENaC, ROMK and BK channels. All these channels are activated by aldosterone. Throughout the basolateral membrane of epithelial cells are expressed the Na^+/K^+-ATPase, potassium chloride cotransporter (KCC4), chloride channel CLC-Kb with accompanying chaperon barttin, sodium-calcium exchanger-1 (NCX1) and the inwardly rectifying potassium channels Kir4.1 and Kir5.1 which drive potassium outside the cell[21,23].

Studies in humans affected from congenital disorders of NCC activity, such as Gitelman syndrome and Pseudohypoaldosteronism type II (PHA II), showed that in case of loss of function of NCC (Gitelman syndrome) patients presents metabolic alkalosis with low potassium levels and low blood pressure, despite increased levels of aldosterone and high renin activity, whereas in case of gain of function of NCC (Pseudohypoaldosteronism type II) patients presents metabolic acidosis with hyperkalemia and high blood pressure[24,25].

2.1. DISCOVERY OF MECHANISMS AFFECTING NCC FUNCTION.

Until the beginning of new millennium the mechanism(s) by which NCC regulates sodium reabsorption and potassium excretion in ASDN was elusive. In 2000 Bing-e Xu et al[26] discovered a new protein kinase lacking the catalytic lysine in residue 72 (Lys^{72}) characteristic of all other known kinases, instead the new kinase possess it's catalytic lysine in residue 233 (Lys^{233}) and they gave the name With- no- Lysine Kinase 1 (WNK1). Subsequent investigation showed that the new family encompasses four members WNK1-4 which showed the capacity of autophosphorylation under circumstances of hypertonicity. One year later Wilson et al[27] discovered that the underlying cause of familial hypertension with acidosis and hyperkalemia, known as Pseudohypoaldosteronism type II (PHA-II) or Gordon's syndrome, is caused by two mutations in genes encoding WNK1 and WNK4. Mutations in WNK1 were large intronic deletions leading to increased activity of the kinase whereas mutations in WNK4 were missense in a short highly conserved segment of the protein leading to decreased catabolism of the kinase.

These discoveries paved the way to resolve the complex mechanism of sodium balance and potassium excretion by ASDN. Short there after Vitari et al[28] showed that downstream substrates of WNK kinases are two other serine-threonine kinases the Ste-20 proline/alanine rich (SPAK) kinase and the oxidative stress responsive kinase-1 (OSR1). These two kinases phosphorylate and activate NCC whereas concomitantly phosphorylate and deactivate the potassium-chloride cotransporter (KCC) located in the basolateral membrane of distal nephron epithelial cells. This opposite action of the kinases produces an accumulation of sodium, potassium and chloride inside the cell.

(Fig 1).

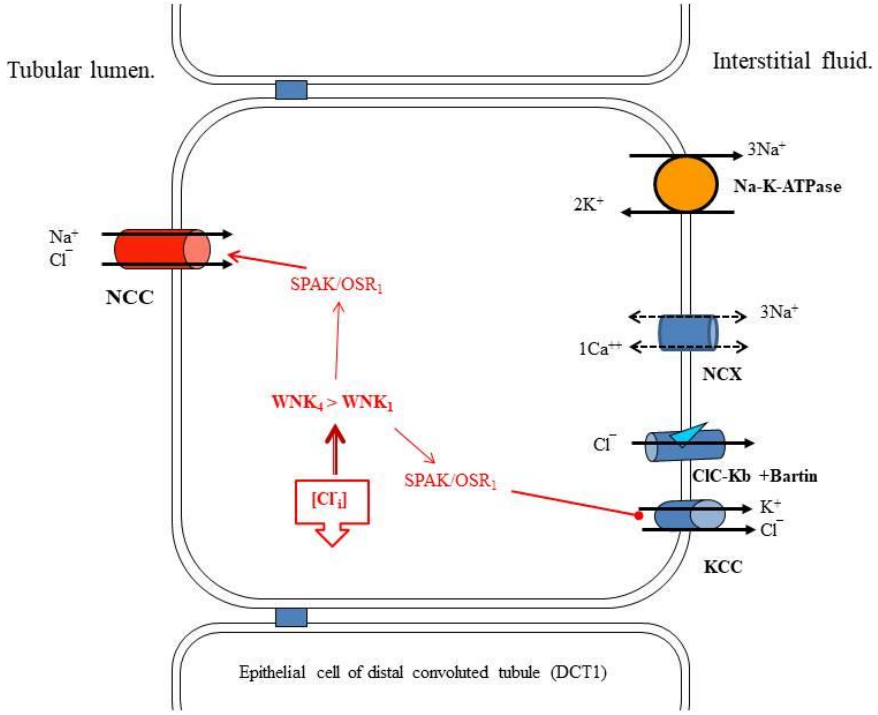

Fig. 1. Solute transport in the DCT1.

Fig. 1: Solute transport in DCT1. Sodium chloride reabsorption in DCT1 is accomplished mainly via sodium/chloride cotransporter (NCC). NCC phosphorylation and activation is governed by WNKs which phosphorylate and activate SPAK kinase and OSR-1 kinase. These two kinases phosphorylate and activate NCC and phosphorylate and deactivate KCC located at the basolateral membrane of the cell. WNKs are auto-phosphorylated and activated by reduction of intracellular chloride concentration.

(*Abbreviations: NCC=Sodium/chloride cotransporter, WNK=With-no lysine kinase, SPAK=Ste-20 Proline-alanine rich kinase, OSR1=Oxidative stress responsive kinase-1, $[Cl^-]_i$= Intracellular chloride, KCC=Potassium chloride cotransporter, CLC-Kb+Bartin= Chloride channel Kb+Bartin, NCX=Sodium/calcium exchanger-1, Na-K-ATPase= Sodium-potassium ATPase.*)

In 2014 Piala et al[29] showed experimentally that intracellular chloride concentration regulates WNK1 autophosphorylation and activation. This process is accomplished via a specialized structure of WNK1 molecule known as DLG motif composed by certain amino acids such as Phe^{283}, Leu^{299}, Leu^{369} and Leu^{371}. This structure is capable to trap one chloride anion by forming hydrophobic chloride-hydrogen bonds. Enzymatic activity of WNK1 molecule is coupled with phosphorylation of a specialized residue Ser^{382} located nearby its catalytic Lys^{233}, autophosphorylation of Ser^{382} is facilitated by its exposure at the surface of the molecule. Trapping of chloride anion in DLG motif produces conformational changes of WNK1 molecule which lead to internalization of Ser^{382} inhibiting its phosphorylation and hence deactivate the kinase. According to the above mechanism increased intracellular chloride concentration prevents WNK1 autophosphorylation and activation conversely when intracellular chloride concentration decreases chloride anion is released from DLG motif and leads to WNK1

autophosphorylation and activation. These findings suggest that WNK1 acts as an intracellular chloride sensor which modulates its own activity according to intracellular chloride concentration. Although WNK1 is the more extensive studied member of WNKs the above described mechanisms are also active among all the other members of the family[29,30].

2.2 EXTRACELLULAR POTASSIUM AND INTRACELLULAR CHLORIDE: THE MAIN PLAYERS IN ASDN.

Studies in experimental animals and humans showed that fluctuations of extracellular potassium concentrations, even in the setting of normal diurnal variations, are capable to affect NCC phosphorylation and activation via different metabolic pathways which are partially independent from intracellular chloride/WNK/SPAK-OSR1 activation especially in case of increased extracellular potassium concentration[31].

In 2015 Terker et al[32] showed, in a detailed experimental study in mice, that low potassium diet activates NCC even under circumstances of high salt diet and increases blood pressure on the other hand normal potassium diet deactivated NCC and reduced blood pressure. NCC activation was dependent upon extracellular potassium concentration and concomitant alteration of basolateral membrane voltage. In detail they showed that low potassium intake reduces extracellular potassium concentration with resultant potassium exit from the intracellular space. This potassium leak produces basolateral membrane hyperpolarization which in turn increases chloride exit from the cell and decreases intracellular chloride concentration with resultant increase in WNK/SPAK/OSR1 activation which at the end increase NCC phosphorylation and activation[32].

Further investigation showed that the main potassium channels in the basolateral membrane of ASDN cells are two members of the inwardly rectifying potassium channels Kir4.1, which is the product of KCNJ10 gene, and Kir5.1, which is the product of KCNJ16 gene. These two channels are capable to form a functional heterotetramer of 40 pS K+ conductance channel (Kir4.1/Kir5.1) which drives potassium outside the cell. Kir4.1 possesses the capacity of sensing extracellular potassium concentration and in cases of low extracellular potassium activates the channel and drives potassium outside the cell with resultant membrane hyperpolarization[33,34].

Membrane hyperpolarization activates the chloride channel CLC-Kb, located also in basolateral membrane, and increase chloride exit outside the cell which, in turn, leads to decreased intracellular chloride concentration. This cascade of events results in activation of WNK/SPAK/OSR1/NCC axis and increases NCC phosphorylation (pNCC) and activation. Experimental studies in animals showed that deletion of Kir4.1 in kidney specific Kir4.1 knock out mice (KS-Kir4.1 KO) abolished potassium and chloride current as well as hyperpolarization of cell membrane during low potassium diet. In vivo studies in mice showed also that low potassium diet activates Kir4.1 channel and increases potassium exit outside the DCT basolateral cell membrane with resultant membrane hyperpolarization whereas high potassium diet deactivates Kir4.1 and decreases potassium exit outside the cell with resultant membrane depolarization[33,34,35].

(Figure 2)

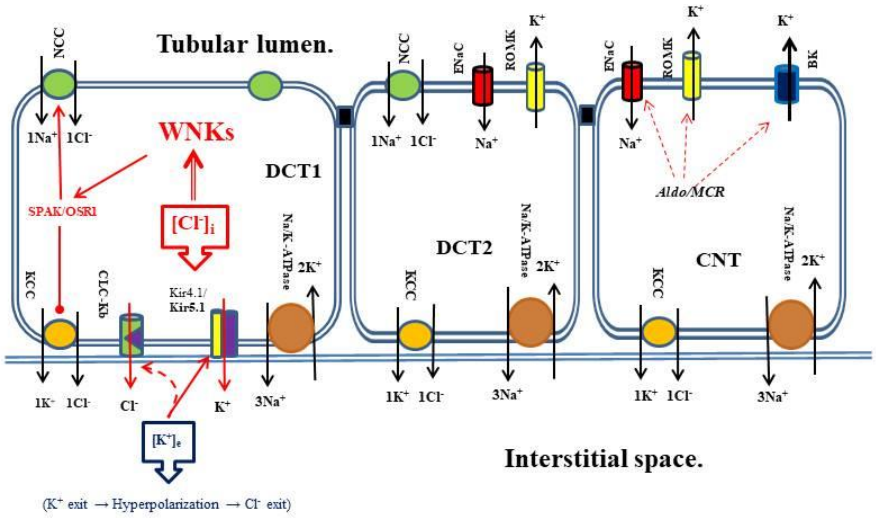

Fig. 2. Solute transport in distal nephron.

Fig 2: Solute transport in distal nephron. DCT1 has no ability to reabsorb potassium but it plays a crucial role in potassium homeostasis in ASDN by regulating the amount of sodium and solute delivered in downstream segments of the nephron. Potassium excretion in ASDN is mainly achieved via ROMK and is coupled with sodium reabsorption via ENaC. In cases of excessive potassium burden big potassium channel (BK) is activated also. Both channels are activated by aldosterone and the increase of solute delivery to the tubular lumen. NCC activity in DCT1 is regulated by WNK_s which in turn are activated by low intracellular chloride concentration. The main potassium channels in the basolateral membrane of distal tubule epithelial cells are two members of the inwardly rectifying potassium channels Kir4.1 and Kir5.1. Kir4.1 is a sensor of extracellular potassium concentration and in cases of low potassium levels Kir4.1 is activated and together with Kir5.1 drive potassium outside the cell. Potassium leaking outside the cell produces hyperpolarization of cell membrane with resultant activation of the chloride channel CLC-Kb which drives chloride outside the cell and reduces intracellular chloride concentration which results in activation of WNKs/SPAK/OSR1/NCC axis and increase sodium chloride reabsorption in DCT1.

(*Abbreviations: NCC=Sodium chloride cotransporter, KCC=Potassium chloride cotransporter, CLC-Kb=Chloride channel Kb+Bartin, Na/K-ATPase=Sodium potassium ATPase, Kir4.1=Inwardly rectifying potassium channel 4.1, Kir5.1= Inwardly rectifying potassium channel 5.1, WNKs=With no-lysine kinases,* $[Cl^-]_i$*= Intracellular chloride concentration,* $[K^+]_e$ *= Extracellular potassium concentration, ENaC= Epithelial sodium channel, ROMK=Renal outer medullary potassium channel, BK=Big potassium channel, Aldo/MCR=Aldosterone + mineral corticoid receptor.*)

Although the mechanism by which low extracellular potassium levels activate NCC is clearly dependent upon the Cl/WNK/SPAK/OSR1/NCC axis the mechanism by which high extracellular potassium dephosphorylate and deactivate NCC seems more complex and ill-defined until now.

It is well documented that high potassium diet increases extracellular potassium concentration, even in the range of normal values, and leads to rapid NCC dephosphorylation within 5 to 15 minutes. Accumulated evidence from experimental studies suggest that NCC dephosphorylation

by plasma potassium is feasible in the range of normal potassium concentration (3.0-5.0 mmol) and an increase of 0,1 mmol of extracellular potassium concentration produces a decrease of pNCC about 15 %[25].

In a recent double-blind randomized and placebo-controlled crossover trial, in healthy humans, Wu et all[36] examined the effect of KCl supplementation upon the excretion of urinary extracellular vesicles (uEVs) obtained from the urine of 18 healthy adults and estimated the excretion of NCC and phosphorylated NCC (pNCC) in response to increased dietary potassium intake. All subjects were under a high sodium (4.5 gr/day) and low potassium (2.3 gr/day) diet. Intervention consisted of KCl supplementation (24 mmolX3 per day) for five days. Authors showed a considerable decrease of NCC and pNCC in urine during KCl supplementation more over they showed a negative correlation between plasma potassium levels and NCC excretion in urine. They failed to show any significant decrease in blood pressure probably because all the participants were normotensive[36].

Experimental studies by Penton et al[31] showed that NCC dephosphorylation by increased extracellular potassium is partially independent from the Cl/WNK/SPAK/OSR1/NCC axis and they proposed that an alternative pathway, presumably involving intracellular phosphatases, may be involved. They failed to show an inhibition of NCC dephosphorylation after incubation with caliculin A, a known inhibitor of protein phosphatase -1 (PP1) and protein phosphatase-2A (PP2A) nor after incubation with tacrolimus, a known inhibitor of PP2B (also known as calcineurin or PP3). Subsequent investigation by Shoda et al[37] showed, in adult C578L/6 mice, that a high potassium diet (1.7 %) administered by oral gavage produced a rapid NCC dephosphorylation. Pretreatment of the animals with tacrolimus (calcineurin inhibitor) and W7 (calmodulin inhibitor) prevented NCC dephosphorylation. In a more recent publication the same authors showed in an experimental study, using HEK293 cells and C57BL/6 mice, that NCC dephosphorylation under circumstances of high potassium concentration or high potassium diet (1.7 % potassium gluconate) was dependent upon increased intracellular calcium $[Ca^{++}]_i$ concentration and calcineurin (CAN) activation. In the same experiment they showed also that intracellular calcium concentration was dependent upon the functional integrity of sodium/calcium exchanger 1 (NCX1) because suppression of NCX 1 with a specific inhibitor (SEA0400) abolished $[Ca^{++}]_i$ increase and NCC dephosphorylation[38].

These findings suggest that increased extracellular potassium concentration activate NCX1, in its reverse mode of function, and increase $[Ca^{++}]_i$ concentration which in turn activate the calmodulin/calcineurin complex and leads to NCC dephosphorylation. Activation of NCX1 is probably due to membrane depolarization because of increased extracellular potassium[38].

Based upon these observations as well as their own findings Ewout Hoorn et al proposed that activation of intracellular phosphatases (PPs) are responsible for rapid NCC dephosphorylation and inactivation under circumstances of rapid extracellular potassium concentration increase. This hypothesis is

further supported by the clinical evidence of calcineurin inhibitors, such as cyclosporine and tacrolimus, used therapeutically in transplanted patients or patients suffering from autoimmune diseases who frequently exhibit hypertension and hyperkalemia, a situation resampling to mild Pseudohypoaldosteronism type II[25].

(Figure: 3)

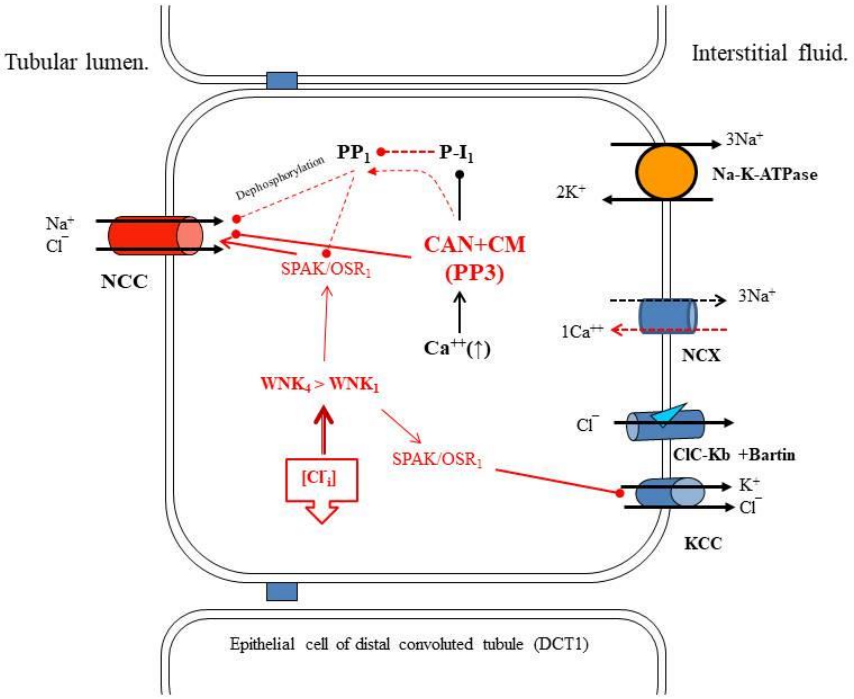

Fig. 3. NCC dephosphorylation by extracellular potassium.

Fig 3: NCC dephosphorylation by extracellular potassium. Elevated extracellular potassium levels rapidly induce NCC dephosphorylation and deactivation. Increased extracellular potassium leads to membrane depolarization which in turn enhances the reverse mode activity of NCX-1. This subsequently augments intracellular calcium concentration. The elevated intracellular calcium then activates the calcineurin/calmodulin complex. Calcineurin can directly dephosphorylate and deactivate NCC as well as WNKs, SPAK and OSR1 kinases. An alternative pathway suggests that activated calcineurin/calmodulin complex dephosphorylates and deactivates the PP1 inhibitor-I ($P\text{-}I_1$). In its basal state, the $P\text{-}I_1$ molecule is phosphorylated, active, and impedes PP1 which would otherwise dephosphorylate NCC. Once P-I1 is dephosphorylated, it becomes deactivated, removing its inhibitory action on PP1. This indirectly revs up the activity of the phosphatase. PP1 can dephosphorylate and deactivate WNKs, SPAK and OSR1 kinases and potentially NCC itself. It is possibly that this alternative pathway deactivates the cell machinery responsible for NCC expression and activation.

(Abbreviations: NCC=Sodium chloride cotransporter, KCC=Potassium chloride cotransporter, CLC-Kb=Chloride channel Kb+Bartin, Na/K-ATPase=Sodium potassium ATPase, NCX=Sodium/calcium exchanger-1, $[Cl^-]_i$ = Intracellular chloride concentration, WNK4=With-no lysine kinase 4,WNK1= With-no lysine kinase 1, SPAK=Ste-20 Proline-alanine rich kinase, OSR1=Oxidative stress responsive kinase-1, CAN=Calcineurin, CM=Calmodulin, $P\text{-}I_1$= Protein phosphatase 1 inhibitor, PP_1=Protein Phosphatase 1.)

Protein phosphatases are serine/threonine phosphatases activated by cAMP, Insulin, Protein Kinase-A (PKA) and certain metals. Candidates PPs for NCC dephosphorylation encompass the PP4, PP1, the PP3 (calcineurin/calmodulin complex) as well as the PP1 inhibitor 1 (I1). Detailed description of these phosphatases and mechanism of function is available in reference 39. The interplay between these molecules and NCC activity is very complex and incompletely elucidated until now.

Sufficient evidence suggest that PP1 is implicated in NCC activity but not directly through dephosphorylation of the molecule because NCC lacks a binding site for PP1 whereas it is truth for NKCC1 and NKCC2. On the other hand it is known that PP1 is capable to dephosphorylate and inactivate WNK1, WNK4 and their downstream substrates such as SPAK and OSR1 kinases so it is possible that PP1 downregulates NCC activation through this metabolic pathway. In other wards it is possible that PP1 does not directly dephosphorylate NCC but inactivates the cell machinery which phosphorylates and activates NCC and the net result is a reduced abundance of pNCC. Another molecule which may be implicated in this interplay is the I1 inhibitor of PP1. I1 is a regulatory subunit of PP1 which is phosphorylated and activated by Protein Kinase-A (PKA) at threonine 35 and acts as a potent inhibitor of PP1. I1 molecule activity is also sensitive to calcineurin/ calmodulin complex which is capable to dephosphorylate and inactivate I1 and hence removes the inhibition upon PP1 leading to indirect inactivation of NCC. Never the less direct dephosphorylation of NCC by PP1 is until now questionable. Concerning the other two members of PPs expressed in kidney epithelial cells, namely PP2A and PP4, there is no sufficient experimental evidence supporting their implication in NCC dephosphorylation[40].

3. Dietary habits and life style changes during mankind evolution.

Data collected from Paleontological and Anthropological studies suggest that our primitive ancestors (hominins) appeared on Earth between 8 and 6 million years ago. These primitive humans underwent a gradual evolutionary adaptation affected by environmental conditions and dietary habits. It is believed now that we are the descendants of Homo sapiens emerged on Earth about 300,000 years ago. The elapsed time between hominins and Homo sapiens achieved a perfect genome adaptation capable to support a healthy life of these species under certain environmental conditions and dietary habits[41].

Paleolithic era extents from about 3.3 million years ago until the end of Pleistocene period terminated about 11,650 years ago. This time period is characterized by the use of stone tools by humans mainly for hunting, butchering and fishing or to make other artifacts mainly of bone or wood origin for other tasks needed in everyday activities. During this period humans lived in small communities and they were fed mainly by hunting and gathering leafs, fruits, tubers, nuts, seeds etc. and hence the name "Hunter-Gatherer[41,11]."

Thorough investigation of fossil remnants such as bone, teeth, dental calculus or remnants of food preserved in containers provide scientists with valuable information about the diet of these humans. Available data suggest that hominin's diet was similar to that of primates and consisted mainly of plant derived foods such as fruits, nuts, leaves, grass, roots, and tubers occasionally supplemented with bird-eggs, birds, insects, lizards, frogs, small rodents and crustacean. During the Pleistocene period which begins about 2.6 million years ago, humans continued to be nature dependent and their food obtained mainly from gathering plant derived foods and hunting (hunter-gatherer man). It is believed that the food of Paleolithic human consisted of plants, about 80 % and flesh of wild animals and fishes, about 20 %.

Estimated content of nutrients in this diet is approximately 37% protein, 41 % carbohydrates and 22 % fat but this type of diet was not uniform for all species of humans during this period. For example there is sufficient evidence suggesting that Neanderthals consumed large quantities of meat obtained from hunting large herbivores animals. Investigation of isolated communities living until nowadays as "hunter-gatherers" shows that the diet of these humans consists of about 70 % plant derived and 30 % animal derived food whereas humans living in very cold climate fed mainly with meet and only 1 % of their diet derived from plants. In another analysis of nowadays "hunter-gatherers" communities focusing upon the energy consumption of these people argues that the energy supply is as high as 45-65 % derived from animal origin foods and only a small percentage of these communities, about 14 %, exhibit an energy supply of 56-65 % from plant origin foods[41,42,43].

3.1. REVERSAL OF DIETARY HABITS AND LIFE STYLE: THE DISCORDANCE HYPOTHESIS. The above described pattern of life and diet changed gradually after the end of the last Ice Age about 12,000 years B.C. This geological transition made Earth's climate more warm and humid and hence suitable for plant cultivation. After that agriculture emerged gradually and humans made the first more crowded settlements. The next step was the emergence of livestock by domestication of wild animals. These changes altered the life style, dietary habits and economy status of humans. Instead of gathering and hunting they had to gather annually crops and slaughtering domesticated animals for meet. Food resources increased dramatically and the first communities in the form of villages and cities emerged in human history they also acquired a more sedentary life style. The type of diet changed also dramatically because humans cultivated certain species of cereals and legumes suitable for the soil of their territory and soon thereafter they learned to make breads and added to their diet milk and dairy products, they also learned to extract plant oils such as olive oil. The meet of domesticated animals has a different composition of wild type animals because of greater content of fat with altered percentage of unsaturated/saturated fatty acids. All these changes altered the analogy of carbohydrate, protein and fat consumed and reached gradually to the nowadays pattern of 15 % protein, 34 % fat and 49 % carbohydrates. It is believed that during this period obesity emerged for first time in human history. Another novelty in their life was the use of salt because they needed to stockpile the crops for use during the winder or to transfer them in long distances for trading. They used also salt as a spice because it makes more suitable the taste of food[41,44].

All these novel dramatic changes in dietary habits and life style occurred in a short time period in evolutionary scale which is unable to produce any significant genome adaptation and as a result faced modern humans with dietary challenges never experienced by their ancestors and hence produced a situation characterized by discordance between their genome and their dietary habits and life style. This discrepancy further aggravated during the Industrial Revolution emerged the last 300 years of human history because modern human's diet is dependent upon highly processed foods, supplied by the food

industry, which contain a high amount of salt and processed carbohydrates. It is believed now that this discordance between our genome and our dietary habits and life style represents the underlying cause of the exponential increase of non-communicable diseases of modern humans such as obesity, diabetes, hypertension, atherosclerosis, cardiovascular diseases, bone and mineral disease and certain types of cancer[44].

One of the most striking changes in modern human's diet is the increased consumption of salt and decreased consumption of potassium containing foods. It is estimated that Homo sapiens consumed about 30 mmol (=1,755 mg) of salt/day and 500-700 mmol (=19,550-27,370 mg) of potassium/day. The same is truth for wild animals living nowadays, carnivores consume about 20-40 mmol of salt per day whereas herbivores consume less than 10 mmol/day. It is obvious that salt was absent from the diet of Paleolithic humans and they faced a continuous threat of volume depletion for this reason their kidneys underwent an evolutionary adaptation to conserve sodium and excrete potassium. When humans changed their dietary habits hypertension emerged as a result of their kidneys maladaptation to excrete the excess of salt consumed by the novel diets. Available data from isolated communities living until nowadays as hunter-gatherers such as Papua in New Guinea and Yanomani Indians in Amazon shows that these populations do not develop hypertension and don't exhibit blood pressure increase as they get old[45,46].

Although there is a continuing debate until nowadays concerning the optimal amount of salt which we have to consume with our diet there is no doubt that restriction of dietary salt reduces effectively blood pressure in humans and experimental animals. Sufficient evidence suggests that populations with salt consumption lower than 50 mmol/day does not exhibit hypertension were as it is truth for populations with salt consumption greater than 100 mmol/day. Large scale epidemiological studies such as the International Study of Salt and Blood Pressure (INTERSALT) and the Dietary Approaches to Stop Hypertension (DASH) diet study showed clearly that an increase in dietary salt consumption greater than 100 mmol/day produces a significant increase in systolic and diastolic blood pressure and a decrease in salt consumption produces a decrease in blood pressure either in hypertensive or normotensive individuals irrespective of race and sex. These changes were more pronounced for changes in salt consumption greater than 50 mmol/day[47,48,49].

3.2. POTASSIUM/SODIUM RATIO AND HYPERTENSION.

Very early observations pointed to the possibility that salt consumption alone is not responsible for blood pressure elevation but its action is strongly affected by potassium consumption. The first who reported that not merely sodium but the ratio of sodium/potassium is the principal factor which determines blood pressure elevation were Meneely and Ball in 1958. Based upon observations in experimental animals they showed that animals fed with toxic amounts of sodium chloride survived longer if they concomitantly administered high amounts of potassium chloride. Authors argued that the natural diet of humans contains high amount of potassium and low amount of sodium and the reverse of sodium/potassium ratio in

modern diet is responsible for the detrimental effect of this diet in hypertension[50].

Available data in the literature suggests that Paleolithic humans consumed 20-40 mmol of sodium/day and 400-500 mmol of potassium/day, ratio of K^+/Na^+ >10. On the other hand estimations of contemporary diets, especially in Industrialized communities, fed mainly with processed foods supplied by food industry, shows that the modern humans consume about 30-70 mmol of potassium/day and 100-400 mmol of sodium/day, ratio of K^+/Na^+ =0.3-0.17. The origin of dietary sodium consumed by modern humans is 80 % derived from food processing, 12 % is naturally originated in foods and the remainder 8 % is added as a condiment[47].

Analysis of data from the Third National Health and Nutrition Examination Survey (1998-2006) included 12,267 US adults with a mean follow-up of 14.8 years showed that higher sodium intake was associated with an increase in all-cause mortality (HR 1,20; 95 % CI=1,03-1,41 per 1000 mg/d) were as higher potassium intake was associated with lower mortality (HR 0,80; 95 % CI=0,67-0,94 per 1000 mg/d). The increase of sodium/ potassium ratio was associated with a significant increased risk of all-cause mortality, cardiovascular disease and ischemic heart disease mortality which was independent of age, sex, race and ethnicity[51].

In a relatively recent meta-analysis of 8 RCTs, examining the possible beneficial effect of Paleolithic diet (PD) upon cardiovascular disease risk factors, Ghaedi et al[12] showed that PD significantly decreases anthropometric indexes such as body weight, waist circumference, body mass index and body fat percentage. They found also a significant decrease in systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, triglycerides and CRP levels as well as a significant increase in HDL-cholesterol. Although this meta-analysis is based upon RCTs with a considerable heterogeneity and the exclusion of some studies altered the effects upon biochemical parameters of the participants they showed an unequivocal beneficial effect upon anthropometric indexes and blood pressure[12].

There is no doubt that the diet of modern humans is characterized by a diminished ratio of K+ /Na+ and as our kidneys remain adapted to Paleolithic diets they continue to reabsorb sodium but they have also to manipulate effectively the amount of ingested potassium. Potassium excretion in distal nephron is coupled with sodium reabsorption and in cases of low potassium ingestion, as it is the rationale with contemporary diets; nephron has to diminish the amount of solute and sodium delivered from the DCT1 to ASDN in order to preserve potassium excretion in this segment of the nephron via ROMK and prevent fatal hypokalemia. This goal is achieved by increasing the activity of NCC which reabsorbs NaCl and decreases delivery of sodium to the downstream segments of the nephron, by this way diminishes potassium excretion but increases sodium chloride reabsorption with resultant increase of extracellular volume and blood pressure. This priority of nephron to regulate the extracellular potassium concentration in expense of extracellular volume seems likely to represent the underlying mechanism of sodium sensitivity which leads to sodium sensitive hypertension[35,52].

On the contrary when dietary potassium ingestion increases internal potassium balance is immediately activated and potassium distribution in intracellular space prevents fatal hyperkalemia but the final regulation of external potassium balance is achieved in ASDN. Increased potassium ingestion produces an increase of extracellular potassium concentration even in the range of normal diurnal variation but this increment is capable to produce an increase in aldosterone production and a rapid decrease of NCC activity either by reduced activation or increased dephosphorylation. These events lead to increased delivery of sodium chloride to the downstream segments of ASDN where aldosterone increases reabsorption of sodium via ENaC and excretion of potassium via ROMK. The amount of sodium reabsorbed via ENaC is not enough to counterbalance the diminished activity of NCC and the net result is an increase in kaliuresis and natriuresis which leads to reduced blood pressure. It is believed that this cascade of events explains sufficiently the hypotensive action of potassium rich diet even in the case of increased salt consumption[35,52].

4. Conclusions.

I. Potassium cation is one of the most important elements of our organism. The main distribution of potassium in intracellular space ensures the stability of intracellular volume which is fundamental for normal cell function. On the other hand the ratio of extracellular/ intracellular potassium determines the resting membrane potential which is essential for the normal function of excitable cells such as cardiac muscle, neurons and skeletal muscles. For this reason extracellular potassium concentration has to be maintained in a narrow range limit to avoid fatal derangements of hypo or hyperkalemia.

II. Kidney is the principal organ which achieves an effective balance of ingested potassium and maintains our survival and normal function of our organism. External potassium balance by the kidney is accomplished in ASDN and is mainly coupled with sodium reabsorption. Available data suggest that kidney shows a priority in potassium balance than extracellular volume maintenance and as a consequence increased potassium ingestion leads to increased kaliuresis with concomitant natriuresis which leads to extracellular volume depletion and blood pressure lowering.

III. History of human's evolutionary path shows that during 99 % of this long journey their survival was relied upon hunting-gathering which means that their diet was characterized by salt deprivation and excess potassium intake. Evolutionary adaptation of their kidneys resulted in avid sodium reabsorption and potassium excretion. The last 10,000 years humans changed dramatically their dietary habits in favor of salt intake and reversed the ratio of K^+/Na^+ intake and as their kidneys remain adapted to Paleolithic diet prioritize potassium conservation in expense of extracellular volume maintenance and hence ASDN increases sodium chloride reabsorption in the early segment of DCT which in turn increases extracellular volume and blood pressure. The only way to stop this vicious cycle is to reduce drastically salt consumption and increase potassium ingestion via potassium rich foods, in other words to adapt our diet as close as it is possible to Paleolithic diet.

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