Proteomics & Bioinformatics
PB, 2(1): 62-67
www.scitcentral.com

ISSN: 2641-7561

Review Article: Open Access

Homeostasis of Sodium (Na) and Potassium (K) in Epidermis as a Self-Organized Criticality Phenomenon

VI Petukhov[1*], EV Dmitriev[2], L Kh Baumane[3], AV Skalny[4], Yu N Lobanova[4] and AR Grabeklis[4*]

*[*1]Vladimir State University, Vladimir, Russia*

[2]Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow, Russia

[3]Latvian Institute of Organic Synthesis, Riga, Latvia

[4]ANO "Centre for Biotic Medicine", Moscow, Russia.

Received June 14, 2019; Accepted July 07, 2019; Published January 11, 2020

ABSTRACT

Using atomic emission spectrometry, the content of Sodium (Na) and Potassium (K) in an epidermal derivative was measured in healthy subjects (n=9991). According to the spectrometry data, 4 groups were formed depending on the value of the Na/K ratio: Group 1: Na/K<1 (n=1834), Group 2: Na/K – 1 to 5 (n=6884), Group 3: Na/K – 5 to 10 (n=893) and Group 4: Na/K>10 (n=380). A correlation analysis (Pearson) of the K-Na bond tightness was conducted in the total sample (n=9991) and in each of the groups with different values of Na/K.

It was found that the correlation coefficient ***r*** in the total sample ($r_{K\text{-}Na}$=0.61; p<0.05) was noticeably lower than in any of the four groups ($r_{K\text{-}Na}$=0.85-0.97; p<0.05). It was also established that the reduction of $r_{K\text{-}Na}$ was due to the presence of the spectrometry data of Group 1 (where Na/K<1) in the total sample. As a hypothesis, the authors suggest that there is a connection between the brain electrical activity (BEA) and the synchronous (critical) work of membrane K^+/Na^+-ATPases in epidermal cells.

Keywords: Na- and K-homeostasis, Electrical activity of the brain, Oxidative/nitrosative stress, Epidermis, Self-organized criticality

INTRODUCTION

In our previous studies [1-8] were obtained evidence accessories for the homeostasis of electrogenic metals (K, Na, Ca) in epidermis to the phenomena of self-organized criticality (SC). This was evidenced by:

1) Power dependence between the content of K, Na and Ca in epidermis and the number of individuals in certain intervals of concentration values;
2) Fractal distribution of the spectrometry data of these metals in epidermis;
3) Synchronous (critical) nature of operation of Na^+/K^+-ATPase, which is the main transporter of Na^+ and K^+ ions through the cell membrane.

The conclusion about the possibility of synchronous (critical) functioning of Na^+/K^+-ATPases was made by us after we had established a reliable and stable linear relationship (Pearson) between the concentration values of these metals (according to the spectrometry data) [9].

However, the $r_{K\text{-}Na}$ coefficient, which ranged from 0.6 to 0.7 in different samples, seemed to us too 'humble' for the synchronous (as a 'single mechanism') operation of membrane pumps. This parameter, apparently, should be significantly higher if we are talking about critical processes. Therefore, we tried to find out what it was that contributed (directly or indirectly) to the probable 'understatement' of the K-Na level.

It is known that an important parameter of sodium and potassium homeostasis in the human body is the ratio of $[Na^+]$ and $[K^+]$ concentrations inside the cell and in the extracellular medium. Normally, when the volume of water inside the cells is 28 L (and in the whole organism is 42 L), the intracellular content of potassium is 110 mmol/L, whereas outside the cell it is only 4 mmol/L. The distribution of sodium (under the same conditions) is the opposite: 135

Corresponding author: VI Petukhov, Professor, Vladimir State University, Vladimir, Russia, E-mail: vip-val@yandex.ru

Citation: Petukhov VI, Dmitriev EV, Baumane LK, Skalny AV, Lobanova YN et al. (2020) Homeostasis of Sodium (Na) and Potassium (K) in Epidermis as a Self-Organized Criticality Phenomenon. Proteomics Bioinformatics, 2(1): 62-67.

mmol/L outside the cell and only 10 mmol/L Na inside the cell [5]. Based on these figures, the total (intra- and extracellular) ratio of $[Na^+]/[K^+]$ in the whole body is ~1.3.

It is significant that the ratio of the average values of [Na] and [K] (bootstrap-method), according to our data, in such a substrate as hair in 947 healthy individuals was almost identical – 1.5 [7].

At the same time, by spectrometry of epidermis (hair), we observed pronounced scattering of individual metal concentrations: sodium – 0.645 μg/g to 9240 μg/g; and potassium – 0.045 to 6505.1 μg/g [8], which allows for the existence of a spread among the individual values of the [Na]/ [K] ratio. It was interesting to find out the individual [Na]/[K] fluctuations in healthy individuals of most productive working age (20 to 49 years).

At the same time, one cannot exclude the connection between the [Na]/[K]-ration and the critical (synchronous) mode of operation of the membrane Na^+/K^+-ATPase. We analyzed correlations between [Na] and [K] depending on the value of [Na]/[K] to confirm or reject such a possibility. The analysis results are presented in this paper.

MATERIALS AND METHODS

Determination of sodium (Na) and potassium (K) in hair was done in a laboratory of the Center for Biotic Medicine (Moscow) using mass spectrometry with inductively coupled plasma (ICP-MS) on a NexION 300D spectrometer (Perkin Elmer Inc., Shelton, CT, USA). Practically healthy Moscow residents aged 20 to 49 were under observation (n=9991), of which 4999 (50.04%) were males and 4992 (49.96%) – females.

Hair samples for the spectrometry study were taken from the subjects following a mandatory informed consent procedure. In the occipital region, a tuft of hair 2 cm long and 0.5 cm thick was cut off close to the scalp.

To minimize the possibility of environmental contamination, hair samples were washed with acetone and then rinsed thrice with deionized water with subsequent air drying at 60°C. Further treatment of the samples was performed using microwave degradation. Specifically, 50 mg hair samples were introduced into a Teflon container and added to 5 ml of concentrated analytical grade HNO_3 (Sigma-Aldrich Co, St. Louis, MO, USA). Decomposition was performed in a *Berghof speedwave four* system (Berghof Products & Instruments, Germany) for 20 min at 170-180°C. After decomposition, deionized water was added to get a final volume of 15 ml.

A correlation analysis (Pearson) of the obtained data was carried out with determination of the correlation coefficient $r_{K\text{-}Na}$ (pairwise correlations between the concentration values of K and Na in the substrate). We tested the normal distribution hypothesis using the Jarque-Bera test [1] and the Kolmogorov-Smirnov test [4]. Because of this test, it was possible with high probability to refute the hypothesis of normal distribution of chemical elements. Therefore, an alternative approach (the bootstrap method) was used, which does not require a normal distribution of the priori ensemble [2].

The Matlab software tool was used for statistical data processing.

RESULTS AND DISCUSSION

The distribution of individuals depending on the [Na]/[K] ratio was as follows: [Na]/[K]<1 was detected in 1834 subjects (18.4%); [Na]/[K] from 1 to 5 – in 6884 subjects (68.9%); [Na]/[K] from 5 to 10 – in 893 subjects (8.9%); [Na]/[K]>10 – in 380 subjects (3.8%). The correlation coefficient ***r*** between [Na] and [K] was found in each of these groups. The results are presented in **Table 1**.

Table 1. The correlation coefficient $\mathbf{r}_{K\text{-}Na}$ for different values of Na/K.

Parameters	Subgroups with different Na/K ratios				Total sample
	1	2	3	4	
	Na/K<1	Na/K (1-5)	Na/K (5-10)	Na/K>10	
n (%)	1834 (18.4%)	6884 (68.9%)	893 (8.9%)	380 (3.8%)	9991 (100%)
$r_{K\text{-}Na}$	0.86	0.87	0.98	0.90	0.61

As can be seen from **Table 1**, the values of coefficient ***r*** were higher in all the four subgroups (regardless of the [Na]/[K] ratio value) as compared to the total sample.

It was interesting to find out which one of the presented subgroups contributed the most to the 'understatement' of ***r*** in the general sample as compared to all the other subgroups. In that respect, the most 'suspicious' was subgroup 1 with the [Na]/[K] ratio<1, which fundamentally distinguished it from all the others.

Therefore, we decided to find out in what way the presence of subgroup 1 in the total sample affected the ***r*** coefficient value alone or in conjunction with each of the subgroups or any combinations thereof **(Table 2)**.

Table 2. Correlation coefficient $\mathbf{r}_{K\text{-}Na}$ in combined groups.

Parameters	Combinations of subgroups with different Na/K ratios									
	1+2	**1+3**	**1+2+3**	**1+2+4**	**1+3+4**	**1+4**	**2+3+4**	**2+3**	**2+4**	**3+4**
n (%)	8718 (87.3)	2727 (27.3)	9611 (96.2)	9098 (91.1)	3107 (31.1)	2214 (22.2)	8157 (81.6)	7777 (77.8)	7264 (72.7)	1273 (12.7)
$r_{K\text{-}Na}$ ($p<0.05$)	0.69	0.52	0.66	0.64	0.40	0.47	0.79	0.84	0.81	0.98

It is significant that the addition of subgroup 1 (where Na/K<1) to each of the three other subgroups (separately and in various combinations, **Table 2**) resulted in a noticeable (almost twofold) decrease in $r_{K\text{-}Na}$. That does not seem accidental. It seems highly likely that it was the presence of individuals from subgroup 1 (Na/K<1) in the total sample that accounted for such an extraordinary 'humble' (0.61) value $r_{K\text{-}Na}$ for general sampling.

The synchronous (critical) mode of operation of Na^+/K^+-ATPases, as we noted earlier, is combined with a high level of $r_{K\text{-}Na}$. Interestingly, the value of this parameter in subgroup 1 itself ($r_{K\text{-}Na}$=0.86; $p<0.05$) is indicative of synchronous operation of the Na^+/K^+ pump in individuals with an 'inverted' Na/K coefficient (<1). This fact has little relation to the inhibitory influence of subgroup 1 on the $r_{K\text{-}Na}$, which requires further investigation of the possible causes of such an effect. In this regard, the level of Na and K in the biosubstrate (hair) depending on the value of the Na/K ratio was of special interest.

Using the bootstrap-method [2], which does not require a normal distribution of a priori ensemble, the mean and interval values of these metals were found pursuant to the hair spectrometry data. The results are presented in **Table 3**.

Table 3. Interval estimate of the average content of Na and K in epidermis.

Parameters	Interval estimation of the average in different for Na/K subgroups (μg/g)			
	1	**2**	**3**	**4**
	Na/K<1	**Na/K (1-5)**	**Na/K (5-10)**	**Na/K>10**
n	1834	6884	893	380
[Na]	208.9<**223.4**<238.2	249.4<**260.6**<272.4	307.4<**347**<390.5	454.5<**539.4**<635.4
[K]	359.5<**384.8**<410.4	122<**127.5**<133.5	46.5<**52.4**<58.9	27.2<**32.7**<39.3
Na/K	0.64<**0.65**<0.66	2.29<**2.32**<2.35	6.7<**6.8**<6.9	20<**22.6**<25.8

Note: The significance of intergroup differences between the mean values of [Na] and [K] ($p<0.05$)

The results **(Table 3)** indicate a marked variability in the Na/K ratio (subgroup average) from 0.65 to 22.6. The mean values of [Na] and [K] differed significantly among the subgroups **(Table 3)**. The minimum average level of sodium (223.4 μg/g) was in subgroup 1, the maximum (539.4 μg/g) in subgroup 4; whereas for potassium, the average minimum (32.7 μg/g) was in subgroup 4, while the maximum (384.8 μg/g) was in subgroup 1.

When analyzing the presented data, a natural question arises: why does the correlation coefficient $r_{K\text{-}Na}$, while being extremely high (~0.9) in each of the subgroups, become noticeably lower (0.61) when subgroup 1 is added to the total sample?

As already mentioned, the most significant difference of subgroup 1 from the rest is the 'inverted' Na/K ratio. The connection between this 'inversion' and the decrease of $r_{K\text{-}Na}$ may be regarded as one of the possible reasons for the decrease. Let us explain this in detail.

A close relationship between [Na] and [K] in the substrate ($r_{K\text{-}Na}$ ~0.9), indicating the synchronous (critical) nature of the membrane Na^+/K^+-ATPases, was found in all (without exception) the subgroups studied (including subgroup 1, where Na/K<1). It was combined with significantly ($p<0.05$) different content of sodium and potassium in the biosubstrate for each of these subgroups **(Table 3)**. This allows us to assume the existence of some kind of an external synchronizer for the membrane Na^+/K^+-ATPases, which should be heterogeneous in its frequency characteristics (and/or consisting of several oscillatory systems). In the role of such a synchronizer, one can imagine, at least hypothetically, the brain electrical activity

(BEA) with a known set of different-frequency rhythms detected by the electroencephalography (EEG) rhythms.

The physiological frequency ranges of EEG rhythms are known - δ (delta): 0.5-4.0 Hz; θ (theta): 4.0-8.0 Hz; α (alpha): 8.0-13.0 Hz; β1 (beta 1): 13.0-20.0 Hz; β_2 (beta 2): 20.0-30.0 Hz. These rhythms differ not only in frequency, but also in other parameters that have an important diagnostic value (amplitude, power, topography, etc.). The main is the α-rhythm, most pronounced in the caudal (occipital and parietal) areas of the cerebral cortex.

It cannot be ruled out that exactly α-rhythm may turn out to be the most demanded synchronization factor Na^+/K^+-ATPases (or *order parameter*) in individuals of subgroup 2 (68.9%) with the average values of basic indicators found in them (according to our data): Na/K=2.3; [Na]=260.6 μg/g and [K]=127.5 μg/g.

An indirect confirmation of the possible effect of BEA on the level of potassium and sodium in the epidermis can be found in our work [7], where we studied the dynamics of the level of Na and K (hair spectrometry) in 10297 healthy individuals (5160 men and 5137 women) of different age groups (2 to 85 years). The results are presented in **Table 4**.

Table 4. Age-related dynamics in K and Na levels in the epidermis [7].

Age (years)	Median K (mcg/g)	CI boot low	CI boot up	Median Na (mcg/g)	CI boot low	CI boot up
60-85	121.4	87.97	161.5	293.9	222.9	346.7
50-59	104.3	95.37	117.56	228.1	211.8	241.6
30-49	56.06	53.4	58.46	117.71	113.4	122.6
20-29	38.18	35.7	41.04	82.2	78.1	86.2
10-19	54.4	41.2	84.8	88.9	67.1	137.6
2-9	376.88	231.9	972.26	324.9	233	580.7

Note: CI boot – confidence interval (the bootstrap method)

The level of Na and K in the epidermis was found as a median with the boundaries of the confidence interval (the bootstrap method). The ratio of medians (Me [Na]/Me [K]) in each age group was as mentioned in **Table 5**.

Table 5. The ratio of medians (Me [Na]/Me [K]) depending on age [7].

Age (years)	Me[Na]/Me[K]
60-85	2.4
50-59	2.2
30-49	2.1
20-29	2.1
10-19	1.6
2-9	0.86

In the absolute majority of healthy subjects **(Table 5)**, which we investigated in the cited paper [7], the ratio [Na]/[K] (median) ranged from 2.1 to 2.4 (starting from the age of 20). It is should be noted that it is quite close (2.3) to the same parameter ([Na]/[K]) obtained in the present work for most individuals (68.9%) but using the mean values of [Na] and [K] **(Table 3)**. After replacing the average with the median, the [Na]/[K] ratio was almost unchanged (2.1 *vs.* 2.3).

The [Na]/[K] ratio in the younger age group (2 to 9 years) turned out to be less than 1 (0.86), i.e. the same 'inverted' ratio as in subgroup 1 **(Table 3)**. In **Table 3**, this ratio (0.65) is calculated from the mean values of [Na] and [K]. The replacement of the average by the median had practically no effect on the value of this parameter (0.68 *vs.* 0.65).

Why is the fact of 'inversion' of [Na]/[K] ratio in children from 2 to 9 years old so important? The answer is that at this age (up to 13 years old) the dominant EEG rhythm is the θ rhythm [3], whose participation in the appearance of the 'inverted' [Na]/[K] coefficient in 18.4% of people of mature age (20-49 years) in our observations seems likely. This requires verification and refinement in combined

(EEG+spectrometry) studies, but at the same time allows for the possibility of the BEA influence (as an order parameter) on the operation of membrane ATPases. Moreover, this assumption (in addition to the possible 'synchronizing' action of BEA on the operation of membrane pumps) will include, as shown by our data, the probability of a significant effect of BEA on the level and the ratio of [Na] and [K] in the substrate.

It is not very clear why the presence of subgroup 1 ([Na]/[K]<1) in the total sample causes a noticeable decrease in the tightness of the relationship between [Na] and [K], whereas in subgroup 1 itself the $r_{K\text{-}Na}$ turned out to be high (0.86; **Table 1**). One possible explanation for such 'inconsistency' can be as follows:

As already mentioned, the [Na]/[K] ratio for the whole body is ~1.3 with the predominant localization of sodium in the extracellular space and potassium - inside the cell [5]. The main membrane pump, Na^+/K^+-ATPase, which works against the electrochemical gradient of these metals, under whose influence Na^+ ions tend to get into the cell and K^+ ions tend to leave it, provides this distribution. An important feature of the Na^+/K^+-ATPase operation is its ability (per unit time) to remove more Na^+ ions from the cell than K^+ ions, which this pump has time to 'pump' into the cell. By the way, this explains the existence and relative constancy of the membrane potential.

The ratio of [Na] and [K] we found earlier (by average values) in such biosubstrate as hair amounted to 1.5 [7], i.e., almost did not differ from that for the whole body (1.3). Therefore, it seemed that distribution of these metals in the epidermis (with a predominance of Na) is normative and may be found in all healthy individuals without exception. However, that is not confirmed by the data we obtained.

In 18.4% of healthy individuals (subgroup 1, **Table 1**) [Na]/[K] was <1 (average 0.65). In addition, the presence of this subgroup in the general population explains the noticeable decrease in $r_{K\text{-}Na}$ (down to 0.61), compared with the same parameter in each of the fractions and its average value ($r_{K\text{-}Na}$=0.9).

Therefore, we are ready to assume that a decrease in the Na content in a substrate with predominance of K may indicate (at least in some individuals with the lowest [Na] value and the highest [K]) significant changes in the distribution of these metals inside and outside the cell. This, in our opinion, may be due to a change in the direction of the electrochemical gradient of Na^+ and K^+ ions or, in other words, the reversal of the pump function of Na^+/K^+-ATPase ('pumping' K^+ ions from the cell and 'pumping' Na^+ ions into the cell). In this case, the known proportion of ion exchange for a given pump (3 Na^+ ions *vs.* 2 K^+ ions) can be maintained.

It is known that such a reversion (due to changes in the membrane potential and the content of sodium and calcium in the cell) occurs with the sodium-calcium exchanger (NCX) [6].

Due to the high level (0.86) of $r_{K\text{-}Na}$ in individuals with [Na]/[K]<1 **(Table 1)**, technical reasons are less likely to explain the reduction of sodium in the biosubstrate (storage conditions of the sample and/or its processing).

Another aspect of sodium-potassium homeostasis in the epidermis (which is closely related to the results of this work) needs to be discussed. We are talking about the interpretation and diagnostic value of the data of hair spectrometry and the possibility of their extrapolation on the body as a whole.

The results of the study have convinced us that these data do not reflect changes in metal homeostasis at the level of the whole body, and, therefore, they neither allow us to judge about the adequate availability of Na and K, nor help us to identify their dangerous deficit or excess.

Thus, the mean values of [Na] and [K] in all subgroups differ from each other with high reliability **(Table 3)**. At the same time, the average value of [Na] in subgroup 1 is more than twice lower than in subgroup 4, and the average value of [K] in subgroup 1 is almost 12 times higher than in subgroup 4 (!). The scattering of individual values of these metals in the epidermis, which we have already mentioned, is even more impressive: Na – from 0.645 μg/g to 9240 μg/g; K – from 0.045 to 6505.1 μg/g. It must be noted that all the measurements were carried out in practically healthy subjects showing no pathological symptoms.

Therefore, to avoid unjustified generalizations, the results of hair spectrometry, as well as possible changes in metal homeostasis, should only be attributed to the given substrate - epidermis, which, as shown by our experience, can be productively used in studying the complex problems of modern bioelementology.

REFERENCES

1. Bera AK, Jarque CM (1980) Efficient tests for normality, homoscedasticity and serial independence of regression residuals. Econ Lett 6: 255-259.
2. Davison AC, Hinkley VD (1997) Bootstrap methods and their application. Cambridge University, UK.
3. Евин ИА (2008) Синергетика сознания. – М. – Ижевск: НИЦ «Регулярная и хаотическая динамика». – 128 с.
4. Lilliefors H (1967) On the Kolmogorov-Smirnov tests for normality with mean and variance unknown. J Am Statistical Assoc 62: 399-402.
5. Маршалл В.Дж (2000) Клиническая биохимия. – М. – СПб.: «БИНОМ» – «Невский диалект». – 368 с.

6. Nicholls JG, Martin AR, Wallace BG, Fuchs PA (2001) From neuron to brain. Sinauer Associates, Inc., Publ., Sunderland, Massachusetts, p: 672.

7. Petukhov VI, Dmitriev EV, Baumane LKh, Skalny AV, Lobanova YuN (2016) Electrogenic metals in epidermis: Relationship with cell bioenergetics. Insights Biomed 1: 9-14.

8. Petukhov VI (2017) What are the limits, if any, of normal content of electrogenic metals (K, Na, Ca) in epidermis? Insights Biomed 2: 13-17.

9. Petukhov VI, Dmitriev EV, Kalvinsh I, Baumane LKh, Reste ED, et al. (2011) Metal-ligand homeostasis in epidermic cells of Chernobyl accident liquidators. Vitamins Trace Elements 1: 1-8.