ROLE OF POTASSIUM IONS AND ION CHANNELS IN THE MUSCLE OR WHY IS ONE PLATE MEAT SOUP SO DELICIOUS?

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Abstract

The sensory pleasure of a good soup represents a complex synthesis of molecular and cellular inputs of ions. Here we are focusing on the intake of potassium ions affecting the muscles along with the sensorineural science of eating a satisfying bowl of soup. Unbalanced ionic homeostasis and modified expression of ion channels is presumably involved in the inhibition of normal physiological functions. Salts are necessary components of soup with the flavorful broth that the salt complements turn out to activate another components of the sense of taste, the sense of savoury. Here we show the properties, molecular composition and pharmacological effects of potassium ions for the main channels of Kv-type, Kir and connexin channels in the ear system and the muscle components under physiological concentration of K-ions. However, the high concentration of K^+- and Na^+-ions evokes an aversive response, which is curiously not well understood at molecular level that respond to sour or bitter flavors. The ionic homeostasis has the main role to keep the cell tone in the muscle cells and, within all cells, what is supported by soup containing a wide variety of ions and flavors.

Keywords: ions, meal, potassium ion, ion channel complexes

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Introduction

About 98 % of total potassium in the body is located in the intracellular space, and muscle 44 containing 80% of the intracellular potassium. But in the extracellular space only 2% of the total potassium ion (K^+) is present, and the remaining amount is distributed in the bone, liver and erythrocytes. K^+ in the extracellular space critically determines the resting membrane potential of the cells and, together with intracellular K-ions, connected with the cellular potassium homeostasis. The movement of K^+ in and out of the muscle plays essential role in extracellular potassium homeostasis mediated by plants by their transporters. The K^+ uptake is processed by Na^+-, K^+- adenosine triphosphatase (Na^+, K^+-ATPase) and released by inward-rectifier K^+ channels.

To keep our health we intake several ions from meals which are needed to keep and regulate the physiological function of cells. The sensory pleasure of a good soup represents complex formulation of molecular and cellular inputs of ions. Here we are focusing on the intake of potassium ions to take a look into the muscle by the sensorineural science of eating a satisfying bowl of soup.

Ions in the organs serve as structural and functional elements; classified as primary, secondary and micronutrients. The primary elements in plants are nitrogen, phosphorus, and potassium, originated from the soil and are often used in relatively large amounts by the transport system of plants. Ions involve both anions and cations: NO_3^-, NH_4^+, $H_2PO_4^-$, HPO_4^{2-} and K^+ ions.

The animals contain the same ions but the concentration depends on the species and also on the organs. Secondary nutrients are available in adequate supply and the main components are calcium, magnesium and sulphur [1]. These are usually used in large amounts. In contrast, the microelements are iron, zinc, molybdenum, manganese, boron, copper, cobalt, and chlorine known as micronutrients or trace elements needed in small concentration in organs.

HIGH POTASSIUM CONTENTS IN ANIMALS AND PLANTS

Potassium in milk and soups

Mammalians are known to have the milk productions which are rich in all type of ions similarly to the case of soups regarding the ionic content (Table 1 and Table 2). The daily potassium demand of a healthy human body under normal physical activity is 2-5 g (50–125 mmol). We can provide this amount for our body through different foodstuffs. Potassium in foods is present in the form of salts. The same amount of foodstuffs can satisfy the demand of our body in different proportions. There is no enormous difference in the potassium content of the most consumed foods, although we can discover 2-4 fold differences.

The potassium content of milk from dairy animals can play a significant role to satisfy our daily potassium demand. Comparing the milk of some milking animal species, several researchers determined that the milk of small ruminants (goats, sheep) contains more potassium than the milk of cows [2-4A].

The potassium content of milk depends on many factors, such as species, feeding (the amount of potassium consumed by the animal) and others. The potassium content of dairy products is, of course, determined by the potassium content of the milk, however, some separation techniques e.g. membrane separation and other concentration techniques can significantly affect the amount of potassium in the products.

A tight negative correlation was observed between lactose content and calcium and potassium content in goat and other species milk (Table 1). This suggests that osmotic pressure may also affect the amount of different elements in milk.

Table 1. Potassium content of milk-types and products of milk

Products	Value ($g\ l^{-1}$)	Value ($g\ kg^{-1}$)	References
Milk-types and milk drinks			
Whole milk		1.5	Walstra et al. 2006, Rehmann and Hõth 1971
Whole milk		1.204 – 1.348	Csapó, Csapó-Kiss 1983
Whole milk		1.09	Lante et al. 2006
Whole milk		1.150 – 2.000	Fox et al. 2015
Skimmed milk		1.50 1.64	Tamime 2009
Plain yogurt		1.345	Souza et al. 2018
Flavoured milk drinks	1.482 2.623		Andres et al. 2016
Whey		1.6	Bylund (Tetra Pak)
Whole buffalo milk	0.860		Stocco et al. 2016
Whole goat milk		1.5-1.8	Konar et al. 1971,
		1.70 – 2.42	Jennes 1980
		1.64-2.74	Moreno-Rojas 1994
Whole sheep milk		1.4-1.54	Richardson et al. 1974
		1.8-1.96	Misic, Petrovics, 1976
		0.960 - 1960	Park 2006
		1.32-1.85	Csapó et al. 1998
Concentrates			
Evaporated whole milk		3.00 3.68	Tamime 2009
Evaporated skimmed milk		3.24–3.30	Tamime 2009
Sweetened condensed whole milk		3.57–4.02	Tamime 2009
Sweetened condensed skimmed milk		4.45–4.75	Tamime 2009
Whey protein concentrate		5.52	Noël et al. 2008
Other products			
Processed cheeses		3.38 – 3.52	Noël et al. 2008
Acid casein		0.026	Noël et al. 2008
Powders			
Whole milk powder		12.00	Noël et al. 2008
Whole milk powder		11.57–13.00	Tamime 2009
Skimmed milk powders		16.0 - 17.8	Noël et al. 2008
Skimmed milk powder		16.03 17.90	Tamime 2009
Whey powder		23.60	Noël et al. 2008
Freeze-dried cheese (Gouda)		1.14	Noël et al. 2008
Casein and whey protein powders, concentrates			
Ca-caseinate	100		Noël et al. 2008
K-caseinate	1650		Noël et al. 2008
Na-caseinate	20		Noël et al. 2008
Casein (rennet)	30		Noël et al. 2008
Low-protein whey protein concentrate(~35 g 100 g−1)	11.90		Noël et al. 2008
High-protein whey protein concentrate (65 g 100 g−1)	6.50		Noël et al. 2008

References: [8-9], [12], [60-74]

Examining the effect of lactation, some authors observed a continuous decrease in minerals, but in contrast to other macro elements, there was no change in the observed potassium level during lactation [5-6]. According to the results, the potassium content increases in the first 3 months [7],and then decreases slightly (but continuously) until the end of lactation (1.386 - 1.419 - 1.267). The alteration can be described by quadratic equation [8]. In contrast, in milk samples coming from merino ewes, a slight but continuous decrease was observed in the first 30 days of lactation [9].

Examining the effect of different feeding systems, significant difference could be detected not only in the main milk components and milk quantities, but also in the minerals partially bound to the main milk components [10]. It is emphasized that the concentration of the ingredients can be very important in case of some milk products and considering the processing plant capacity. It is especially important for specialty products such as therapeutic products and infant formulas. At the same time, they draw attention to significant changes in the composition of milk through feeding which can affect the thermal stability of milk during processing.

Effect of the processing of milk

Examining the potassium content of different flavoured milk drinks [11], higher potassium values were determined in samples containing orange juice, but the statistical variance of the results was also greater. Without orange, the potassium content ranged from 1.482 to 2.623, while that of the milk drink with orange juice ranged from 2.93 to 3.95 g / kg.

As a result of nanofiltration, the decrease in the potassium content of cheese whey can be approximately 31% in the retentive [12]. However, examining the effect of heat treatment and advanced technology (High Pressure Treatment)[13], it was found that the potassium content of milk samples did not change significantly (1.926-2.022 g /L).

Potassium in meat

Meat and meat products usually contain more potassium than milk. In average, potassium content of meats can be characterized with a range of 2.5 – 4.00 g/kg, affected by many factors as well as by species differences (Table 2) [14]. Not only pure meats but different edible meat by-products contain remarkable potassium. These values stand close to the values of meats. In case of different species we can say that the range of potassium is similar as follows (in g/kg): beef 0.16-4.29, pork 0.55-3.58, lamb 2.38-4.28, and veal 2.43-4.33 [15-16].

Table 2. Potassium content of meat in different species

Products	Values (g/kg)	References
Beef	3.45	Toscani, Buniak 1947
Veal	3.01	Toscani, Buniak 1947
Lamb	2.49	Toscani, Buniak 1947
Chicken	0.29-1.13	Kravis et al. 1960
Camel	2.28-8.10	Kadim and Isam 2013
Peking Duck	3.65-3-76	Kokoszynski et al. 2019
Donkey	3.43	Polidori et al. 2008
Fish	3.1	Cowgill et al. 1968
Rabbit	3.88	Hermida et al. 2006
Deer	2.48 3.35	Soriano et al. 2020

References: [16], [75-81]

It is important to note that the body weight gain of animals depends on the potassium content of feeds, but this fact alone does not affect the potassium level in tissues. Considering the moisture content and the potassium salts used as additive in the production of some meat products, the end products may contain more potassium than the raw meat.

Potassium content in plants and soups

The highest concentration of K^+ content is in kale (savory cabbage, brussels sprout too) among plants, and also in salmon and seaweed is the richest with potassium and another macro- and micronutrients. The king is kale because it contains vitamins C, A and K1. Vitamin B6, potassium, calcium, magnesium, copper and manganese are also in high concentrations in kale. Furthermore, it has 2 grams of fiber, 3 grams of protein per 100g, rather high amounts, and only 50 calories [17]. Most probably kale is healthier than spinach. Both are very nutritious, but kale contains less amount of oxalate, which can bind minerals like calcium in your intestine, preventing them from being absorbed. Kale and other green leaves also contain high amount of various bioactive compounds, including isothiocyanates and indole-3-carbinol, which have been shown to fight cancer in test-tube experiments and animal studies [18].

Table 3. The main minerals in meat soups. Values of minerals are in mg/100 g

Soups	Moisture	Ash	Iron	Calcium	Phosphorus	Sodium	Potassium
Beef	40.16±0.03	2.18±0.11	5.00±0.29	110±1.52	270±1.15	150±2.87	**320±1.53**
Chicken	57.78+0.05	4.69+0.10	1.10+0.10	190+2.51	100+1.04	190±2.89	**140±1.15**
Fish	40.30⊥0.25	3.95⊥0.10	1.00⊥0.12	130⊥2.65	500±1.53	140⊥1.73	**430±1.78**
Turkey	41.96⊥0.05	6.47⊥0.05	5.00⊥0.50	200⊥1.15	1830±1.27	160⊥1.00	**200±1.73**
Beans + Vegetable	74.67⊥0.63	1.36⊥0.03	1.80⊥0.13	90.0⊥1.15	304±1.53	467⊥1.15	**480±1.53**

1.) Data = mean ± SD; n = 3

2.) References: https://d1wqtxts1xzle7.cloudfront.net/47034644/Micro_Nutrient_Content_of_Selected_Indig20160705-6328-1i1mm3h.pdf?1467748336=&response-contentdisposition=inline%3B+filename%3DMicro_Nutrient_Content_of_Selected_Indig.pdf&Expires= 1593202399 &Signature=AdmRUZh1GZM9hhOs

The measured pivotal macro- and micro-elements in the studies indicated that these concentration variable in different meat soups (Table 3).

We were interested in to get an answer to our question: Why are potassium ions (along with their channels) so important ion in our life? The hypothesis is that the ionic homeostasis changes under stress (i.e. stress or hungriness) in cells and balanced by ions in meal to keep the tone of cells. Potassium ions and ion channels are dominant in the muscle cells.

Role of potassium ions in cells and organs, focusing on muscle

The physiological role of potassium ions with channels in the healthy muscle is widely studied [19]. At physiological ion concentrations (3–5 mM K^+ extracellularly, 140 mM K^+ intracellularly), the electrochemical gradient for K^+ (the driving force for movement of K^+ through a K^+ channel) is outward. Potassium is mainly an intracellular ion. The Na^+, K^+-ATPase pump is primarily responsible for regulating the homeostasis

between sodium and potassium which pumps out sodium in exchange for potassium which moves into the cells.

Vascular smooth muscle (VSM) cells, in small arteries and arterioles that develop myogenic tone when pressurized, are relatively depolarized, with membrane potentials on the order of -45 to -30 mV [20-21]. When the K^+ channels are open, it causes K^+ diffusion out of the cell, leading to the loss of positive charge and membrane hyperpolarization [22]. Conversely, the closure of open K^+ channels will result in a decrease in this hyperpolarizing current, and membrane depolarization. Voltage-gated Ca^{2+} channels contribute substantially to the regulation of intracellular Ca^{2+} and contraction of differentiated, contractile VSM cells, particularly in resistance arteries and arterioles. Depolarization (voltage- dependent activation) and deactivation (hyperpolarization) by these channels importantly regulates VSM contraction.

The structure of the pore of K^+ channels is supposed to be similar across all of the channels based on the studies of two transmembrane (TM) domain K^+ channels [23].

Potassium disorders are related to cardiac arrhythmias. Hypokalemia occurs when serum potassium levels under 3.6 mmol/L. Weakness, fatigue and muscle twitching present in hypokalemia. Hyperkalemia occur when the serum potassium levels above 5.5 mmol/L; which can result in arrhythmias. Muscle cramps, muscle weakness, rhabdomyolysis, myoglobinuria present the signs and symptoms in hyperkalemia [24].

Potassium channels in vascular smooth muscle

Potassium ions and another ion channels contribute to the regulation of vascular smooth muscle (VSM) in contraction and growth. These ion channels are dominant in the ion conductance of the VSM cell membrane; determine and regulate the membrane potential of VSM cells. They are expressed in multiple isoforms (five classes) of K^+ channels and contribute to the regulation of contraction and cell proliferation. The membrane potential regulates several physiological functions of voltage-gated Ca^{2+} channels (VGCC), the open-state probability, also the Ca^{2+} influx, intracellular Ca^{2+}, VSM contraction and affects release of Ca^{2+} from internal stores and the Ca^{2+} sensitivity of the contractile machinery [25-26, 19].

The large-conductance Ca^{2+} -activated K^+ (BKCa) channels, intermediate-conductance Ca^{2+}-activated K^+ (KCa3.1) channels, the isoforms of voltage-gated K^+ (KV or Kv) channels, ATP-sensitive K^+ (KATP) channels, and inward-rectifier K^+ (KIR) channels in both contractile and proliferating VSM cells [19]. The members of the two-pore K^+ (K2P) channel family have a role of K^+ channels. The accessory β1-subunits slow the gating kinetics, increase the Ca^{2+} sensitivity, and affect the pharmacology of the channels [27]. Generally, K^+ channels participate in all aspects of regulation of VSM contraction. Furthermore, they contribute to the regulation of proliferation of VSM cells [28, 29].). The Kv3.4 channels modulate proliferation of smooth muscle cells mediated by cell cycle-dependent expression in human uterine artery.

The Ca-dependent big conductance (BKCa) K- channels are macro-complex in expression but the activity of BKCa channels is depressed in obesity [30]. In diabetic patients the impaired function reduced expression and function of the β1-subunits was measured in smooth muscle of retinal arteria ([31]. Voltage-gated K^+ channels are active at the resting membrane potential of VSM cells in blood vessels displaying myogenic tone; closure of these channels leads to membrane depolarization and vasoconstriction [25-26]. The function of VSM ATP dependent K- ion channels (KATP) seems to be decreased in obesity.

VSM cells also express one or more members of the strong inward rectifier K^+ channels, with Kir2.1 being the dominant isoform expressed in small resistance arteries and arterioles [32]. These channels act to amplify the hyperpolarization induced by opening of other K-ion channels or cel-

lular processes, i.e. the Na^+/K^+ ATPase, and thus, may contribute to the mechanism of action of a number of vasodilators. The effects of hypertension on Kir channel function are not clear; increases, decreases, or no change in function was all observed. In diabetes it has been reported to increase.

Role of potassium channels in skeletal muscle

The role of potassium channels located on the skeletal muscle membrane is the in vivo and in vitro reduction of muscle contractile activity. Activation of voltage-gated potassium channels (Kv7) represented in many tissues including the excitable cells-neuronal and muscular.

The voltage gating Na^+ and K^+ channels together with Cl^- channels are the main ion channels involved in muscle excitability. Several mutations of the genes encoding the pore forming subunits of these channels can cause muscle hyper-excitability and stiffness or hypo- excitability and weakness or paralysis. However, the Ca^{2+} channels have a pivotal function in the excitation-contraction events of skeletal muscle. From the development of action potential (AP) of the sarcolemma through the increase in intracellular Ca^{2+} which activates contraction anchored to transverse tubular membrane, plays an essential role of voltage-sensor: controlling the release of Ca^{2+} ions into the cytosol.

KCNQ channels have been identified in all type muscle tissues. However, their role in vasoregulation and chronic vascular diseases remains elusive. These data suggest that KCNQ channels play a pivotal role in vasoregulation and forming the shape of action potentials along with electrocardiogram. More than 300 mutations have been detected in genes for KCNQs causing mild and severe diseases [33].

Energy homeostasis in mitochondria is pivotal for proper muscle cell function. The proper physiological function of mitochondrial K-ion channels and uncoupling proteins may both regulate the generation of reactive oxygen species despite the molecular differences between these proteins [34]. The mitoKATP channel can protect cardiac tissue against ischemia; even the details of this protective mechanism are still unknown because the macromolecular composition of the mitoKATP channel is still remains unclear. Earlier studies suggested that the inward rectifying K^+ channel subunit Kir6.1 is a pore-forming unit of the mitoKATP channel, but it is still not evaluated. However, a screen using pharmacological and genetic manipulations provided evidence that a splice variant of the renal outer medullary potassium channel (ROMK) is a pore-forming unit of the cardiac mitoKATP channel.

The mitochondrial Ca-dependent big-conductance (mitoBKCa) ion channel constitutes a unique potassium channel in the mitochondria of cardiac muscle. In contrast to the KATP channel, which is also present in the surface membrane, the mitoBKCa channel is present only in the inner mitochondrial membrane in skeletal and cardiac muscles [35].

Potassium channels in heart and cardiomyopathy

In cardiomyocytes we can detect the outward and inward currents linked to more than 32 ion channels and more than 70 isoforms [36-38]. They form big macromolecules with accessory subunits and regulator elements. The Kir2.x K^+ channels (encoded by KCNJ genes) maintain and regulate the inward rectifier current (IK1) contributing to the final repolarization phase of the action potential (AP) in cardiomyocytes. Kir-type ion channels share structural similarities [39] and have a role in a wide variety of physiological functions including insulin release, vascular tone, heart rate, buffering of potassium, and renal salt flow [37-38]. These ion channels strongly modulate cell excitability and repolarization of AP, and determine the cellular resting membrane potential [40-42]. Kir2.x subunits (Kir2.1, Kir2.2, Kir2.3,

Kir2.4 and Kir2.6), assemble to form homo- or hetero-tetrameric inward rectifier potassium channels in cardiomyocytes. These channels interact with protein complexes that may be important to target and traffic ion channels, anchor and stabilize the channels into the plasma membrane [41- 43]. There are sex differences in the expressed potassium channel proteins. We revealed in earlier results that endogenous five isoforms of Kir2.x channels associate with anchoring protein of synaptic associated protein97 (SAP97) (Figure 1), forming specific signaling complexes [41, 44]. Kir 2.1, Kir2.2 proteins strongly bind SAP97 and they show co-localization near the T-tubules. In cardiomyopathic tissue, studying the human dilated cardiomyopathic (DCM) samples in the heart, the expressed Kir2.1, Kir2.2, Kir2.3 isoforms are drastically decreased with the anchoring and modulator protein SAP97 at gene and protein level too. The physiological studies evaluated that when the density of inward rectifier currents (IK1) decreased of Kir channel expression in cardiomyopathy, the genes and protein level of Kir ion channels decreased comparing to the healthy heart samples (Figure 1). Also the KvLQT ion channels with accessory subunits and two-pore ion channels, K2P (TWIK1, TASK1) are less than 50% decreased in the heart tissues of DCM patients [45-46].

The Kv –type ion channels are responsible for the transient outward currents (ITO1). To test the toxin effects on the outward potassium channels for Kv4.3 and anchoring protein SAP97 channels also decreased these genes and proteins using 6-epi-ophiobolin A (6EOPA) toxins in heart cell culture (Kv4.x) [46]. We measured the physico-chemical parameters which also changed, and less amount of kv4.3 ion channel macro complex were stained on the surface of heart cell line (Figure2) [42]. The elasticity of cardiomyocytes after treatment with 6EOPA suffered a mild change. The altered function found in DCM patients, however, may lead to severe heart disease, even sudden death. DCM is a myocardial disorder leading to left ventricular dilation and systolic dysfunction often, also to progressive heart failure, arrhythmias, and premature death [36-38, 41-42, 46-48]. The impaired mitochondria were studied where KATP ion channels are damaged in the cardiovascular system [49].

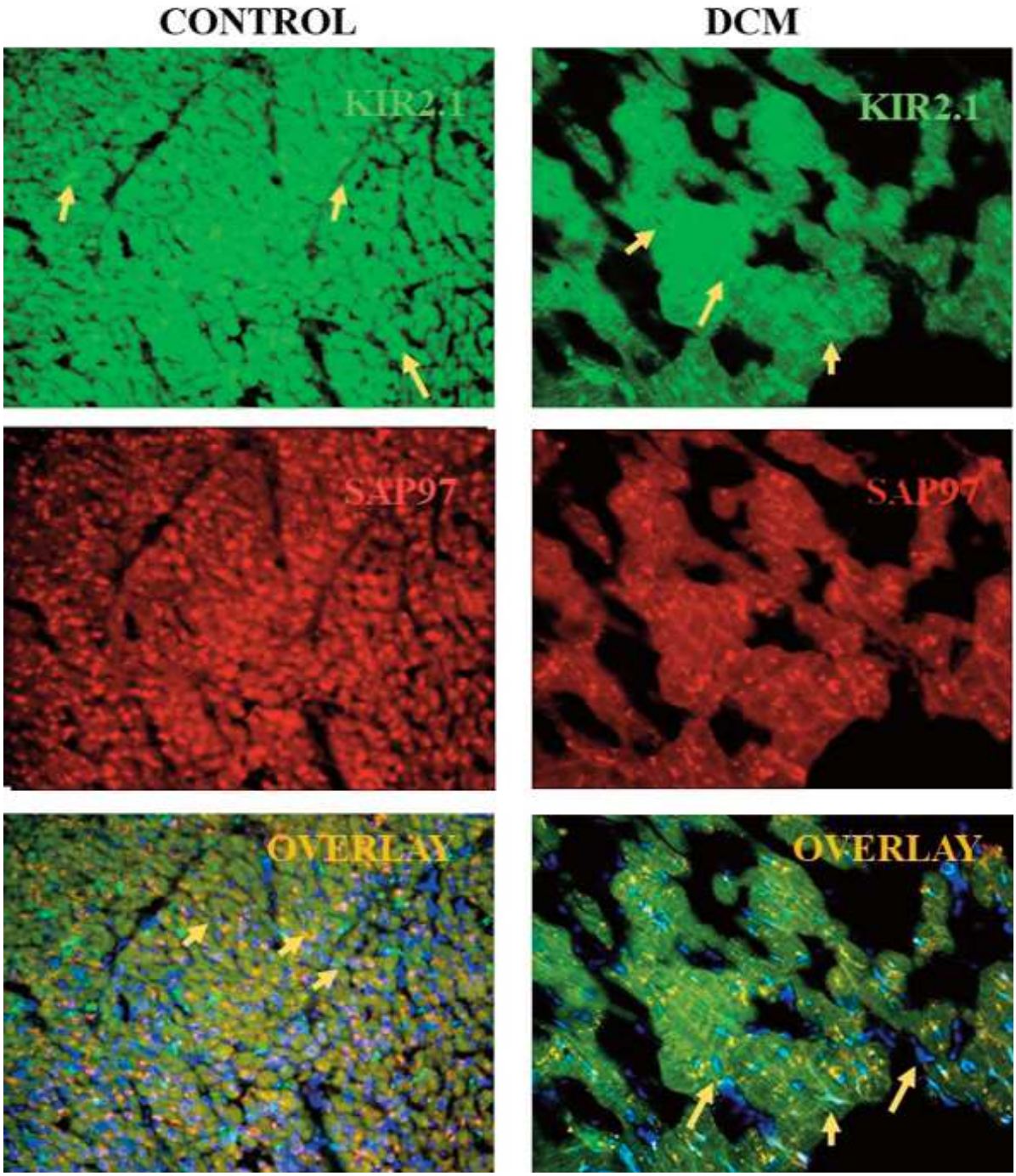

Fig. 1. Alteration of Kir2.1 ion channel complex in dilated cardiomyopathy (DCM). Arrows show the Kir2.1 ion channels labeled with green dye, synaptic associated protein97 (SAP97 anchoring protein) with red and nucleus with 2,4-diamino-2-phenylindole (DAPI, blue). Tissue was a kind gift of Professor Dr. Andras Varro.

These results suggested us that the measured mild effects on physiological parameters may be causing severe alteration in the macro-complexes of potassium channels that can change the proper gating of these channels.

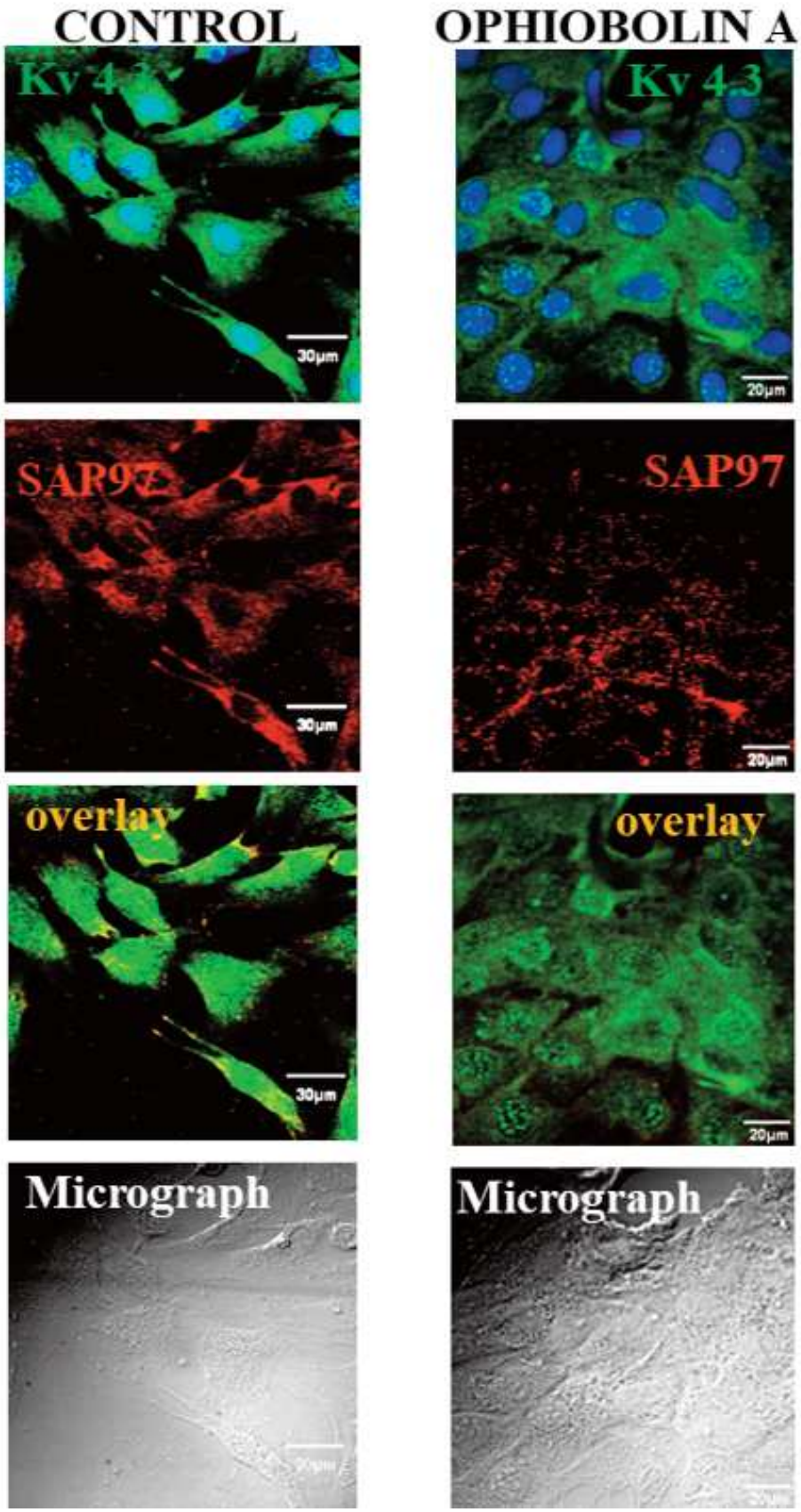

Fig. 2. Alteration of Kv4.3 ion channel complex on the heart in the presence of ophiobolin A toxin. The Kv4.3 ion channel (Cx43) protein was labeled with green, synaptic associated protein97 (SAP97) with red d nucleus with 2,4-diamino-2-phenylindole (DAPI, blue).

Potassium ions and channels in the cell-cell contact of human body

Hypercholesterolemia suppresses inwardly rectifying K^+ channels in aortic endothelium *in vitro* and *in vivo* [50]. Connexins have a major role in cell-to-cell interactions and in the permeability of the channels carrying diverse ions and small molecules, which maintain the physiological condition of the cells (muscle, neural, cochlea etc.) [51]. Connexin 43 (Cx43) expression decreased in myocardial tissues of DCM patients, showed positive dyeing spots in the heart tissues, and these were different in size, distribution, color and disparity, some of them were distributed in the form of particles, compared to control group. Quantitative data showed that there was significant difference between the two groups in Cx43 expressive area, but there was no difference between the left and right ventricles in each group itself [41, 52-53].

Role of potassium channels in the sensorineural cells focusing on ear system

Connexin26 (Cx26) and connexin43 (Cx43) have a major role in cell-to-cell interactions and in the permeability of the channels for diverse ions and small molecules which maintain the physiological condition of the sensorineural system as well as in the cochlea [51-56]. Different connexins may be important factors in the flawless linked to cell-to-cell interactions that maintain the fast electrogenic mechanisms between the cochlea and neuronal system.

Connexins, Kv-type ion channels, and pannexins have a dominant role in maintaining the potassium ion homeostasis in the cochlea. The cellular background currents are sustained by Kir2.1 ion channels; however, their involvement in the hearing system is less clear. Over 50% of hearing loss or nonsyndromic deafness cases in different human populations investigated in the last decades [54-56]. There are mutations in a few genes causing deafness.

Even in the early childhood, it should be very important the detection of genetic mutations for inner ear impairment which is crucial to provide hearing rehabilitation with an outstanding functional outcome, i.e. to maintain the development of the peripheral and central auditory pathway for unhindered future benefits. Cx26 proteins were localized in the outer membrane of the cochlea forming hemichannels in the cochlea where the Cx26 channels are the most abundant and are involved in the potassium-recycling pathway. In non-syndromic hearing loss it causes mutations in connexin26 (Cx26) and connexin30 (Cx30) which have frequently been associated with hearing loss and deafness [54]. Hereditary hearing diseases are known to be associated with mutations, i.e. the autosomal recessive non-syndromic hearing loss (ARNSHL), seizures, and sensorineural deafness [56]. Pendred syndrome (PDS), deafness, and the hearing loss overlap with Andersen-Tawil syndrome rarely. The Andersen-Tawil syndrome is characterized by malfunctioning Kir2.1 proteins, which can cause deafness with cardiomyopathy too [54-57].

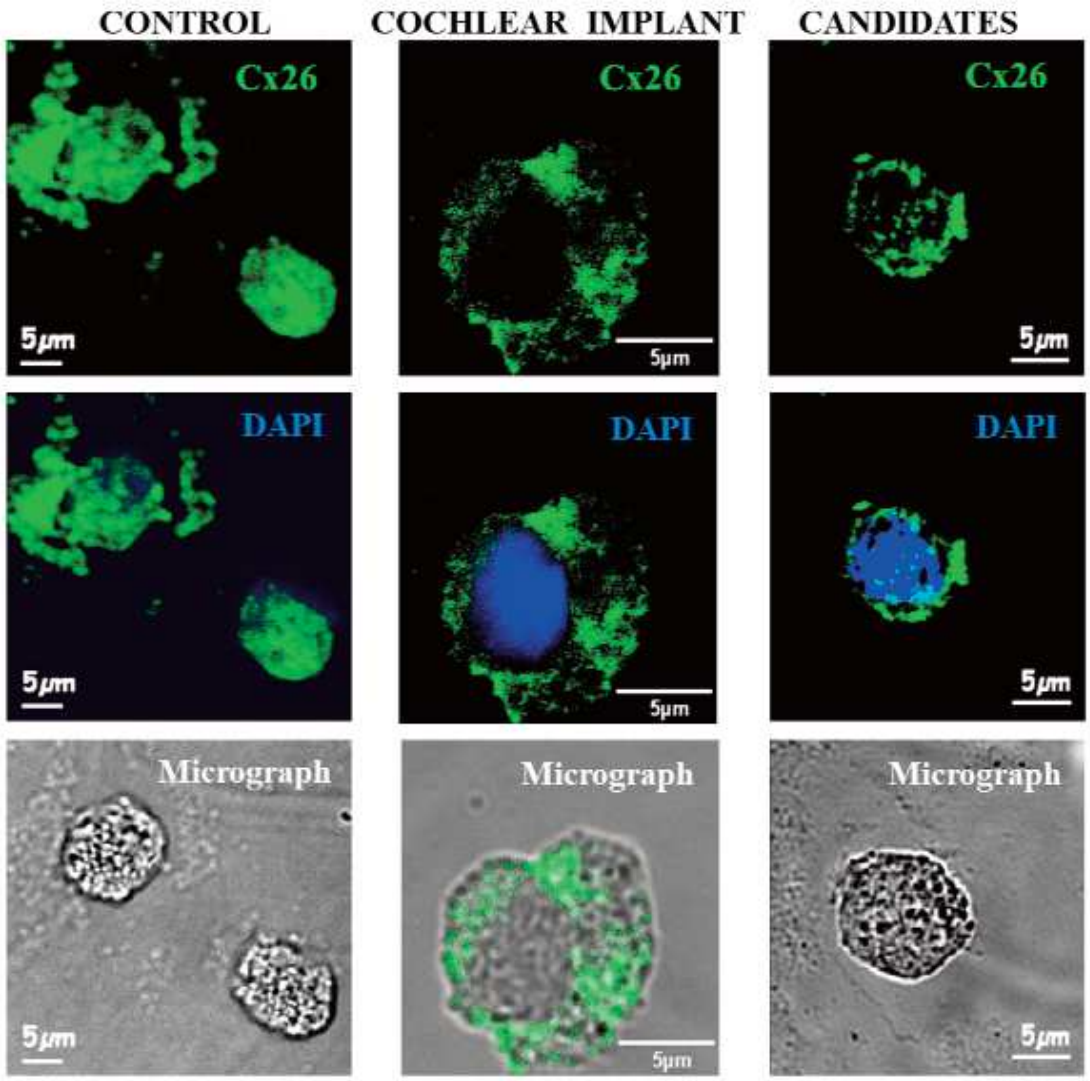

Fig. 3A. Expression of Cx26 proteins is abundant on control cells and decreased in the presence of the GJB2 gene mutation. The connexin 26 (Cx26) protein was labeled with green and nucleus with 2,4-diamino-2-phenylindole (DAPI, blue)

We investigated non-randomized, profoundly hearing-impaired cochlear implant candidates. All patients in the diseased group had nonsyndromic sensorineural hearing loss, altogether 80 Hungarian patients including with overlapping diseases. Prior Objective tests were used for the evaluation of hearing sensitivity on patients. Otoacoustic emissions (OAEs) indicate the functional integrity of the outer hair cells in the inner ear [54, 58]. Our representative results evaluated the levels of connexins 26 and connexins 43 proteins of non-diseased patients compared to deafness in Figure 3A and B. Earlier we investigated gene mutation analysis of connexins. The results are shown that 25.0% of hearing loss patients carried a mutation in the GJB2 gene (encoded Cx26), and only 1.2% had a mutation in the GJB3 gene (encoded Cx30) out of 80 Hungarian patients [54].

The high intensity staining on the surface of lymphocyte cells indicated a high abundance of Cx26 in Figure 3. In the presence of the GJB2 gene mutation, the Cx26 protein level decreased and the pattern of the distribution was disrupted in deafness. Kir2.x isoforms colocalized with Sap97 in healthy patients but it was reduced in disease. The regulation and modulation of these ion channel complexes have a strong effect in the development of different tissue types in hereditary diseases associated with cardiomyopathy and deafness too [54].

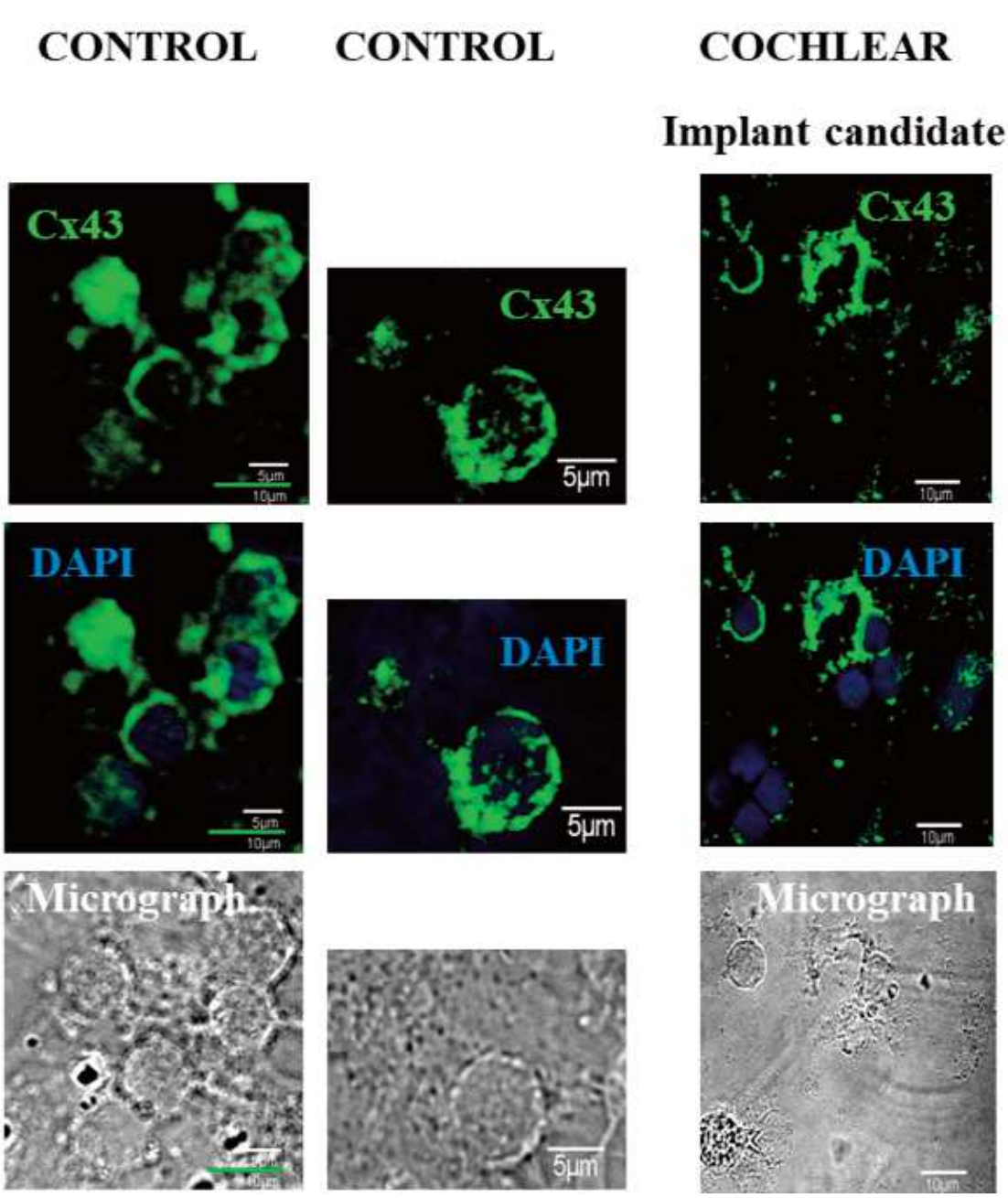

Fig. 3B. The level of Cx43 ion channel protein decreased in hearing loss patient. The connexin 26 (Cx43) protein was labeled with green dye and nucleus with 2,4-diamino-2-phenylindole (DAPI, blue)

Direct and/or indirect interactions are essential for the normal physiological function of the Kir2.1 complex and inward rectifier currents contributing to normal potassium ion homeostasis. These genes have demonstrated gender differences and have been remodeled in cardiomyopathy too [38].

Drugs, antibiotics and other molecules may cause fatal deafness or heart diseases i.e. acetyls, semicillin in high dose or frequently used drugs. Not only the drugs but the low amount of potassium intake can also cause several diseases in our life [59].

Summary

The purpose was to demonstrate that the muscle tissues and the sensorineural system in the ear affect ion homeostasis originating from potassium. We could understand when the harmonic ion balance is impaired, and the non-balanced K-ion channels blocked, how it can be

restored the normal physiological functions partially or not.

The low level of SAP97 anchoring protein decreased drastically in hearing loss patients. Our earlier studies confirmed the colocalization of Kir2.1 ion channel with SAP97 anchoring protein in non-diseased patients but only partial colocalization with disrupted clustering occurred on the surface of blood cells in patients with DCM and deafness.

Milk and milk products are the richest foods with all kind of elements. Kale, salmon, seaweeds are rich in potassium and kale is one of the most nutrient-dense vegetables you can eat, containing large amounts of vitamins, minerals and cancer-fighting compounds. Fish, salmons, beef and other meats are carrying high amount of K-ions.

Even we have learnt a lot about the expression and function of K-ion channels in the regulation of muscle contraction and proliferation in the past 40 years, there remained several outstanding questions. First, why are do expressed so many different KV-type channels in muscle cells? Whether this is simply a matter of redundancy or the pattern of the expression of these channels tunes the particular electrophysiology of VSM cells in different vascular beds is not yet clear [19]? Second, while is it clear that, like all ion channels, the existence in multi-protein signaling domains [41-42], our knowledge about understanding of the regional heterogeneity in nature and composition of these signaling domains in different vascular beds is yet incomplete. Finally, our understanding of the regulation of expression and function of K^+ channels in major cardiovascular disease states also remains elusive, especially that they relate to different vascular beds all around the body [19, 26].

Potassium, first of all, is a "good friend" for our healthy system [91]. Nowadays some studies evaluated that the beneficial effects of potassium intake on blood pressure and clinical outcomes. In a meta-analysis it was found that higher potassium intake resulted in blood pressure lowering in the overall population studied, with more pronounced effects in patients with hypertension or consuming a high sodium diet [17, 33]. Furthermore, analysis of 11 cohort studies with a total of 127,038 participants showed that potassium intake in high range (90–120 mmol/day) was associated with a decreased risk of stroke. Based on these studies the World Health Organization (WHO) recommends daily potassium intake of at least 90 mmol/day[1], while the Institute of Medicine recommends an intake at least 155 mmol/day.

Take home messages

Potassium channels participate in all aspects of regulation of VSM contraction.

K^+ channels have a dominant role in excitability in muscle cells to keep the tone of cells and regulate the outward and inward flow of K ions mediated by KV-, Kir-type and other ion channels in human body.

K-ions contribute to the cell-cell communication with connexins (Cx 26, 30, 32, 42, 43, 45) in muscle, endothelial and neural tissues.

Serving our body, we have to consume enough potassium with foodstuffs. We know, that many foodstuff contain outstanding amount of potassium, but it is coming from the use of additives e.g. potassium sorbate, potassium nitrate, potassium polyphosphates. Furthermore, we know that foods may also contain substances that inhibit the absorption of ions, such as spices. We serve our health if we consider these facts and we create a well-balanced, mixed diet from animal and plant origin meals preferably with additive-free foods.

Methods and ethical statement

All the methods were described in the references of [41-42, 46 and 54]. Human heart tissues were a kind gift of Professor Dr. Andras Varro and prepared in the University of Szeged, Faculty of Medicine, Department of Pharmacology and Pharmacotherapy, Szeged, Hungary [41]. The samples were obtained from organ donors

whose hearts were explanted to obtain pulmonary and aortic valves for transplant surgery. The investigations conform to the principles of the Declaration of Helsinki. Experimental protocols were approved by the University of Szeged and National Scientific and Research Ethical Review Boards (No. 51-57/1997 OEj and 4991- 0/2010-1018EKU (339/PI/010.)).

The investigations conformed to the Declaration of Helsinki. Experimental protocols were authorized by the University of Szeged and National Scientific Research Ethical Review Boards (No. 38/2014 and 2017). The blood cells were taken and kept in cold (4–6°C) for 2–4 hours prior to investigations.The Cx23, Cx43, kir2.x and kv4.x channels were labeling as we reported earlier both in tissue and cells using confocal microscopy after immunofluorescence labeling [41-42, 54].

Conflict of interest

The authors declares no conflict of interest.

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Resumo

La sensa plezuro de bona supo reprezentas kompleksan sintezon de molekulaj kaj ĉelaj enigoj de jonoj. Ĉi tie ni fokusiĝas pri la ingestaĵo de kaliojonoj influantaj la muskolojn kune kun la sensneŭrala scienco manĝi kontentigan bovlon da supo. Malekvilibra jona homeostazo kaj modifita esprimo de kanaloj estas supozeble implikitaj en la inhibicio de normalaj fiziologiaj funkcioj. Saloj estas necesaj eroj de supo kun la bongusta buljono, kiun la salo kompletigas por aktivigi aliajn erojn de la senca gusto, la sento de sekeco. Ĉi tie ni montras la proprajĵojn, molekulan konsiston kaj farmakologiajn efikojn de kaliojonoj por la ĉefaj kanaloj de specoj Kv, Kir kaj koneksinaj kanaloj en la orela sistemo kaj la muskolaj komponantoj sub fiziologia koncentriĝo de K-jonoj. Tamen la alta koncentriĝo de K^+ kaj Na^+ jonoj elvokas avidan respondon, kurioze ne bone komprenatan ĉe molekula nivelo, kiu reagas al acidaj aŭ amaraj gustoj. La jona homeostazo havas la ĉefan rolon konservi la ĉelan tonon en la muskolaj ĉeloj kaj, ene de ĉiuj ĉeloj, kio estas subtenata de supo enhavanta ampleksan varion de jonoj kaj gustoj...

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