MECHANISM OF CHANGES IN LYMPHOCYTIC DEHYDROGENASE ACTIVITY DURING TRANSPLANTATION OF THE HEART

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Succinate dehydrogenase (SD) and α-glycerophosphate dehydrogenase (α-GPD) activity were studied in the peripheral blood lymphocytes and grafted myocardium in CBA mice after transplantation of the heart from newborn C57BL/6 mice subcutaneously into the concha auriculae. The ratio SD/α-GPD was shown to be greater than 1 in the myocardium and lymphocytes of intact animals and in recipients of a transplanted isolinear heart. After allogeneic (heterolinear) transplantation the ratio between the activities was reversed (SD/α-GPD less than 1) on account of activation of α-GPD in the blood lymphocytes, and this was preceded by inversion in the myocardium of the graft. This phenomenon is assumed to be connected with the development of immunological conflict.

KEY WORDS: transplantation; lymphocytes; myocardium; dehydrogenases.

Investigations [7-9] have shown that the development of the immunological response during allografting of skin and heart in mongrel dogs and inbred mice is combined with changes in dehydrogenase activity of the lymphocytes. The most characteristic manifestation of the change in cell metabolism under these conditions was an increase in α-glycerophosphate dehydrogenase (α-GPD) activity, which began to exceed succinate dehydrogenase (SD) activity at the beginning of clinical manifestations of the rejection reaction.

Normally SD activity is higher than α-GPD activity, i.e., the ratio SD/α-GPD is greater than 1; between 72 and 24 h before disturbance of the function of the grafted heart, this ratio began to fall below 1, heralding a rejection crisis [9]. The reasons for this reversal have not been explained.

Considering that lymphocytes play a leading role in the formation of transplantation immunity, and that the earliest manifestation of the response of the cell to any stimulus is a change in its mitochondrial system [10], it might be supposed that the changes observed are the result of involvement of the lymphocytes in the immunological process. This hypothesis is confirmed by data showing that α-glycerophosphate is oxidized in preference to succinate when rapid mobilization of the energy resources of the cell is required [2]. Consequently, the appearance of reversal is evidence of a sudden increase in the energy requirements of the lymphocytes, possibly as a result of a change in their immunological reactivity and participation of the cells in the mechanism of immunological conflict.

Meanwhile other workers [4, 6] have shown significant correlation between the enzymic status of the lymphocytes and biochemical processes in the internal organs, especially the myocardium. Changes in dehydrogenase activity of the lymphocytes after heart transplantation may possibly be a reflection of disturbance of the tissue metabolism of the grafted heart and one of the most probable causes of this disturbance is the development of the rejection reaction.

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TABLE 1. Ratio between SD and α-GPD Activities in Lymphocytes of Recipient Mice

Characteristics of group	Ratio SD/α-GPD		
	before operation	7 days after operation	9-10 days aft. operation
CBA→CBA C57BL/6→CBA	1,2±0,26	1,2±0,09 0,93±0,003 $P>0,05$	1,1±0,084 0,87±0,034 $P<0,01$

TABLE 2. Dehydrogenase Activity in Myocardium

Material tested	No. of animals	Activity	
		SD	α-GPD
Donor's myocardium (before transplantation)	5	11,0±0,79	5,78±0,39
Isografts	8	66,0±7,56	15,5±3,57
Allografts	25	12,9±1,96	10,39±3,31

The object of this investigation was to study the metabolism of the allografted heart during development of immunological conflict and to compare it with the dynamics of dehydrogenase activity in the circulating blood lymphocytes. Such investigations would shed light on the problem whether changes observed in the lymphocytes are primary or whether they reflect disturbances of metabolic processes in the myocardium of the transplanted heart.

EXPERIMENTAL METHOD

Experiments were carried out on 50 CBA mice. The donors for the experimental group were C57BL/6 mice. Isolinear transplantation (CBA →CBA) was performed on the control group.

Activity of the enzymes α-GPD and SD in the blood lymphocytes was determined by Nartsissov's method [3] before the operation and daily from the third to the 12th days thereafter. The function of the grafted heart was recorded electrocardiographically. Dehydrogenase activity in the myocardium of the graft was studied by Nartsissov's method [5] at various times (from the fifth to the 12th day) after the operation. The number of micromoles of formazan formed by 1 mg protein during 1 min at 37°C was taken as the unit of enzyme activity.

EXPERIMENTAL RESULTS

Periodic determination of the enzyme activity of the lymphocytes after isolinear transplantion of the heart into CBA mice showed that the ratio between SD and α-GPD activity exceeded 1 throughout the period of observation (Table 1). Consequently, activation of the α-glycerophosphate shunt in the lymphocytes of the heart recipients was not the result of the operation but was connected directly or indirectly with the immunological response of the recipient, as shown by the results of determination of the enzymes in the lymphocytes after interlinear transplantations.

Determination of dehydrogenases in the myocardium of the graft showed that α-GPD activity was constantly lower than SD activity both before transplantation and on the 5th to the 12th day after isolinear grafting of the heart. Transplantation of the heart in this system led to substantial activation of both enzymes. Under these circumstances the elevation of the SD level was greater than that of α-GPD (Table 2).

Activity of the myocardial enzymes after heterolinear heart transplantation was substantially less than after isolinear grafting ($P < 0.05$). The fact that in seven animals of this group the ratio between the activities of the myocardial enzymes was reversed (SD/α-GPD = 0.69 ± 0.098) deserves particular attention. As a rule this reversal was found in animals with marked activation of α-GPD in the lymphocytes. Reversal of the activity of the two dehydrogenases in the lymphocytes always preceded the analogous changes in the allograft. This state of the enzymes in the myocardium was relatively short lasting, and the precise periods between the appearance of reversal of the SD/α-GPD ratio in the myocardium of the transplanted heart and in the peripheral blood lymphocytes could not be established.

Correlation analysis showed that significant feedback exists with respect to these two enzymes between the enzymic status of the myocardial allograft and the recipient's lymphocytes, whereas in the isolinear system such correlations were absent.

The results indicate that during cardiac transplantation in a heterolinear system analogous changes arise in the metabolism in the lymphocytes and the transplanted myocardium, as shown by reversal of the dehydrogenase activity (α-GPD > SD); these changes are manifested earlier and more clearly in the cells responsible for the formation of transplantation immunity, i.e., the lymphocytes.

This sequence of affairs, as well as the absence of any such changes in the enzymes after isolinear transplantation, suggests that the reason for activation of the α-glycerophosphate shunt in the lymphocytes is the development of a rejection reaction, in which these cells play a varied and key role.

The increase in α-GPD activity in the transplanted myocardium may also be the result of development of immunological conflict, at certain stages of which considerable mobilization of the energy resources of the cells is required in order to maintain their vital activity under the hypoxic conditions caused by disturbance of the hemodynamics and by the infiltrative and other changes characteristic of the rejection reaction.

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