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The Ratio of Cell Structures is a Parameter that Determines the Functional Capabilities of the System Responsible for Adaptation

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ABSTRACT

The notion that the level of function regulates the activity of the genetic apparatus through the energy balance of the cell and the concentration of energy-rich phosphorus compounds explains only the phenomena of organ hypertrophy under prolonged load and atrophy under inactivity. Meanwhile, in the process of adaptation, a significant change in the power of functional systems is often associated with small changes in their mass. Therefore, there is no reason to think that the expansion of the link limiting function and the increase in the power of the systems responsible for adaptation can be achieved by a simple increase in the mass of organs.

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The notion that the level of function regulates the activity of the genetic apparatus through the energy balance of the cell and the concentration of energy-rich phosphorus compounds explains only the phenomena of organ hypertrophy under prolonged load and atrophy under inactivity. Meanwhile, in the process of adaptation, a significant change in the power of functional systems is often associated with small changes in their mass. Therefore, there is no reason to think that the expansion of the link limiting function and the increase in the power of the systems responsible for adaptation can be achieved by a simple increase in the mass of organs [1-5].

In order to understand the real mechanism providing the expansion of the limiting link, it should be kept in mind that the actual consequences of changes in the load on an organ are not exhausted by simple activation of the genetic apparatus and an increase in organ mass. It turned out that, depending on the amount of additional load, the rate of synthesis of certain structural proteins and the ratio of cellular structures change to a different degree [6]. Thus, when studying the heart, we found that, depending on the amount of load on the organ, three variants of its long-term adaptation, differing in the ratio of cellular structures, develop [7-14].

1. Under periodic exertion of increasing intensity, i.e.. at natural or sports training, moderate hypertrophy of the heart develops, accompanied, as already indicated, by an increase in: the power of adrenergic innervation; coronary capillaries - muscle fibers ratio; myoglobin concentration and activity of enzymes responsible for transport of substrates to mitochondria: the ratio of heavy H-chains and light L-chains in myosin heads of myofibrils and ATP-ase activity of myosin. At the same time in cells there is an increase in the content of membrane structures of sarcoplasmic reticulum, physiological changes develop, indicating an increase in the power of mechanisms responsible for calcium ion transport and relaxation of cardiac muscle. As a consequence of this preferential increase in the power of the systems responsible for control, ion transport, energy supply, and energy utilization, the maximum rate and amplitude of contraction of the heart muscle of adapted animals increases, the rate of relaxation increases to an even greater extent; the efficiency of oxygen utilization also increases. As a result, the maximum amount of external work that can be generated by a unit of myocardial mass and the maximum work of the heart as a whole under the formed adaptation increase significantly.

2. In heart defects, hypertension and other circulatory diseases, the load on the heart appears to be continuous; accordingly, continuous compensatory cardiac hyperfunction (CCH) occurs. A variant of this process, caused by increased resistance to blood ejection into the aorta, entails a large increase in the activity of the genetic apparatus of myocardial cells and a pronounced hyperfunction of the heart - an increase in its mass by 1.5-3 times [15-18].

This hypertrophy is an unbalanced form of growth, as a result of which the mass and functional capabilities of structures responsible for nerve regulation, ion transport, and energy supply increase to a lesser extent than the mass of the organ. As a result, a complex of changes develops, which are opposite to the changes in heart adaptation just described. The resulting decrease in the functional capabilities of myocardial tissue is compensated for a long time by an increase in its mass, but then may cause heart failure. This kind of overstressed adaptation, characteristic of CCH, has been labeled as overadaptation [4-11].

3. With prolonged hypokinesia and reduced cardiac workload, the rate of protein synthesis in the myocardium and the mass of the

heart ventricles decrease. This atrophic process is characterized by a preferential decrease in the mass and power of structures responsible for nerve regulation, energy supply, and ion transport. As a result, the ratio of structures in the myocardium and its functional capacity in myocardial tissue appear to be altered in the same way as in CCH. Since the mass of this tissue is reduced, the functional capacity of the heart is always reduced; this condition is labeled as cardiac de-adaptation [18-23].

Comparison of these states, which, apparently, are characteristic not only of the heart but also of other organs and systems, leads to the idea that one and the same intracellular regulatory mechanism provides the formation of three states of the system, namely: adaptation in the proper sense of the term, de-adaptation and over-adaptation. The difference between these states is determined by the ratio of structures in cells. It is reasonable to evaluate the validity of this view by directly analyzing the ratio of myocardial cell ultrastructures and the main parameters of cardiac contractile function during adaptation induced by animal training [19-22].

Numerous practical experience and experimental data unambiguously testify that a relatively small increase in heart mass during adaptation to physical exertion entails a large increase in maximum minute volume and external work that can be performed by the heart. Quite similarly, a relatively small, difficult-to-determine decrease in heart mass during hypokinesia is accompanied by a pronounced decrease in the functional capacity of the organ. In other words, the enormous advantages possessed by the adapted heart and the functional failure of the de-adapted organ cannot be explained by a mere change in myocardial mass. To the same extent, this result of adaptation cannot be explained by the action of extracardiac regulatory factors, since it is clearly revealed in the isolated heart and in papillary muscles under conditions when the myocardium does not depend on the regulatory factors of the whole organism. Thus, the main question of long-term adaptation of the heart, the mechanism of the increase in functional capacity of both the trained heart and the failure of the detrained heart has remained open until recently [15].

In the developed hypothesis, it is implied that with prolonged increase in the load on the heart, the realization of the connection between the genetic apparatus and function leads to a selective increase in the biosynthesis and mass of key structures limiting the function of the myocardial cell, i.e. membrane structures responsible for ion transport, providing ATP utilization in myofibrils and its resynthesis in mitochondria. As a result, the functional capacity of the heart increases significantly with a small increase in its mass. Prolonged reduction of the heart load in hypokinesia entails selective reduction of biosynthesis and atrophy of the same key structures; the functional capabilities of the organ decrease again with a small change in its mass [14-19].

The experiments were performed on male Wistar rats. The volume of myocyte structures was measured by electron microscopic steriologic study. This method allows quantitative assessment not only of the volume of mitochondria and myofibrils, but also of the volume of membrane systems of sarcolemma and sarcoplasmic reticulum responsible for Ca2+ transport [11-19].

To obtain adaptation, animals were forced to swim for one hour daily for two months at a water temperature of 32°C. From the data on contractile function of papillary muscles of control and swimming-adapted rats, it was evident that the maximum velocity and amplitude of isotonic shortening of cardiac muscle in adapted animals were twice as high as in controls. The attainment of adaptation during these high-amplitude fast contractions is realized very convincingly. Such a result agrees well with the fact that in the process of adaptation to physical loads a significant increase in ATP-ase activity of myosin has been proved due to an increase in the content in myosin heads of carriers of this activity - short-lived H-chains [1-5].

In terms of our presentation, it is significant that such an increase in the basic parameters of contraction obviously implies an increase in the amount of calcium entering the sarcoplasm and interacting with myofibrils. This means that long-term stable functioning in the mode of rapid high-amplitude contractions can be realized only under the condition of intensive work of the mechanisms responsible for calcium removal and relaxation process [7-14].

In further experiments, data were obtained that indicate that the relaxation process in the trained heart is activated. Thus, firstly, the rate of relaxation of the heart muscle of trained animals was increased to a greater extent than the amplitude of contraction. As a result, there was an increase in the relaxation index, i.e., the ratio of the relaxation rate to the contraction amplitude increased. Second, the stretchability of cardiac muscle strips of trained animals was increased compared to the control. It was stated in the data that to stretch the myocardial strips of control animals by 10%, 1.5 times more weight had to be applied than to stretch the cardiac muscle of trained animals. The reason for the increased extensibility, in our opinion, is a more complete removal of calcium from the sarcomeres of the trained heart - a decrease in the number of residual calcium-troponin complexes and actomyosin bridges in them that persist after the completion of relaxation [15-17].

An increase in sarcoplasmic reticulum calcium pump capacity should logically contribute to accelerated calcium accumulation in sarcoplasmic reticulum cisternae, and this in turn may lead to increased positive inotropic effects on the heart.

The facts seem to indicate an increase in the power of membrane calcium transport mechanisms in the heart muscle of animals adapted to exercise, and the totality of the presented physiological data leads to the idea that a selective increase in the power of these mechanisms may play an important role in increasing the functional capacity of the trained heart.

This controversial inference was tested by directly measuring the volume of sarcolemma structures, sarcoplasmic reticulum, and mitochondria and myofibrils in adapted and de-adapted animals [20].

The main result of this study is summarized in two points. First, the heart mass as a whole, as well as the volume of mitochondria and myofibrils per unit of myocardial mass did not change significantly under the adaptation regimes we used. Only the size of each mitochondrion was reduced, and, naturally, the number of such smaller mitochondria per unit area of the slice increased by 30%, and the surface area of mitochondrial membranes per unit tissue volume increased by 28%. Secondly, the volume and surface of membrane structures of sarcolemma and sarcoplasmic reticulum changed quite significantly [2-14].

In animals adapted to physical loads, the surface of longitudinal tubules of sarcoplasmic reticulum increased by 50%. At the same time in the process of adaptation to physical loads the volume of the Golgi apparatus, where according to modern concepts

the processes of cell membrane formation, and in particular the membranes of the sarcoplasmic reticulum, take place, increases almost 3 times. This may indicate a significant activation of myocyte membrane structures formation during heart adaptation to physical loads [12-17].

Membranes of longitudinal tubules of sarcoplasmic reticulum and sarcolemma according to the currently accepted view are the localization site of Ca-activated M-dependent ATP-ase and play a decisive role in the realization of relaxation by removing calcium from sarcoplasm and myofibrils, and in the realization of contraction by transporting calcium to the points from where it leaves during excitation. Thus, the results of electron-steriological and physiological studies coincide and give grounds for the conclusion that a preferential increase in the mass and capacity of membrane calcium transport systems plays an important role in increasing the functional capacity of the heart during adaptation to exercise [16-23].

When evaluating this position, it should be kept in mind that the preferential accumulation of membrane structures responsible for calcium transport is only one of the manifestations of the principle of selective increase in biosynthesis and accumulation of key structures, on which cardiac adaptation is based. It has now been proven that during adaptation, moderate cardiac hypertrophy is combined with an increase in the activity of the adenylate cyclase system and an increase in the number of adrenergic fibers per unit myocardial mass. As a result, the adrenoreactivity of the heart - the possibility of urgent mobilization of its function – increases [12-18].

At the same time, there is an increase in the number of H-chains, which are carriers of ATP-ase activity in myosin heads; ATP-ase activity increases, and as a result, the speed and amplitude of cardiac muscle contraction increase. The power of sarcoplasmic reticulum and, as a consequence, the speed and depth of diastolic relaxation of the heart are increased [12-17].

It has been found that in parallel with the noted shifts in the myocardium, the number of coronary capillaries increases, the concentration of myoglobin and the activity of enzymes responsible for the transport of substrates to mitochondria increases. This increase in the power of the energy supply system naturally entails an increase in the heart's resistance to fatigue and hypoxemia [1-7].

Thus, in the process of cardiac adaptation, the organism does not follow the path of global myocardial growth, but a more economical path of preferential or selective increase in the mass or power of key structures limiting cardiac function. Such a selective increase in the power of structures responsible for control, ion transport and energy supply is not an original feature of the heart. This process is naturally realized in all organs of functional systems responsible for long-term adaptation under the action of various environmental factors on the organism. It is due to this fundamental mechanism, realized at the genetic level, that the organism in the process of adaptation to the environment increases the functional capacity of its systems without significant changes in their mass. In essence, this means that the ratio of structures is the main internal characteristic of the adapting system, predetermining its "target parameter" - the maximum achievable work [18].

This position and the concept of the structure of transcriptons of higher animals led us to the assumption that the change in the ratio of cellular structures during adaptation, overadaptation, and deadaptation is determined by the fact that transcriptons encoding short- and long-lived proteins differ quantitatively from each other in the structure of their regulatory compartment. This, in turn, leads to different inclusion of transcriptons encoding short- and long-lived proteins when the RF (Rheumatoid factor) and the RF-dependent regulatory factor are equal [10-15].

The difference is expressed in the fact that the inclusion of transcriptons encoding short-lived proteins is greater than that of transcriptons encoding long-lived proteins when RF and factor-regulator are equal. The dependence of operon inclusion on the concentration of the metabolite-regulator has the form of a monotonically increasing function with an inflection and subsequent saturation plateau [15-20].

When the load is increased within physiological limits, i.e. during adaptation, the amount of the regulator factor and the difference in the inclusion of both transcriptons increase. At excessive load increase, i.e. at CCH, the amount of RF-dependent factor-regulator increases even more and ceases to limit the inclusion of these transcriptons. In this case, the inclusion of all transcriptons approaches the maximum, and the difference in the inclusion of transcriptons encoding short- and long-lived proteins is minimal. At a significant decrease in load and RF, i.e. at hypokinesia and deadaptation of the heart, the amount of the factor-regulator is significantly reduced - the inclusion of all transcriptons and the difference in the inclusion of transcriptons encoding short- and long-lived proteins is also reduced to a minimum [2].

In the light of the sufficiently substantiated by molecular biology position that the inclusion of each transcripton through the mechanism of transcription and translation predetermines the content of the protein encoded by the transcripton in the cell [14].

Indeed, in accordance with this hypothesis, the increase in the inclusion of all transcriptons observed during adaptation (with an increase in the difference in the inclusion of transcriptons encoding short- and long-lived proteins) should lead to some increase in the mass of the whole heart and an increase in the ratio of the mass of short-lived structures to long-lived structures compared with the norm; this is the situation that actually exists in the adapted heart [13].

Maximal inclusion of all transcriptons and decreased differences in the inclusion of transcriptons encoding short- and long-lived proteins during over-adaptation (CCH) should result in a large increase in heart mass and a significant decrease in the mass ratio of short-lived structures to long-lived structures; this is the situation that actually exists in the adapted heart. Finally, a decrease in the inclusion of all transcriptons and a decrease in the difference in the inclusion of transcriptons encoding short- and long-lived proteins during deadaptation should lead to a decrease in heart mass and a decrease in the ratio of short- to long-lived structures in the myocardium, which actually exists during deadaptation caused by hypokinesia [12].

Thus, the developed hypothesis about the key link of long-term adaptation consists in the fact that load through RF and intracellular regulation mechanism determines: first, the total activity of the genetic apparatus of the cell and thus the rate of protein synthesis and cell mass; second, the ratio of inclusion of transcriptons encoding short- and long-lived proteins and thus the ratio of structures in cells, organs, and systems [3-9].

This hypothesis, which requires testing, implies that the mechanism linking the level of function and the activity of the

genetic apparatus works in such a way that, in response to an increase in function, the transcription rate of genes encoding short-lived enzyme proteins and membrane proteins, which are the key function-limiting proteins of the cell, increases to the greatest extent [6].

One possible way to test the hypothesis is to compare the dynamics of adaptive accumulation of different isozymes of a certain enzyme, one of which is less stable and yet functionally more efficient under loading conditions. Since the subunits forming different isozymes of an enzyme are usually encoded by different genes, preferential accumulation of such a short-lived functionally active isozyme would be a significant argument in favor of the idea being developed [7].

One enzyme that could be used in this kind of study is muscle cell CPK (creatinephosphokinase), which is a vital enzyme system responsible for the transport of energy-rich phosphate groups from mitochondria to myofibrils. CPK activity increases dramatically in hyperfunction of cardiac and skeletal muscle. This increase in activity is naturally prevented by puromycin administration and is therefore the result of an increase in the enzyme population - its selective accumulation during adaptation to load [8].

In animal tissues, CPK is represented by three isozymes: MM, consisting of two M-type polypeptide chains (muscle type); BB, consisting of two B-type chains, characteristic of embryonic tissues and brain; MB, consisting of two different subunits and characteristic only of myocardium. At the same time, BB-isozyme, firstly, is synthesized faster and, apparently, has a shorter lifetime than MM-isozyme, and, secondly, having a greater affinity for KF and ADP, can function more efficiently under conditions of cardiac overload, when the content of energy-rich compounds in the myocardium is reduced. Based on these data, we studied the dynamics of activity and isozyme spectrum of myocardial creatine kinase during cardiac adaptation to continuous load, i.e. during CCH induced by stable aortic constriction [14].

This kind of processes of compensatory hyperfunction of organs under irreversible increase of the load falling on them are interesting because during their development three states that can exist stationary in organs change each other at a rapid pace, namely: the initial stage, which is characterized by preferential accumulation of key structures limiting cell function; the stage when the ratio of structures returns to the initial norm; finally, the final stage of overadaptation, when stable structures prevail over enzyme and membrane structures This means that by measuring the activity of CPK and the ratio of isozymes of this enzyme during compensatory hyperfunction of an organ, we can indeed assess the validity of the notion of the role of the ratio of the activity of short- and long-lived proteins in the mechanism of adaptation [18].

Experiments were performed on white male rats. Two groups of animals were used: young rats aged 3-4 months, weighing about 200 g; rats aged 9-10 months, weighing about 400 g. CCH was created by coarctation of the abdominal aorta according to the previously described methodology. Animals with CCH were represented by two groups: I - early stage of hyperfunction - 1, 2, 3, 5, 7 and 9 days after creation of aortic coarctation; II - late stage of hyperfunction (6-7 months after aortic coarctation). Rats of appropriate age and weight served as controls to these groups [15].

The method proposed by Otsipgo was used with some modifications for the separation of CPK isozymes [13-15].

Results of determination of total activity of CPK in heart homogenates: the activity of CPK in myocardium of control animals is 1100 IU per 1 g of crude weight and increases already on the 2nd day after the beginning of CCH. The maximum increase of CPK activity develops on the 3-5th day after the beginning of CCH and reaches 50-40% per unit mass of the organ. Total CPK activity calculated for the whole heart increases by 63-42% during this period.

Thereafter, CPK activity per unit mass decreases to normal, and per whole heart remains slightly increased as late as the 9th day of CCH; 6 months after the onset of CCH, CPK activity per unit mass of myocardium compared with animals of the same age is decreased by 15%, and per whole hypertrophied heart is increased by 25%.

The electrophoregram of CPK isozymes on agarose provided that the myocardium of control rats contained three CPK isozymes (MM MB and BB). According to the result of fluorimetric assay, the activities of MM-, MB and BB isozymes are 65-66, 30-31 and 4-5%.

Electrophoretic separation of extracts of hyperfunctioning cardiac muscle was performed at 1, 2, 3, 5, 7 and 9 days after the onset of CCH. It was found that 1 and 2 days after the onset of hyperfunction, the population of creatine kinase proteins in the myocardium did not undergo visible changes. However, on the 3-5th day, a significant transformation of the isozyme spectrum is observed in the hyperfunctioning heart. The activity of BB-isozyme sharply increases, the activity of hybrid MB-isozyme increases, and the activity of MM-isozyme decreases. If in norm the activity of BB-isozyme fluctuates within 4-5%, then on the 3rd day after the onset of cardiac hyperfunction the activity of BB-isozyme in myocardium reaches 15%. On the 5th day after aortic coarctation the activity of this isozyme equals 12%. On the 7th day after hyperfunction creation the activity of BB-isozyme decreases and makes 7%, and after 9 days of hypertrophy it does not differ from the control.

At 6 months after the onset of hyperfunction, total CPK activity per unit heart weight appeared to be reduced, similar to that of other key cardiac enzymes during overadaptation and large, long-standing cardiac hypertrophy.

Thus, the peak of BB-isozyme activity develops on the 3rd to 5th day of CCH and coincides in time with the peak of total CPK activity. The activity of MB heterodimer at this time also increases and reaches 39-40%, and the activity of MM-isozyme, on the contrary, decreases to 45%, i.e. makes less than a half of the total CPK activity. In further development of CCH, changes in the isozyme spectrum of CPK gradually level out and approach the control level by the 9th day [15].

The main result of the experiment is that in the emergency stage of CCH, simultaneously with the increase in the total CPK activity, there is a significant change in its isozyme spectrum towards an increase in the BB-isozyme and a decrease in the MM-isozyme.

To understand this fact, it is reasonable to consider three questions: in what heart cells are the established changes in the CPK system realized, what is the probable mechanism of activity dynamics and changes in the isozyme spectrum of CPK, what is the biological significance of this phenomenon?

In principle, shifts in the activity of CPK and its isozyme spectrum can be realized both in muscle cells of the heart and in fibroblasts of its interstitial connective tissue, where there is also B-isozyme CPK. In our opinion, there are at least three circumstances that allow us to consider that this shift of the isozyme spectrum, as well as the general increase in CPK activity, is realized mainly in muscle cells composing the heart [9-15].

First, the activity of CPK in muscle cells, according to data obtained in tissue culture, is more than 16 times higher than in fibroblasts, and the mass of muscle cells is about 80% of the myocardial mass. This means that myocytes were the source of the major population of CPK molecules, which we separated into isozymes [11].

Secondly, at CCH we observed activation of DNA synthesis and mitotic activity in myocardial interstitial connective tissue cells; the peak of this process is reached on the 7th day of CCH the increase of B-subunits and relative decrease of M-subunits is realized much earlier - on the 3rd day of CCH, as it is related to events in muscle cells, not in connective tissue cells [11-16].

Thirdly, the transformation of the isozyme spectrum of CPK in CCH is expressed by an increase in the activity of not only BB-, but also MB-isozyme. This allows us to think that both isozymes are synthesized in the same cells, and since MB-isozyme is present only in myocytes, it is myocytes that are the most probable site of biosynthesis of both isozymes [14-16].

Thus, the increase in CPK activity and the increase in the share of BB-homodimer in its isozyme spectrum that we have found can most likely be localized in myocytes of cardiac muscle [11-16]. The increase in CPK activity, naturally observed in muscle cells with an increase in their function, as already noted, is due to the activation of the biosynthesis of CPK molecules and an increase in their population. In order to understand the changes in the isozyme spectrum of CPK that we have established in the course of this process, it is reasonable to quantitatively evaluate the effect of CCH on the content of M- and B-subunits in cardiac muscle on the basis of the obtained data. In normal heart the content of MM-, MB- and BB-isozymes is 65, 30 and 5%, respectively; respectively, B- and M-subunits are related as 20:80. On the 3rd day of CCH, MM-, MB-, and BB-isozymes account for 45,40, and 15% in the myocardium; respectively, B- and M-subunits are related as 35:65. Total CPK activity increases to 153% of normal by this time, and consequently, the total number of B-subunits increases 2.5-fold and M-subunits 1.5-fold compared with controls. Since DNA synthesis does not occur in rat myocytes and the number of genes does not change, this fact suggests that the significant increase in contractile function of cardiac muscle, realized in the form of CCH, caused a multiple increase in the transcribing rate of the gene encoding a relatively short-lived and functionally effective B-isozyme, and had less effect on the transcribing rate of the gene encoding a less effective MM-isozyme for this situation. Such an explanation corresponds to the fact that the increase in the activity of CPK and its BB-isozyme is not realized in the emergency stage of CCH in isolation, but is only one of the components of the complex of adaptation changes expressed in the accumulation of structures limiting the function of muscle cells [13-16].

Indeed, it is known that the average half-life period for the main proteins of myofibrils of cardiac myocytes is about 12 days, and for proteins - components of the respiratory chain of mitochondria - 5-6 days; for heavy chains of myosin heads, which are carriers of ATP-ase activity, the half-life period is shorter than for light chains inhibiting this activity [15].

Accordingly, in the initial stage of CCH and during adaptation to physical exertion, there is a natural increase in membrane proteins and Ca-activated ATP-ase, mitochondrial mass and activity of mitochondrial enzymes per unit heart weight, predominance of H-chains over L-chains in myosin heads, accompanied by an increase in ATP-ase activity of myofibrils, and, finally, in the activity of CPK and its BB-isozyme. This accumulation of short-lived structures gives the heart an opportunity to adapt to a large and continuous load and thus prevents the death of the organism [14].

The specific adaptive significance of the increase in the activity of CPK and transformation of its isozyme spectrum is determined in this situation by the fact that in the emergency stage of CCH there is initially a lag of ATP resynthesis in mitochondria from its consumption and ATP resynthesis is restored due to a significant increase in respiration and oxidative phosphorylation in mitochondria. Under these conditions, the increased activity of CPK and its BB-isozyme, which has an increased affinity for CPK and ADP, provides a solution to a vital task - an increase in the rate of transport of energy-rich phosphate groups from mitochondria to myofibrils [11].

Thus, changes in the ratio of transcribing rates of certain genes and the resulting changes in the ratio of cellular structures become the basis of adaptation to prolonged load increase. The fact that the change in the ratio goes in the direction of accumulation of short-lived structures does not seem to be a private property of the heart, but represents a more general feature of the molecular mechanism of adaptation. Thus, for example, it was found that of the 46 protein-enzymes of the liver cell, 12 proteins had the shortest half-lives and it was these proteins that formed either the initial or rate-limiting links of the most important metabolic pathways. The enzymes that possessed the longest half-lives did not fulfill such a role in any case.

In complete agreement with this, the adaptive activation of the biosynthesis of neoglucogenesis enzymes that develops in the liver under the influence of the stressor hormone corticosterone is realized in a manner that leads to the accumulation of short-lived isozymes of these enzymes that can be rapidly degraded after the stressor situation is over. As a result, the notion that it is the short-lived proteins that are functionally the most important, function-limiting proteins of the cell is emerging. The significance of this feature of the biological machine is that the high rate of biosynthesis and degradation of such proteins makes it possible to rapidly change their content, and thereby change the functional capabilities of organs and systems in the process of adaptation to the external environment [23].

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