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Chloride anion and sodium sensitive hypertension
A historical review

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):117–124

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Ανιόν χλωρίου
και νατριοευαισθησία
στην υπέρταση:
Μια ιστορική ανασκόπηση

Περίληψη στο τέλος του άρθρου

Arterial hypertension is one of the most devastating diseases in modern societies. As early as 1920, Frederick Allen showed that sodium restriction ameliorates hypertension. After that, in 1929, Robert Berghoff and Angelo Geraci showed in an observational study that administration of high sodium chloride increases blood pressure where as substitution of sodium chloride by an equimolar quantity of sodium bicarbonate has no effect on blood pressure. It was the first clinical study in humans showing that chloride anions may be responsible for the high blood pressure observed with increased salt consumption. During the '70s, it was experimentally proven that chloride anions play a crucial role in intracellular volume regulation and in signalling renin secretion via macula densa cells. In the mid '90s, the discovery of sodium chloride transporter mutations as candidates for Bartter and Gitelman syndromes pointed toward the possibility that chloride anions may play a crucial role in blood pressure regulation. In the beginning of second millennium, the discovery of a new class of protein kinases, named with-no-lysine kinases (WNKs), and shortly thereafter the discovery that two mutations in WNK1 and WNK4 are candidates for an inherited form of familial hypertension with hyperkalemia and acidosis known as pseudohypoaldosteronism type II or Gordon's syndrome raised the question of the possible pathogenic role of sodium-chloride co-transporters in the distal nephron in hypertension. Subsequent research supports that WNKs act as intracellular chloride sensors and regulate the activity of transepithelial sodium-chloride co-transporters in the distal nephron. Moreover, it was experimentally shown that the sodium-independent chloride-bicarbonate exchanger pendrin in the collecting tubule plays a crucial role in transepithelial sodium chloride transport in this nephron segment. In conclusion, after nearly a century of intense research, it has been shown that sodium transcellular transport in distal nephron epithelia is accomplished mainly via chloride co-transport. Furthermore, chloride anions play a crucial role in renin secretion and in cell volume regulation. WNKs are the housekeepers of intracellular chloride concentration. We suggest that it may be time to talk of "chloride-sensitive" and not of "sodium sensitive" hypertension.

Key words

Chloride anion
Pendrin
Sodium sensitive hypertension
With no-lysine-kinases

1. INTRODUCTION

Arterial hypertension is one of the most devastating diseases in modern societies. In the early 1900s, the use of the Riva-Rocci sphygmomanometer in clinical practice showed that hypertension was encountered almost exclusively in the USA and European population, being very rare or absent in the rest of the world, as in Africa, Asia, Oceania, Australia and South America, suggesting that environmental factors and especially dietary habits play a crucial role in the pathogenesis of the disease.

As early as 1920, Frederick Allen[1] showed that sodium restriction ameliorates hypertension. After that, in 1929, Robert Berghoff and Angelo Geraci[2] showed experimentally that high sodium chloride administration leads to increased blood pressure, where substitution by sodium bicarbonate failed to increase blood pressure. It was the first clinical observation that chloride anions may be responsible for the high blood pressure observed with increased salt consumption.

Berghoff's and Geraci's pioneering observation was

neglected for a long time, until the 1970s, when Floyd Kregenow[3] showed experimentally that chloride anions play a crucial role in cell volume regulation under hyperosmotic stress. After that, Theodore Kotchen[4] showed that chloride anions regulate renin secretion by signalling to the macula densa cells.

In the early 1980s, the discovery of Na-K-2Cl co-transporters in the thick ascending limp of Henle's loop and Na-Cl co-transporters in the distal convoluted tubule proved that sodium trans-cellular transport in distal renal tubular epithelia is accomplished via chloride co-transport.[5]

In the beginning of new millennium, it became evident that mutations of the newly-discovered "with-no-lysine" kinases are responsible for the pathogenesis of a familial form of inherited hypertension.[6] After that, it was shown experimentally that these kinases directly affect the function of NCC and NKCC2 and that their activity is modulated by intracellular chloride concentration, because they act as intracellular chloride sensors and are capable of modulating their own activation and deactivation according to intracellular chloride concentrations.[7]

Meanwhile, it was shown experimentally that β-intercalated cells in the collecting tubule can transport sodium and chloride via the coupled action of the sodium-driven chloride bicarbonate exchanger (NDCBE) and the chloride bicarbonate exchanger pendrin, both located on the luminal surface of the cell membrane.[8]

In this review article, we attempt to elucidate the early steps pointing to the importance of the anion, which accompanies sodium and mediates its capacity to increase blood pressure under circumstances of increased salt consumption until the new discoveries, which emphasise the importance of chloride anions in cell volume regulation and sodium transport in the distal nephron.

1.1. The importance of anions in hypertension

The first experimental evidence that chloride anions play a crucial role in increased salt consumption-induced hypertension came in 1929, from a primitive study performed by Berghoff and Geraci.[2] The study comprised 50 patients with various morbidities but without serious complications, seven of them were hypertensive. Patients were administered 6 drams (=10.6 g) of sodium chloride per day for one month. After a one-month washout period, salt was substituted by 6 drams (10.6 g) of sodium bicarbonate per day for another month. Although they did not perform a statistical analysis, they concluded that: (a) *"An excessive intake of sodium chloride (six drams) markedly elevates blood pressure in true nephritics and almost equally so in arteriosclerosis".* (b) *"An excessive intake of sodium chloride even in individuals with a normal and subnormal vascular tension elevates blood pressure".* (c) *"An equal amount of sodium bicarbonate does not cause similar results".*

Authors performed a meta-analysis on the original data presented by Berghoff and Geraci and compared systolic blood pressure (SBPns) and diastolic blood pressure (DBPns) under normal salt consumption with systolic blood pressure (SBPhs) and diastolic blood pressure (DBPhs) under high salt consumption and we found that increased sodium chloride administration produced a statistically significant increase in systolic blood pressure (t=-2,049, p=0,043), (fig. 1) and a statistically marginally significant increase in diastolic blood pressure (t=-1,973, p=0,051), (fig. 2). When we compared systolic and diastolic blood pressure under normal salt consumption with systolic blood pressure (SBPbcn) and diastolic blood pressure (DBPbcn) after substitution with an equal amount of sodium bicarbonate, we found no statistically significant difference (SBPns vs SBPbcn: t=-0,075, p=0,940 NS and DBPns vs DBPbcn: t=0,359, p=0,719 NS).

After that, we compared systolic and diastolic blood pressure under high salt consumption with systolic and diastolic blood pressure after substitution of sodium chloride with an equal amount of sodium bicarbonate and we found a statistically significant reduction in systolic and diastolic blood pressure (SBPhs vs SBPbcn: t=2,062, p=0,041 and DBPhs vs DBPbcn: t=2,610, p=0,010), (figures 1, 2). These new data confirm Berghoff's and Geraci's original state-

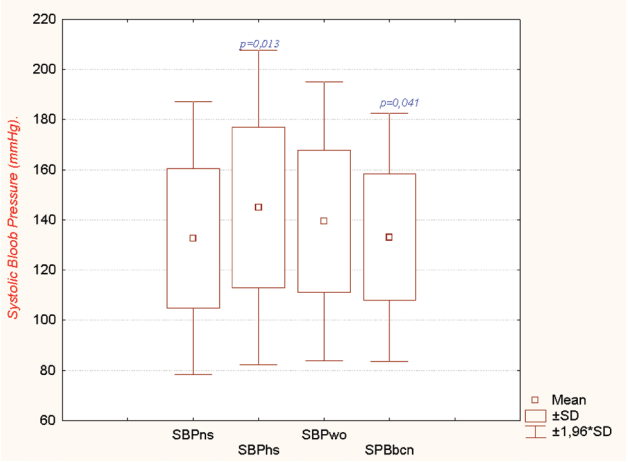

Figure 1. Systolic blood pressure shows a significant increase during high salt consumption (SBPhs) compared to basal conditions (SBPns). No alteration of SBP was observed after substitution of salt with an equal amount of sodium bicarbonate (SBPbcn). Conversely, systolic blood pressure exhibits a significant decrease during sodium bicarbonate administration compared to high salt consumption.

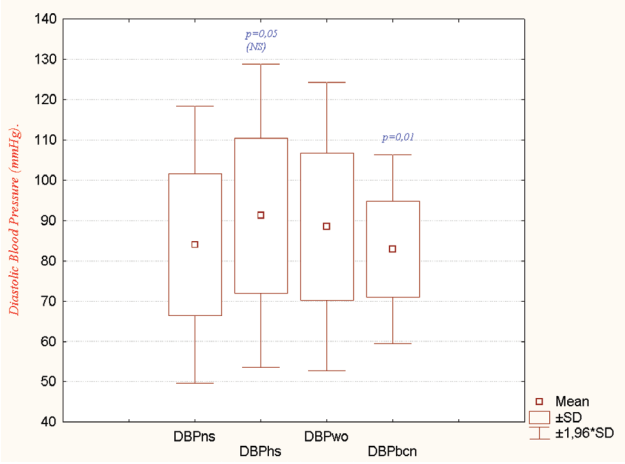

Figure 2. Diastolic blood pressure shows a significant increase during high salt consumption (DBPhs) compared to basal conditions (DBPns). No alteration of DBP was observed after substitution of salt with an equal amount of sodium bicarbonate (DBPbcn). Conversely, diastolic blood pressure exhibits a significant decrease during sodium bicarbonate administration compared to high salt consumption.

ments and concern all patients and not only hypertensives, as usually cited in the literature.

Berghoff's and Geraci's study was long neglected, mainly because investigators perceived the harmful effect of increased salt consumption on blood pressure as an exclusive effect of sodium, overlooking the obligatory presence of chloride.

Many years later, Theodore Kurtz et al in 1987 repeated Berghoff's and Geraci's experiment in five hypertensive patients and showed that administration of sodium chloride (240 mmoL Na^+/day for one week) increased blood pressure whereas administration of sodium citrate (240 mmoL Na^+/day) for one week had no effect. Furthermore, when blood pressure was increased by sodium chloride administration substitution for sodium citrate, in equal amounts, blood pressure returned to normal values.[9]

Studies in experimental animals such as stroke-prone spontaneous hypertensive (SHPSP) rats, Dahl salt-sensitive rats and DOCA-salt hypertensive rats showed that substitution of sodium chloride with equal amounts of sodium coupled with other anions such as bicarbonate, phosphate, aspartate, glutamate and glycinate failed to increase blood pressure.[10]

1.2. Physiological role of chloride anions

Chloride anion (Cl^-) is the most abundant anion in mammals because it counteracts the positive charge of sodium (Na^+) and potassium (K^+) cations, as well as other positively charged macromolecules, to ensure electroneutrality in biological fluids. Its distribution in the extracellular and intracellular space exhibits a wide variation. In mammals, extracellular chloride anion concentrations are about 120 mEq/L while intracellular concentrations vary between approximately 5–10 mEq/L among neuronal cells, reaching up to 40 mEq/L in epithelial cells.[11]

Although its physiological role was long neglected, it plays a crucial role in biological systems such as intracellular vesicle acidification through its transmembrane transport, osmoregulation and cell volume regulation acting as osmolyte, together with other positively charged osmolytes. It can also bind with certain proteins such as cathepsin C and with WNKs, modifying their function. Chloride transport through cell membranes generates electrical currents if its moving is not coupled with an equal amount of cations to ensure electroneutrality (co-transporters) or with exchangers in a 1:1 stoichiometry.[10]

As early as 1956, Otto Hutter and Padsha S. Mahmood showed experimentally that chloride anions contribute to skeletal muscle membrane conductance.[12] One year later, Allan Hodgkin and Paul Horowicz obtained the same results in isolated skeletal muscle fibres.[13] Hodgkin's publication overshadowed Hutter's because it concerned isolated muscle fibre and because of Hodgkin's careful presentation. After that, Hutter continued his experiments and in 1960, together with Denis Noble, showed, in frog skeletal muscle, that chloride anions contribute by about 68% to the muscle's resting membrane conductance and can pass the cell membrane, increasing its intracellular concentration in a very labile way, affected by pH and metallic cations.[12] It was shown experimentally for the first time that chloride anions can pass the cell membrane and stabilise the resting potential of the membrane, contributing in cell effective excitability.

In 1971, Floyd Kregenow[3] showed experimentally that duck erythrocytes, placed in a hyperosmolar environment after initial shrinkage, retain their normal volume via the moving of potassium and chloride ions in intracellular space. Subsequent investigations showed that cellular volume regulation is accomplished by discrete mechanisms in two phases. The first takes place after a few seconds and mainly triggers ions moving across the cell membrane. The second last a few hours and concerns the production and moving of organic osmolytes via the cell membrane.[14] Under hyperosmotic stress, the cell inwardly transfers sodium, potassium and chloride ions by activation of Na^+/H^+ exchangers, Cl^-/$HCO3^-$ exchangers and Na^+:K^+:$2Cl^-$ co-transporters (NKCC1). Under hypo-osmotic stress, the cell

outwardly transfers potassium and chloride ions via activation of K^+:Cl^- co-transporters (KCC) and separate potassium and chloride channels.[14] In hyperosmotic stress, chloride anions predominate amongst ions moving inwards in the cell and play a crucial role in acute cell volume regulation.

In 1978, Theodore Kotchen and colleagues experimentally showed, in sodium-deprived rats, that chloride anions and not sodium signals to macula densa cells and inhibit renin secretion from the juxtaglomerular apparatus.[4] Tianxin Yang and colleagues experimentally showed, in isolated mouse macula densa cell lines, that a low chloride content and not sodium, in perfusate medium, increases cyclooxygenase-2 (COX-2) expression and prostaglandin E2 (PGE2) production.[15] Macula densa cells sensing of chloride content is accomplished via the Na^+:K^+:$2Cl^-$ co-transporter (NKCC2), which is the main sodium chloride co-transporter in the luminal surface of macula densa cells membrane and is chloride-sensitive. COX-2 expression is mediated via phosphorylation of p38 and ERK1/2 kinases.[15] Downstream propagation of the signal is achieved via microsomal fraction of prostaglandin E synthase (mPGES), which increases the synthesis of prostaglandin E2 which in turn via the EP2 and EP4 receptors increase renin release from the juxtaglomerular cells.[16]

1.3. Sodium chloride transport in the distal nephron

In 1981, Rainer Greger and Eberhard Schlatter discovered the sodium potassium 2 chloride co-transporter (NKCC2) in the thick ascending limp (TAL) of Henle's loop in the rabbit kidney.[5] They showed that the presence of potassium ions in the luminal fluid was necessary for the proper function of the transporter and the stoichiometry of ion transport was $1Na^+$:$1K^+$:$2Cl^-$.

A few years later (1987), David Ellison and colleagues discovered the presence of the sodium chloride co-transporter (NCC) in the distal convoluted tubule of rats and they showed that NCC was the main sodium chloride transporter in the early tubule segment. Chloride was necessary for sodium reabsorption because removing chloride from perfusate solutions reduced sodium transport.[17]

In 1993 and 1994, Geraldo Gamba and colleagues cloned and purified the thiazide sensitive sodium chloride co-transporter (NCC) from the urinary bladder of the fish winder flounder and, soon after, the bumetanide sensitive sodium potassium 2 chloride co-transporter (NKCC2) from the rat kidney.[18,19]

A few years later, in 1996, David Simon and colleagues showed that mutations in the *SLC12A3* and *SLC12A1* genes, encoding NCC and NKCC2, respectively, are responsible for Gitelman and Bartter syndromes known as salt loosing tubulopathies and characterised by the presence of hypochloremic-hypokalemic alkalosis, low blood pressure and increased renin and aldosterone levels.[20,21] These discoveries raised the question of the possible role of chloride anions in the regulation of blood pressure because the mutated proteins are mainly chloride transporters and their activity is regulated by chloride concentrations in the luminal fluid.

In 2004, Nikola Jeck and colleagues discovered a mutation in the CLC-Kb chloride channel (T481S) among Ghana's native population, which increases the channel activity almost 7-fold compared to wild type.[22] They subsequently showed that carriers of the mutation exhibited higher plasma sodium concentrations and increased systolic and diastolic blood pressure compared to normal individuals.

In 2010, Leviel and colleagues discovered, in β-intercalated cells of mice cortical collecting ducts, a sodium-dependent chloride bicarbonate exchanger (NDCBE/SLC4A8), which is sensitive to thiazide diuretics, and drives 1 Na^+ and 2 $HCO3^-$ ions inside the cell, exchanging them by 1 Cl^-, ensuring cell membrane electroneutrality.[8] In the same study, they showed that the parallel action of the sodium independent Cl^-/$HCO3^-$ exchanger pendrin (SLC26A4) recycles chloride anions inside the cell and extrudes bicarbonate anions to the tubular lumen. Chloride anions exit the basolateral cell membrane to the extracellular space via the chloride channel CLC-Kb and couples with the sodium cation extruded by the Na^+/K^+-ATPase and contributes significantly to NaCl reabsorption by this nephron segment.

1.4. WNKs and sodium-chloride co-transporters

Our knowledge of the crucial role of chloride anions in regulating blood pressure expanded greatly in the beginning of the new millennium, when Bing-e Xu and colleagues, in 2000, discovered a new protein kinase, from mouse brain extractions, which they termed "with-no-lysine kinase-1" (WNK-1). The name is derived from the fact that the new kinase lacks the characteristic catalytic lysine (Lys-72) in β3-helix of subdomain II, which characterises almost all other known protein kinases. Instead, the new kinase's catalytic lysine (Lys-233) is in an atypical position in β2-helix of subdomain I and it is a serine/threonine kinase.[23] Three more members of this kinase subfamily were subsequently discovered, termed WNK 1, 2, 3 and 4, respectively.

In 2001, Frederic Wilson and colleagues discovered that two mutations in the genes encoding WNK-1 and WNK-4 are responsible for a familial form of hypertension with

hyperkalemia and acidosis.[6] This form of hypertension is transmitted via an autosomal dominant hereditary pattern and it is known as Pseudohypoaldosteronism type II or Gordon's syndrome. Gordon's syndrome is expressed phenotypically as the mirror of Bartter's and Gitelman's syndromes and is manipulated easily with low doses of thiazide diuretics, suggesting that the underlying abnormality represents NCC gain of function in the distal convoluted tubule.

After that, some key questions emerged such as: (a) What are the substrates of WNKs and what is their biological role? (b) How do these kinases regulate the activity of NCC and possibly of other ion transporters in the distal nephron? (c) What is the role of chloride anions in this process?

Subsequent investigations by Alberto Vitari and colleagues, of downstream substrates activation by WNKs, showed that the cellular substrates of WNKs are two serine threonine kinases known as oxidative stress responsive element-1 (OSR-1 kinase) and ste-20 related proline alanine rich kinase (SPAK kinase), which are conserved in many species and distributed in multiple organ systems.[24]

Accumulated evidence suggests that WNKs phosphorylate and activate OSR-1 and SPAK kinases which in turn phosphorylate and activate NCC, NKCC1 and NKCC2 and also phosphorylate and deactivate the KCC co-transporter.[25] Moreover, WNKs inhibit epithelial sodium channel (ENaC) via inactivation of Sgk1 and also inhibit the renal outer medullary potassium channel (ROMK) by promoting clathrin mediated endocytosis (fig. 3). Thus, the coordinated cellular action of WNKs and their substrates points toward increasing the intracellular chloride anion concentration in an attempt to conserve intracellular volume.

Bing-e Xu and colleagues also showed that the WNK-1 molecule has the capacity of autophosphorylation of certain serine residues such as Ser-382 and Ser-378. Phosphorylation of Ser-382 increases enzyme activity by 100% whereas Ser-378 phosphorylation increases enzyme activity by only 50%. Thus, these two serine residues and especially Ser-382 act as the main modulators of enzyme activity.[26]

Alexander Piala and colleagues[7] showed that the WNK1 molecule contains in its kinase domain a specialised structure known as DLG motif, which can interact with a

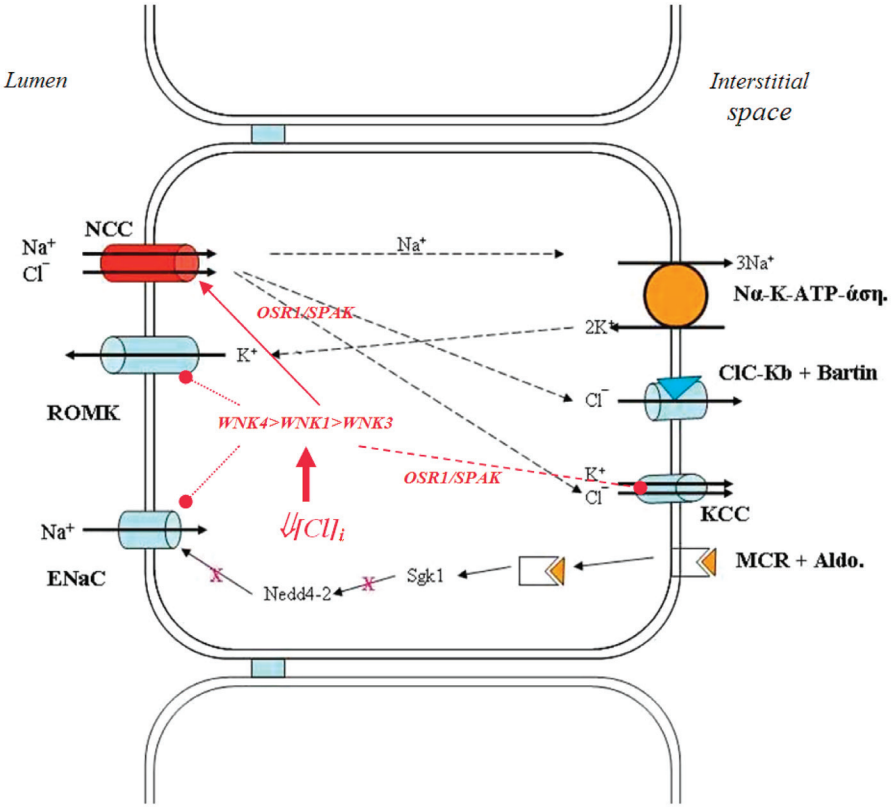

Figure 3. Schematic representation of a distal convoluted tubule epithelial cell. Note that decrease in intracellular chloride concentration leads to WNK activation in a sensitivity manner WNK4>WNK1>WNK3. Downstream activation of OSR1/SPAK kinases leads to phosphorylation and activation of NCC and phosphorylation and inactivation of KCC. WNKs also inhibit the function of ENaC and ROMK via different mechanisms.

chloride anion by making hydrophobic chloride hydrogen bonds between chloride and certain amino acid residues such as Phe-283, Leu-299, Leu-369 and Leu-371. The trapping of chloride anions in the DLG motif produces conformational changes in the WNK1 molecule, which inhibit Ser-382 phosphorylation and hence induce kinase inactivation. These findings suggest that WNK1 acts as an intracellular chloride sensor and modulate its own activation and deactivation according to intracellular chloride concentration changes.

In parallel to the above work, in 2010, Leviel and colleagues showed, on the luminal surface of intercalated mice cells, the presence of a sodium-dependent chloride bicarbonate exchanger (NDCBE), which promotes the electroneutral exchange of 1 intracellular chloride anion with 1 sodium cation and 2 bicarbonate anions from the luminal fluid.[8] NDCBE is sensitive to thiazide diuretics. The exchanger operates in parallel with the sodium-independent chloride/bicarbonate exchanger pendrin, which is also located on the luminal surface of intercalated cells, and drives chloride anions inside the cell by exchanging each with one bicarbonate anion. Chloride anions exit to the extracellular space via the chloride channel CLC-Kb, located on the basolateral cell membrane. In parallel, sodium is driven to the extracellular space via NaK-ATP-ase. The net result of the coupled function of NDCBE/pendrin is the absorption of sodium chloride, in this nephron segment, resulting in increases in extracellular volume and blood pressure.

They further produced a line of transgenic mice with human pendrin gene (*TgB1-hPDS*) overexpression in intercalated cells of the collecting duct and showed experimentally that transgenic mice exhibited increased chloride absorption with a concomitant increase of sodium absorption via the epithelial sodium channel (ENaC) and NDCBE.[27] When animals were fed with an increased sodium chloride diet, they developed hypertension but when an equal amount of sodium bicarbonate was administered, their blood pressure was not altered significantly. These findings indicate that pendrin overexpression in intercalated cells produces a form of chloride-sensitive hypertension.

2. CONCLUSIONS

After almost one century of vigorous research efforts we now know that although sodium is the principal extracellular cation determining extracellular volume and hence blood pressure control, its reabsorption by the kidney and movement to the extracellular space is principally dependent on chloride anion. WNKs are the housekeepers of intracellular chloride concentration, striving to preserve intracellular volume. Pendrin plays a crucial role in sodium chloride reabsorption in the distal nephron. Given this, it may be time to talk of "chloride-sensitive" and not of "sodium-sensitive" hypertension.

ΠΕΡΙΛΗΨΗ

Ανιόν χλωρίου και νατριοευαισθησία στην υπέρταση: Μια ιστορική ανασκόπηση

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Η αρτηριακή υπέρταση είναι μία από τις πλέον καταστροφικές ασθένειες των σύγχρονων κοινωνιών. Ήδη από το 1920 ο Frederick Allen έδειξε ότι ο περιορισμός της πρόσληψης νατρίου βελτιώνει την υπέρταση. Στη συνέχεια, το 1929, οι Robert Berghoff και Angelo Geraci δημοσίευσαν μία κλινική μελέτη στην οποία έδειξαν ότι η χορήγηση αυξημένης ποσότητας χλωριούχου νατρίου σε 50 ασθενείς οδηγούσε σε αύξηση της αρτηριακής πίεσης ενώ η ίδια ποσότητα διττανθρακικού νατρίου δεν είχε καμία επίδραση στην πίεση. Αυτή ήταν η πρώτη κλινική μελέτη σε ανθρώπους η οποία έδειξε ότι πιθανώς η αύξηση της αρτηριακής πίεσης που παρατηρείται σε καταστάσεις αυξημένης πρόσληψης αλατιού οφείλεται στο ανιόν χλωρίου και όχι στο νάτριο. Στη δεκαετία του '70 διαπιστώθηκε πειραματικά ότι το ανιόν χλωρίου έχει ουσιαστικό ρόλο στη ρύθμιση του ενδοκυτταρίου όγκου και στη σηματοδότηση έκκρισης ρενίνης μέσω των κυττάρων της πυκνής θηλής. Στα μέσα της δεκαετίας του '90 η ανακάλυψη ότι μεταλλάξεις των γονιδίων που εφορεύουν τη σύνθεση των συνμεταφορέων νατρίου-χλωρίου, στο παχύ ανιόν σκέλος της αγκύλης του Henle και στο άπω εσπειραμένο νεφρικό σωληνάριο, ευθύνονται για την εμφάνιση των συνδρόμων Bartter και Gitelman, αντίστοιχα, δημιούργησε βάσιμες υπόνοιες ότι πιθανώς το ανιόν χλωρίου παίζει πρωτεύοντα ρόλο στη ρύθμιση της

αρτηριακής πίεσης. Στη χαραυγή της νέας χιλιετίας ανακαλύφθηκε μια νέα ομάδα πρωτεϊνικών κινασών στις οποίες δόθηκε η ονομασία "With no-lysine-kinases" (WNKs) εξ αιτίας της άτυπης θέσης της καταλυτικής λυσίνης στο μόριό τους. Ένα χρόνο μετά ανακαλύφθηκε ότι μεταλλάξεις των γονιδίων των WNK1 και WNK4 ευθύνονται για την εμφάνιση μιας μορφής οικογενούς υπέρτασης που συνοδεύεται από υπερκαλιαιμία και οξέωση γνωστής και ως ψευδής υποαλδοστερονισμός τύπου ΙΙ ή σύνδρομο Gordon. Οι ως άνω ανακαλύψεις έθεσαν επί τάπητος το ερώτημα για τον πιθανό παθογενετικό ρόλο των συνμεταφορέων νατρίου-χλωρίου στον άπω νεφρώνα στην υπέρταση. Η έρευνα που ακολούθησε έδειξε ότι οι WNK κινάσες λειτουργούν ως ενδοκυττάριοι αισθητήρες χλωρίου και ρυθμίζουν αντίστοιχα τη δραστηριότητα των συνμεταφορέων νατρίου-χλωρίου στον άπω νεφρώνα. Επί πλέον αποδείχθηκε ότι ο ανταλλάκτης χλωρίου/διττανθρακικών, γνωστός ως Πεντρίνη (pendrin), που εκφράζεται στα β-εμβόλιμα κύτταρα του αθροιστικού σωληναρίου, παίζει σημαντικό ρόλο στην επαναρρόφηση χλωριούχου νατρίου από το συγκεκριμένο τμήμα του νεφρώνα. Συμπερασματικά μετά από σχεδόν έναν αιώνα επισταμένης έρευνας καταδείχθηκε ότι η διακυτταρική μεταφορά νατρίου στον άπω νεφρώνα επιτελείται κυρίως μέσω συμμεταφοράς με χλώριο. Το ανιόν χλωρίου παίζει πρωτεύοντα ρόλο στην έκκριση ρενίνης και την ρύθμιση του ενδοκυτταρίου όγκου. Οι WNK κινάσες παίζουν το ρόλο ρυθμιστή της ενδοκυττάριας συγκέντρωσης χλωρίου και μέσω αυτού του ενδοκυτταρίου όγκου. Μετά από αυτά ίσως είναι καιρός να μιλάμε για «χλωριοευαίσθητη» και όχι «νατριοευαίσθητη» υπέρταση.

Λέξεις ευρετηρίου: Ανιόν χλωρίου, Νατριοευαισθησία στην υπέρταση, Πεντρίνη, With no-lysine-kinases

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