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VARIATIONS OF TRANSCRIPTION AND TRANSLATION OF MYOCARDIAL CELL IN CARDIAC INSUFFICIENCY DEVELOPMENT

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The relationship of genetic apparatus with physiological function of a cell is known to be indirect, through the RNA, provision of protein synthesis. One-third of these proteins form part and parcel of the cell physiological function [4,9,19].

After the appearance of hyperfunction the intensification of protein synthesis leading to the myocardial hypertrophy should be considered as a result of DNA activity. This activity is expressed by an increased synthesis of specific messenger RNA (mRNA) molecules which makes their way to myocardial cell polysomes, where they act as a matrix on which the synthesis of specialized proteins of activated amino acids supplied by transport RNA (tRNA) takes place.

Thus, the increase in physiological function causes a compensatory growth of the heart, owing to the increase of quantity in proteins forming it, the correlation between separate cell structures and proteins may change.

The regulation of these processes is possible on different molecular levels, such as the transcription level, i.e. the rate of RNA molecules synthesis; on the translation level, i.e. the rate of formation of protein molecules; and at last, on the replication level, where in conditions of intensive hyperfunction the power of genetic apparatus in myocardial cell is found to be insufficient.

However, it is known that in cardiomyocytes DNA replication doesn't take place [6,7], and in this paper only the problems of transcription and translation will be discussed.

The question of the signal nature, directly converting the mechanical overloading of myocardium into biochemical response to hypertrophic growth of a cell seems to be rather complicated and important in the problem of long-term heart adaptation.

The purpose of the present investigation is to study the content, biosynthesis and decay of messenger, transport, ribosomal (rRNA) and chromosomal-nucleous RNA (c-NRNA) in the process of compensatory hyperfunction of the heart, during three years starting with the breakdown stage, developing immediately after the restraining of hyperfunction, when the heart realizes a compensatory growth and the final stage of the wear and development of cardiac insufficiency, caused by resistance load.

Materials and Methods

The experimental investigations were carried out on 250 rabbits.

The isometrical hyperfunction was induced by coarctation of the ascending aorta by 70%. The animals with aortic stenosis were taken for acute experiments after 2, 7, 30 days, 3, 6, 9 months and 1, 1.5, 2, 2.5 and 3 years after creating the experimental model.

In all cases the tissue of the left and right ventricles of the heart was the object of the study.

The content and biosynthesis of rRNA and tRNA were investigated accordingly [2,8,10,23].

The synthesis and decay rates of all types of RNA were estimated by insertion of radioisotopes of sodium phosphate 32P, (14C)-orotic acid or (14C)-uracil. The radioactivity was determined with the help of scintillation counter. The results were statistically analysed by a computer.

Results and Discussion

At first a sharp increase (2.2 times) in mRNA synthesis and its concentration was observed in the process of heart hyperfunction and hypertrophy development in conditions of long-term resistance load.

Figure 1 shows the kinetics of concentration and incorporation of radioactive precursors into mRNA of the left myocardial ventricle. These data show that mRNA synthesis and concentration reach their maximum after 30 days.

Exactly the same dynamics of changes was observed in concentration and biosynthesis of HNA in chromosomal nucleous apparatus (Fig. 2). The curves in figure 3 and 4 characterize the dynamics of changes in the rRNA and tRMA biosynthesis after the coarctation of the ascending aorta. These curves show in the breakdown stage of hyperfunction a sharp acceleration of biosynthesis of all types of RNA, however the mRNA reacts to hyperfunction earlier than rRNA and tRMA.

The data obtained indicate that the genetic apparatus reaction to the cell function increase is not limited to the quantitative increase of transcription, translation and does not lead to synthesis of RNA new for the cell. However, by the genetic apparatus activation, the synthesis of all types of RNA is activated in a different way. Vice versa, mRNA synthesis is faster than that of rRNA and tRMA. The existence of such a heterochronology is conditioned by the fact that in conditions of relatively physiological rest there exist not only

polysomes synthetizing the proteins, but also ribosomes which are not connected with mRNA and don't synthetize proteins. The process of hyperfunction is accompanied by monosomes and lisosomes forming polysomes capable of providing the activation of protein synthesis. It is obvious that the occurring in that case prevalence of polysomes over free ribosomes can be provided only in case of temporary prevalence of mRNA synthesis over the rRNA and tRMA synthesis.

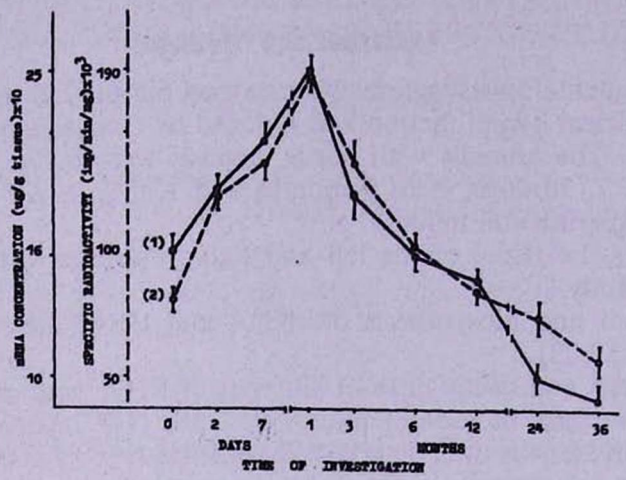

Fig. 1. The concentration (1) and specific radioactivity (2) of the left ventricular myocardium messenger RNA before and after coarctation of the ascending aorta.
C – initial level.

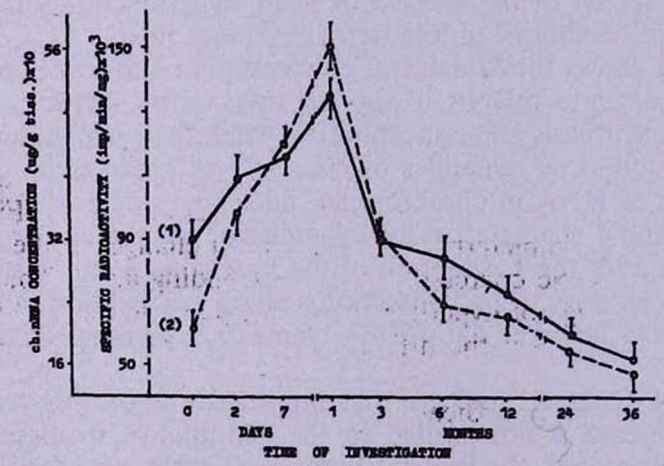

Fig. 2. The concentration (1) and specific radioactivity (2) of the chromosomal-nucleous apparatus RNA before and after narrowing of the ascending aorta.
C – initial level.

The evaluation of the ratio of rRNA and tRMA radioactivity by the compensatory growth of heart revealed that the rate of accumulation of mRNA molecules in cytoplasm increases to a greater level than that of rRNA, and this coincides with the revealed fact of increase in relative amount of polysomes in myocardium in the total population of ribosomes in myocardial cell.

At the stage of the compensatory growth the process of myocardial mRNA decay increases and its half-life reduces. The average lifetime of the bulk of mRNA molecules is normally 4 hours. In the breakdown stage of heart compensatory hyperfunction (HCH) the rate of mRNA molecules decay increases and their lifetime reduces half as long.

The data about the lifetime of rRNA indicate that by the appearance of hyperfunction and hypertrophy the decay rate increases, its life period reduces.

In the early stage of HCH the amount of ribosomes in myocardial cell increases and this change is conditioned by the acceleration of their synthesis, and the rate of ribosomes decay is also increased. On the whole the observed changes characterize a renewal of ribosomes. The study of tRNA decay processes revealed an increase of its decay after the hyperfunction appeared, that is in the period of the maximal increase in tRNA concentration. The results of investigations obviously show that tRNA increase the rate of polypeptide chains' elongation and accelerate the translation processes in the hypertrophic heart.

Thus, the obtained data suggest that the increase in the content of all the types of HNA (mRNA, c-nRNA rRNA, tRNA) in myocardium during the period of compensatory growth is caused exclusively by the acceleration of their synthesis.

As a result of a three-year HCH a complex of changes is being developed in myocardium resulting in a wear of myocardium and the development of cardiac failure.

As appears from figures 1 and 2 that three months after the coarctation of ascending aorta, the concentration and synthesis of mRNA and c-nRNA gradually decrease. This decrease forestalls in time and clearness the analogous one occurring in the cytoplasm. The fact obtained shows that the rate of synthesis and concentration of rRNA begin to decrease after a months (Fig. 3).

The results of described experiments show a slow-down of synthesis and decay rates of all types of RNA in the late stage of hyperfunction and a simultaneous decrease in RNA concentration in myocardium.

At this stage a sharp increase in the stabilization of heart RNA molecules is observed. This process partially compensates the delayed rate of its forming. Probably, the breakdown in myocardial cell occurs not in the system of ribosomes, but most likely in the process of transferring the information from DNA to protein or by direct decrease in genetic apparatus activity. According to the literature data [1,3,13] in the late stage of hyperfunction the relative content of polyribosomes in the total population of ribosomes in the hypertrophic heart reduces insignificantly and the decrease of protein synthesis rate depends neither on ribosomes quantity nor on the change in their ability of protein synthesis [12,14].

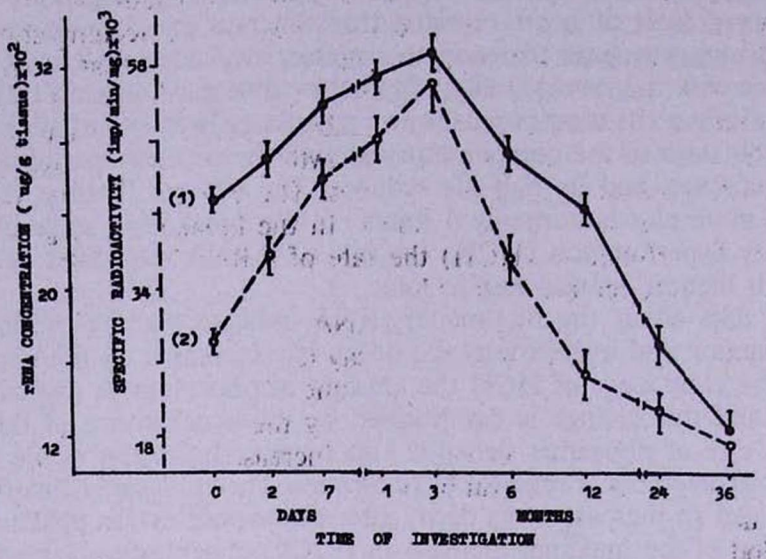

Fig 3. The concentration (1) and specific radioactivity (2) of the ribosome RNA before and after narrowing of the ascending aorta.
C – initial level.

The tRNA is a significant component of protein synthetizing system determining the translation rate, and in the final stage of wear and development of cardiac failure the decrease in synthesis and concentration of tRNA sharply reduces the rate of translation in myocardium (Fig. 4).

Thus, the results of the investigation show that tRNA in the hypertrophic heart realizing the prolonged hyperfunction increase the rate of polypeptide chains elongation. But in the stage of wear and cardiac failure a general shortage of tRNA or some of its isoacceptor forms is observed, which results in a decrease in translation rate.

The investigations of myocardium RNA metabolism in the compensatory growth period, the wear stage and the stage of development of cardiac failure allowed us to substantiate some theses.

As it turned out the RNA synthesis rate and its concentration increase in the hypertrophic heart. The rate of synthesis and the accumulation of mRNA, c-nRNA and rRNA in cytoplasm increases, the mRNA and c-nRMA secretion rate into cytoplasm being higher than that of rRNA [18,21,24].

Our data about the appearance of mRNA molecules in myocardium with a decay rate different from that in norm, in fact, indirectly indicate that the variety of newly synthetized matrix changes in the heart. We cannot exclude also the idea of existence of mRNA with too large sizes for coding of one protein [11,16], and the data permit the suggestion that there is a possibility of mRNA molecules synthesis coding simultaneously several proteins in the process of compensatory heart growth. And this apparently is the reason for the cells not

to use the precedent ribosomes, but to prefer producing new ones. Probably to accelerate the protein synthesis in heart a new class of specialized ribosomes is needed. It must be noted that this process can also be connected with the decrease in stability of low-molecular RNA initiating the translation [15,17,20].

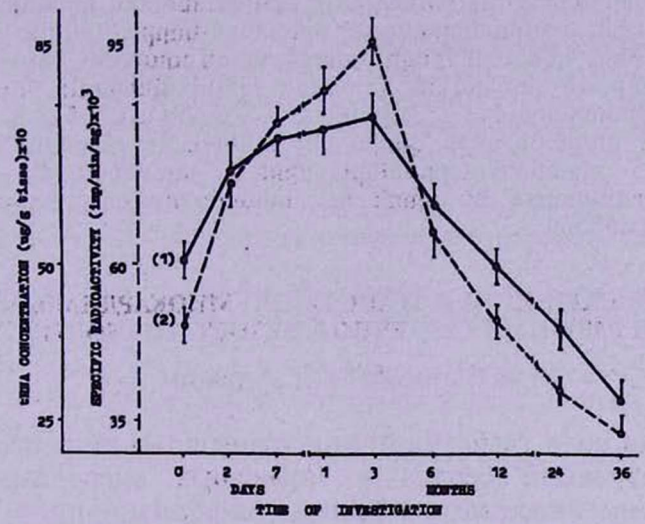

Fig. 4. The concentration (1) and specific radioactivity (2) of the transport RNA before and after narrowing of the ascending aorta.
C – initial level.

Our study allows us to control the course of events developing in myocardium during the heart failure after the long-term resistance overload.

Under the influence of hyperfunction the transcription of genome segments in the heart intensifies activating the mRNA and c-nRMA synthesis. The rate of synthesis of these RNA increases earlier and to a greater degree than that of rRNA. The amount of RNA in myocardial cells increases as a result of transcription acceleration. The proteins present in abundance in cytoplasm at the stage of a relative compensation can bind with RNA molecules [22,24,25]. Such a mechanism obviously will prevent the proteins from penetrating into the nucleus and will stabilize the transcription.

Later on, the rate of synthesis and accumulation of mRNA and c-nRNA in cytoplasm decreases. This decrease is incomparably more expressed than that of rRNA. And, finally, a decrease in tRNA or its separate isoacceptor types limiting the rate of translation is observed.

On the whole we can conclude that in the isometric hyperfunction in hypertrophic heart some changes are observed connected with the decrease in the transcription and translation ability of myocardial cell, which plays a decisive role in the formation of cardiac failure.

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ՍԻՏԱՄԿԱՆԻ ԲՋՋԱՅԻՆ ՏՐԱՆՍԿՐԻՊՑԻՈՆ ԵՎ ՏՐԱՆՍԼԱՑԻՈՆ ՓՈՓՈԽՈՒԹՅՈՒՆՆԵՐԸ ՍՐՏԻ ԱՆԲԱՎԱՐԱՐՈՒԹՅԱՆ ԶԱՐԳԱՑՄԱՆ ԺԱՄԱՆԱԿ

Մ.Հ.Վարոսյան, Կ.Գ.Ադամյան

Սրտամկանի բջջային տրանսկրիպցիայի և տրանսլացիայի դերի գնահատման համար սրտի կոմպենսատոր գերֆունկցիայի պայմաններում կատարվել է ինֆորմացիոն, ռիբոսոմային, տրանսպորտային, քրոմոսոմ-կորիզակային և կորիզային, ռիբոնուկլեյնաթթուների կենսասինթեզի, տեսակարար պարունակության ու տրոհման ուսումնասիրություն մողելային փորձերի պայմաններում: Պարզվել է, որ աորտայի լուսանցքի նեղացումից 2, 7, 30 օր, 3, 6, 9 ամիս և 1, 1.5, 2.5, 3 տարի անց նկատվում են այս ցուցանիշների փոփոխություններ: Իզոմետրիկ հիպերֆունկցիայի առավել ուշ շրջանում տրանսկրիպցիոն և տրանսլացիոն պրոցեսների խանգարումները համարվում են սրտի անբավարարության զարգացման ճնավորման հիմնական գործոն:

ИЗМЕНЕНИЯ ТРАНСКРИПЦИИ И ТРАНСЛЯЦИИ МИОКАРДИАЛЬНОЙ КЛЕТКИ ПРИ РАЗВИТИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

М.А.Варосян, К.Г.Адамян

Для выявления роли транскрипции и трансляции в процессе компенсаторной гиперфункции сердца в модельных экспериментах было изучено содержание биосинтеза и распада информационной, транспортной, рибосомной, хромосомно-ядрышковой и ядерной РНК в миокардиальной ткани, при изометрической гиперфункции, достигаемой путем сужения восходящей аорты спустя 2,7,30 суток, 3,6,9 месяцев и 1, 1.5, 2, 2.5, 3 года. Проведенные исследования дают основание заключить, что при изометрической гиперфункции в гипертрофированном сердце наблюдаются изменения, свидетельствующие о снижении транскрипционных и трансляционных возможностей миокардиальной клетки, что играет решающую роль в формировании сердечной недостаточности.

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