Commentary

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The Author's Commentary on the Article "Distinctive Features of Criticality in the Operation of Membrane Na^+/K^+-ATPases" [1]

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ABSTRACT

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Commentary

The appearance of this commentary on the recently published article "Distinctive features of criticality in the work of membrane Na^+/K^+-ATPases" in the journal *Acta Scientific Clinical Case Reports*, (2021), 2(8): 84-90 [1] is explained by the authors' desire to discuss the correctness of using hair spectrometry for assessment of elemental homeostasis in the human body *in toto*. It is for this purpose that the mentioned methodological approach continues to be applied in many medical centers.

Our own research in this area, which is mainly associated with the study of metal-ligand homeostasis (MLH) using hair spectrometry, casts doubt on the applicability of this method for assessing MLH of the whole organism. The trouble is that the widespread assumption that *the level of one or another metal in the hair is indicative of its content in the whole body* has not confirmed, despite numerous attempts in the clinic and in the experiment. Such extrapolation is not only unjustified but also potentially dangerous, since it can become a source of diagnostic and "treatment-correction" errors.

Our own experience of many years of research and clinical observations gives us grounds to assert that the quantitative shifts of metals in human hair depend mainly on the transmembrane transport of metals at the local (cellular) level and are in no way associated with possible disorders of MLH of the whole organism.

The validity of this statement follows from the already known features of sodium (Na) and potassium (K) homeostasis in the human body, which is usually judged by the content of these metals in plasma, urine (and, if necessary, in other biological fluids), as well as by changes in ECG (in case of potassium imbalance) and characteristic clinical picture.

It is difficult to overestimate the participation of cations Na^+ and K^+ in general homeostasis. Suffice it to recall the ability of sodium cations, which are (unlike K^+) mainly in the extracellular environment, to retain water and (due to osmolality) to take part in maintaining the water-electrolyte balance. The predominantly intracellular localization of potassium cations determines their important role in the generation of membrane potential and in other reactions of cellular metabolism.

It is no coincidence that there is a powerful, well-coordinated regulatory system that works on the principle of feedback to ensure the optimal content of Na and K in the body. It includes endocrine (hypothalamus, pituitary, adrenal cortex) and other organs (kidneys, lungs, intestines, skin), well-known hormones: vasopressin, aldosterone, myocardial natriuretic hormone, etc., as well as vascular baroreceptors and hypothalamic osmoreceptors.

Not all details of this homeostatic control are fully understood, but its rather high level is undoubted, as one can judge by the relatively small fluctuations in the normal content of Na and K in plasma (Na: 135 - 152 mmol/l; K: 3.6 - 6, 3 mmol/l) and in urine (Na: up to 340 mmol/day; K: 39 - 91 mmol/day). And although the given indicators are not adequate to the total amount of these metals in the organism (*in toto*), they convincingly demonstrate the effectiveness of homeostatic regulation in relation to Na and K in the most important biological media.

It is significant that we failed to find such a control in the epidermis and its derivative (hair). The content of Na and K in hair (median), which was measured using atomic emission spectrometry in 10297 apparently healthy residents of Moscow and Riga aged from 2 to 85 years (5160 men and 5137 women *without any symptoms of diselementosis)*, varied widely: sodium - from 0.645 μg/g to 9240 μg/g; potassium - from 0.045 μg/g to 6505.1 μg/g [2].

Such a scatter of spectrometric data can be explained (at least presumably) by the presence of two unrelated systems of Na/K homeostasis: at the organismal and cellular (epidermis and its derivatives) level. And since the measured parameters in each of the autonomously working homeostatic systems should be considered within the framework of only the system in which they were obtained, the extrapolation of the hair spectrometry data to the whole organism cannot be considered justified.

The very possibility of participation of a complex multilevel system providing in toto homeostasis of Na and K (and, possibly, other metals) in the MLH control of constantly (and rather rapidly) renewing epidermis with its derivatives looks unrealistic.

Experience has shown that the “differences” (by several orders of magnitude!) in the values of the concentration of Na and K in the hair of the subjects did not in any way affect their well-being and/or objective status. Along with it, any lethal risks are completely excluded, unlike in toto situations, where such risks are very relevant with much smaller changes in sodium and/or potassium concentrations in plasma.

At the same time, the use of the main provisions of the theory of self-organized criticality (SC) and spectrometric analysis helps to explain some key events in the MLH of the epidermis. We are talking about the emerging opportunity (according to hair spectrometry data) to reliably diagnose the critical and subcritical phases in the operation of the main membrane pumps for the transport of metals in the epidermis - ATPases from the P-type family (and first of all, Na^+/ K^+-ATPase).

The identification of these phases from the results of spectrometry is available when constructing in a logarithmic scale of Pareto plots, reflecting the probability density of the power-law distribution (PDF). In this case, the critical state is characterized by a power-law (fractal) distribution, which on a double logarithmic scale takes the form of a straight line. The starting point of this straight line - C_{thr} (the beginning of linearization on the Pareto plot) means the beginning of the *critical phase*.

Here it is necessary to make an explanation that was not included in the text of the mentioned article but seems important to warn the reader of possible inaccuracy in the author’s interpretation of the data obtained. The fact is that to find the C_{thr} point in our work we used the results of atomic emission spectrometry of hair for the content of Na and K obtained from 10,000 healthy individuals (5,000 men and 5,000 women) at the age of 20-45 years. But as a criterion for the distribution of subjects into two categories (with subcritical and critical modes of operation of membrane Na^+/K^+ -ATPases), the found $\boldsymbol{C}_{thr}$ point on the Pareto graphs for Na and K was used in individuals of different ages: from 2 to 86 years (947 healthy individuals and 954 liquidators of the Chernobyl accident). The age discrepancy between the studied groups can, apparently, affect the results of measuring each of the phases although it is unlikely to significantly affect the conclusions of the authors.

Conclusion

In conclusion, I would like to offer clinicians some recommendations on the use of metal spectrometry in such a biosubstrate as hair. It is hoped that the proposed recommendations will be in demand, since the capabilities and advantages of the spectrometric analysis itself are becoming more and more popular in the clinic.

A. What, first of all, should you pay attention to when analyzing spectrometric data? First of all, you need to make sure that the average values are calculated correctly and compared using the methods of mathematical statistics that are suitable for this purpose. As our investigations have shown, the distribution of the results of spectrometry of all these metals does not obey the “normal law” but is of a fractal nature. Therefore, standard methods for calculating the average and it’s comparing (Student) are unsuitable. In this case, special methods of mathematical statistics are used (for example, the bootstrap-method), which “work” in the absence of normal distribution.

B. In addition, the value of measured indicators is closely related to the sex and age of the subjects. In some metals (for example, Ca, Mg, V, etc.), hair spectrometry revealed significant sex differences in normal values (the "female norm" for Ca may exceed the "male" one by more than two times). The age factor plays an equally important role for the correct interpretation of spectrometric analysis. According to our data, there are significant age-related differences in the content of Na and K in hair. Normal values (median) of these metals (bootstrap-method) in healthy people aged 2 to 9 years: Na - 324.9 μg/g; K - 376.9 μg/g; age 20-49 years: Na - 99.9 μg/g; K - 47.1 μg/g; age 60-85 years: Na - 293.9 μg/g; K - 121.4 μg/g [2]. A possible relationship with age (preliminary data) was also found in other metals (Ca, Al, Cd, Cr, Cu, Fe, Li, Pb, V, Zn). Therefore, a reliable assessment of the results of spectrometry should include mandatory consideration of gender and age.

C. What factors (other than those already mentioned) can affect the value of the measured indicators? First of all, these should include oxidative and nitrosative stress (as evidenced by our own observations). In addition (according to the literature), a significant effect on MLH can apparently be exerted by carbonyl stress, which has an independent significance in diabetes mellitus (regardless of the type of diabetes) and/or as an aggravating addition to oxidative/nitrosative stress in many clinical situations (inflammation, cancer, cytodestructive conditions, infections, etc.). Therefore, the increased production of reactive oxygen species (ROS) and nitrogen (RNS) and, possibly, active carbonyl compounds (ACC), such as glyoxal, methylglyoxal, malondialdehyde, etc., can be accompanied by quantitative shifts in the MLH of the epidermis. It was found that these shifts are synchronous or clustered. In other words, hyperproduction of ROS and RNS leads to unidirectional quantitative changes in MLH, which can be expressed by the following algorithm: [Na] ↑, [K] ↑, [Al] ↑, [Cd] ↑, [Cr] ↑, [Cu] ↓ , [Li] ↑, [Fe] ↑, [Pb] ↑, [V] ↑, [Zn] ↓, where the arrow indicates the direction of the quantitative shift for each metal (increase ↑ or decrease ↓). This circumstance determines the following tactics in obtaining and interpreting spectrometric data.

D. In various clinical situations hair spectrometry can be used to diagnose stress (oxidative, nitrosative, carbonyl?). At the same time, a single analysis of the level of metal in the hair may prove to be less informative and not indicative of the dynamics of the process. At least two (or more) spectrometric measurements with a time interval in acute clinical situations from several hours to several days are required to establish a reliable connection between MLH disorders and hyperproduction of ROS, RNS or ACC (?). In the chronic course of the disease, this interval can be measured in weeks (or months).

Conflict of Interests

None.

References

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2. Petukhov VI, Dmitriev EV, Baumane L Kh, Skalny AV, Lobanova Yu N (2016) Electrogenic metals in epidermis: relationship with cell bioenergetics. Insights in Biomed 1(2): 9-14.

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