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On the Electrolyte Metabolism of Myocardium

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INTRODUCTION

The characteristic of the myocardium consists in the rhythmic contraction of the heart muscle, and this function is maintained by the normal metabolic processes in the myocardium. It is definitely demonstrated by many physiological data that the maintenance of metabolism occurs under suitable electrolytes environments. For many years, in our medical department, we have been carrying out studies on the metabolism of fluid and electrolytes. Here will be reported the results of the investigations made with my co-workers especially on the myocardium from the standpoint of energy production, electric phenomenon and morphological features.

I. ELECTROLYTES IN MYOCARDIUM AND ENERGY

In the study of the metabolism of electrolytes, the subject has hitherto been concerned with body fluid, mainly on its concentration in plasma, urinary excretion and balance. As clearly understood from the role which electrolytes play in living organism, changes of concentration in fluid cannot occur. Under the circumstances in which concentration in

blood remarkably changes, the regulatory functions develop immediately and the concentration is able to be maintained constantly within the fixed limit. Therefore the determination of concentration in blood shows only the results of regulatory function and it is at times insufficient for the detection of changes in electrolytes. For that reason we determined fluid and electrolytes in the myocardium.

It is understood that the unbalanced distribution of electrolytes, mainly Na and K, in intra- and extracellular spaces is due to specific expenditure of energy in the organism. Thus the determination of the high-energy phosphates in the myocardium which have recently come to call the attention of many investigators was made in its relation with the metabolism of electrolytes.

First of all, this experiment was conducted by employing different metabolic poisons and disturbing the metabolic processes in the myocardium. In many instances, both $\Delta 7P$ and K in the myocardium decreased, and in contrast with K, Na increased. However, there seemed not to be found a relation which can be called inverse correlation between these two ions.

Secondly, as to the changes which occurred on an injection of insulin, Na decreased and K together

with $\Delta 7P$ increased in the myocardium. This indicates K is utilized for the synthesis of glycogen.

When we plot all the mean values of the $\Delta 7P$ and K in the myocardium obtained by the experiments in which the above-mentioned metabolic poisons and hormones and different drugs were used, it is inferred that there exists some roughly positive correlation between the two (Fig. 1).

Fig. 1 Relationship between $\Delta 7P$ and K in the myocardium.

In determining the concentration in arterial blood and coronary sinus by means of sinus catheterization, changes of K in some cases are in accordance with the concentration in the myocardium, and there were other cases when it showed changes opposite to the concentration in the myocardium. Therefore this fact shows it still needs some researches to solve the problem of changes in electrolytes by their concentration in blood alone.

It is summarized from the above there exists a close relationship between concentration of K, one of electrolytes in the myocardium, and high energy phosphates, and it indicates that the energy metabolism in the myocardium is closely related to K.

II. ELECTROLYTES AND ELECTROCARDIOGRAM

A. Clinical Observations

We have been investigating the conditions of the patients who presented abnormalities in electrolytes balance from different aspects. In some cases, we frequently found that EKG exhibited considerably characteristic abnormalities.

In a case of hepatic insufficiency, he fell into coma after removal of ascites. In this case, K increased to 7.6 mEq/L and widening of QRS with intraventricular block were observed. And indistinct junction of RS-T with sharp, high T wave in addition to prolongation of QT ratio were prominent.

As Na showed also abnormally low value, it is difficult to make the conclusion at once that changes on EKG are due only to so-called hyperkalemia. At any rate it is definitely apparent that changes on EKG are noted in abnormal electrolyte metabolism.

Inorganic ions are generally considered to be chemical factors which affect the irritability of the heart muscle and at the same time cause electrical phenomenon in nerves and muscles in general. As EKG does not exhibit electrically the action of muscle fibers itself, but shows combined effect in those fibers, there is not parallelism between electrolytes and EKG. However, connection between the two has come to be regarded as important clinical observations on relationship between electrolytes and EKG. Researches on K and Ca will be mainly reported here.

B. Potassium and Electrocardiogram

Among electrolytes which affect EKG, K is frequently discussed, that is, so-called hyperkalemia and hypokalemia in EKG. As shown in many clinical cases, plasma K and QT ratio may not be said to be always correlated. There are practically few cases when changes in K alone are observed. This is because changes practically in K alone seldom occur without accompanying changes in other ions more or less and also because they may be affected by underlying diseases which cause abnormal metabolism. So we made an experimental researches to find changes in EKG by making changes in K alone. At the same time we determined electrolytes in the myocardium as well as in blood plasma to find correlation between EKG and electrolytes.

As to changes of electrolytes in the case of insulin shock in a human being, Na, Cl, and Ca in plasma showed no marked changes, but K alone showed remarkable decrease. EKG revealed peculiar changes. They show, according to the decrease of concentration of blood K, progression of T and flattening of T wave, increase of amplitude and widening of U and negative T. These waves are classified into four types when importance is attached to changes in T and U. The first one is normal which is called type 0. The second is type (-1), revealing increase of U still lower than T. The third is type (-2), revealing increase of U higher than T. The fourth is type (-3), revealing negative T. These types are nearly parallel to degrees of

plasma concentration of K. The decrease of plasma K by administration of insulin may be assumed to result from the transfer of K to the intracellular space from the extracellular space. This is confirmed by the experiment, showing the increase of K and $\Delta 7$, and decrease of Na in the myocardium after the administration of insulin.

The above fact makes it understandable that EKG on administration of insulin has the two aspects, namely, increase of K in the heart muscle, and decrease of K, in blood plasma.

Then we tried to find a case in which the decrease of K both in the heart muscle and in the plasma. We used several steroid hormones and other similar substances, as we recently found those hormones act on some electrolytes, bringing on retention of Na and loss of K. DOCA will be taken up as what shows the most typical changes. By a daily injection of DOCA, plasma Na increased and K decreased, and the same phenomenon occurred in the heart muscle, too. EKG at this time revealed so-called hypokalemia, that is lowering of ST, flattening or inversion of T, prolongation of QT and increase of U (Fig. 2). $\Delta 7P$ in the heart muscle also decreased. Histologically necrotic changes are found.

Fig. 2 Changes in EKG by the administration of DOCA.

Judging from the above instances of insulin and DOCA, so-called hypokalemia in EKG depends upon the concentration of K in blood plasma rather than upon that of K in the heart muscle. Na in the heart muscle is not considered to affect the appearance of EKG.

Next we attempted to produce hyperkalemia experimentally. By intravenous drip injection of KCl, plasma K showed rapid increase after a certain lapse of time, though it showed scarcely any change at first. Also K in the heart muscle increased and the ratio of K in arterial blood and in blood of coronary sinus increased, too. From this fact K can be assumed to transfer into the heart muscle. In EKG at this time the most typical changes were observed. They are lowering of P, increase of T, gradual shortening of QT, widening of P, prolongation of PQ and widening of QRS. From this picture a nearly parallel relationship is considered to exist between the concentration of K in the blood plasma and determined values of EKG (Fig. 3). No remarkable changes were found in the histological picture at the time.

Fig. 3 Changes in EKG by the continuous infusion of 1% KCl solution.

Hindering the processes involved in the metabolism of the heart muscle by using various metabolic poisons, we investigated abnormalities in electrolytes and in EKG. Fluoroacetate is the most typical among them in bringing on increase of plasma K without affecting K in the heart muscle. Plasma K increased and at the same time EKG was that of so-called hyperkalemia revealing flattening of P, increase of T, lowering of ST and sometimes its transition to a-v block. Histologically it showed a so-called picture of acute damage of muscle fibers, $\Delta 7P$ in the heart muscle decreasing.

As what cause decrease of K in the heart muscle and increase of blood K, we can mention monoiodoacetate, sodium cyanide and dinitrophenol etc. In the histologic picture, widespread interstitial edema is found.

The above-stated are results of our researches on the subjects of K and EKG. The summary is as follows. First of all, by plotting relations between K in the heart muscle and that in blood plasma in all the instances, it is assumed that in experiments on acute intoxication such as we made, K in the heart muscle shows tendency to decrease when plasma K remarkably increases, though increase and decrease of K are observed to be varied in degree according to cases. This suggests outflow of K from intracellular space into extracellular space.

Secondly, correlation between plasma concentration of K and determined values in EKG must be taken up. As to relations between QT and K in the heart muscle, prolongation of QT was clearly demonstrated when K showed marked decrease on administration of hormones, but there was no distinct correlation which could be called quantitative correlation. Abnormalities produced experimentally by administration of metabolic poisons or other drugs are complicated, and it is hard to find correlation between QT and K in the heart muscle.

Thirdly, to investigate relation between QT and plasma K, many cases must be considered according to the amount of K and Na in the heart muscle... when Na and K are normal, when both show decreases, when both increase, and when Na increases and K decreases. Some correlations are considered in the last two cases.

Fourthly, as to the ratio of T/R, nearly parallel relation can be observed between T/R and K in plasma.

Fifthly, between $\Delta 7P$ in the heart muscle and QT duration, a certain degree of relation is assumed to exist, excluding special cases. This is quite natural, judging from the above-mentioned relation between energy and QT in EKG, that is heart efficiency, might be properly considered to exist.

Fig. 4 Schematic presentation of the relationship between EKG and K concentrations in plasma and myocardium.

To summarize the relationship between K and EKG, the results are schemed as follows:

When K in blood plasma shows high concentration, abnormalities of the same type are always observed in EKG, irrespective of increase or decrease of K in the heart muscle. It can be called hyperkalemia on EKG.

On the other hand, when concentration of plasma K is low, EKG revealed special abnormalities which is designated hyperkalemia on EKG (Fig. 4).

C. Calcium and EKG

It is already known that in some cases of tetany and acute renal failure, peculiar abnormalities are observed in EKG when plasma Ca decreases.

In order to study EKG when Ca alone was made to decrease experimentally, we gave EDTA to dogs. The results were that among the plasma electrolytes, Ca alone showed decrease and the other electrolytes showed no abnormalities. Accompanying the decrease of Ca, prolongation of QT was found, especially Q_0T , that is, prolongation of ST segment itself was very clear. As to relations between plasma Ca and QT, a certain degree of correlation exists between the two. QT prolongation was found in most cases when Ca is lower than a certain degree.

In the hypercalcemia experimentally caused by an injection of $CaCl_2$, plasma electrolytes showed definite changes, and shortening of QT, prolongation of PQ and QRS and increase of T were noted in EKG. Action of K at this time cannot be ignored, as plasma K increases whereas Na decreases.

From the above mentioned facts it is clearly observed that in affecting EKG, some electrolytes have a certain definite tendency. However, many questions are still to be solved in point of their quantitative relations with EKG. The determination of electric potential by intracellular microelectrode is more appropriate than EKG for investigations on this subject. For this reason, this method has been employed in our department since last year, and reports on this subject will be made in future, as at present the results of our investigations are not yet ready for presentation.

III. DIGITALIS AND ELECTROLYTES.

We made experimental studies on the efficacy of digitalis and intoxication caused by it and also its relation with electrolytes, especially with K, as those subjects have recently come to be discussed.

Concerning the changes of electrolytes in plasma at the time of an administration of digitalis, the results of experiments made hitherto by other workers differed, and by our experiment, too, we found it difficult to find some definite trend. In the case of electrolytes in the heart muscle, decrease of K, increase of Na, and decrease of water and of $\Delta 7P$ were detected, when the amount of injection was large enough to cause intoxication.

Using Starling's heart-lung preparation, we inserted Morawitz's canule into the coronary sinus from the right auricle and determined the amount of the coronary blood flow. The injection of digitalis caused increase of K both in circulating blood and in the coronary sinus blood, and showed negative in value in its balance in the myocardium, as illustrated in Fig. 5, which means the outflow of

K out of the myocardium. It can be said that increase of K in blood depends upon the amount of this outflow of K. K determination in the heart muscle revealed the decreased value (Fig. 6).

The results of an injection of the radioactive isotope Na^{24} into the dog showed that the amount of its transfer into the myocardium was greater than that into the skeletal muscle. This phenomenon was especially conspicuous in use of digitalis (Fig.

7). From that fact, K in myocardium is assumed to flow out into blood accompanying the inflow of Na into the myocardium after the administration of digitalis.

EKG at the time of injection of digitalis

Fig. 6 K and Na in the heart muscle after the administration of digitalis.

Fig. 7 Uptake of Na^{24} into the heart muscle after the administration of digitalis.

sufficient to cause intoxication showed bradycardia and depression of ST segment, shortening of QT duration and then prolongation of QT duration. Histologic findings revealed at times acute damage on the endocardial surface of the left ventricle of the heart.

The efficacy of K on the arrhythmia caused by digitalis intoxication is recently arresting our attention again. We used KCl for the treatment of arrhythmia in general, especially extrasystole, as well as for that of digitalis intoxication. The results were that in many cases KCl was efficacious, sup-

pressing arrhythmia and the average frequency of the occurrence of extrasystole became remarkably lower. However, the concentration of KCl in blood at this time cannot be said always to increase, the prolonged use of KCl in the case of dogs showed some increase of K in the myocardium as well as in blood. This can be judged to indicate that K has the action to change the irritability of the myocardium.

IV. FLUID AND ELECTROLYTES ON AUTOPSIED CASES.

Reports on the fluid in the heart muscle and electrolytes, especially K in the case of autopsy have recently been made by two or three investigators. On autopsy performed by Department of Pathology, Tokyo University, we determined fluid, Na and K from different parts of the heart muscle, analogized the results with the histologic picture. From the standpoint of the constructive factors, we divided the histological pictures into six types and the characteristics of each types are illustrated in each of the pictures shown on the right (Fig. 8). In contrast with the first type, that is the normal

Classification of Histological Findings of Heart Muscle	
Group No.	Cardinal histological findings
I	Normal
II	Interstitial production
III	Chronic, atrophic change of muscle fiber
IV	Edema (Including edematous change of muscle fiber)
V	II + III + IV
VI	Newborn

Fig. 8 Classification of histological findings of heart muscle.

form, these pictures show differences in increase and decrease of fluid, Na and K. The second with proliferation of the interstitium shows decrease of K, little change in Na and decrease of fluid. The third type with the atrophic change in the muscle fiber shows decrease of Na and K. In the fourth type with edema in tissue, increase of water and Na, and decrease of K are found. In the type with changes both of the interstitium and of the muscle fiber, decrease of K is most noteworthy and decrease of fluid is also seen, without any remarkable change in Na. (Fig. 9). As is clear in the above instances, nearly analogical changes

are seen between the constructive factors of the tissue... muscle fiber, interstitium, edema etc.... respective amount of Na, K and fluid contained in the heart muscle. This phenomenon arouses our interest in point of connections between the morphological changes and the fluid and electrolytes.

Histological Findings and the Change of Tissue-water and Electrolytes

Fig. 9 Histological findings and the changes of tissue-water and electrolytes.

CONCLUSION

What is reported above is the results of our investigations on connection between the functions of the heart muscle and electrolytes. Those results show, I assume, close correlations between the two, not only theoretically but also practically illustrating two or three facts. They make it clear that electrolytes have very important relation with energy in the heart muscle, electric phenomenon, cardiac glycosides and further with the constructive factors from the morphological standpoint. However, there still remain many problems to be solved in this field, for especially in our country this field has not yet been widely investigated and no sufficient reference data for researches collected. My reports show only the present stage attained in the studies on this field.

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