TREND OF SPLENIC LYMPHOCYTE ACTIVITY IN A MODEL OF CHRONIC DENERVATION AND DELYMPHATIZATION OF THE KIDNEYS IN MICE

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It is generally agreed that the clinical manifestations of nephropathies associated with rejection of a transplanted kidney are determined by the severity of ischemic damage and by the degree of its histoincompatibility. Meanwhile the contribution of factors of denervation and delymphatization of the donated kidneys to the manifestations of rejection nephropathy have not been paid their due regard.

In the investigation described below the response of the lymphoid tissue of the body was studied in a model of chronic denervation and delymphatization of both kidneys.

EXPERIMENTAL METHOD

There were four groups of experiments on 718 male CBA mice (Table 1). The model of denervation and delymphatization of the kidneys and also a mock operation were produced by decapsulation of both kidneys and also by dissection, scarification, and removal of the adventitia around the vessels. Completeness of denervation was verified by monitoring the fall in the adrenalin and noradrenalin levels in the kidney tissues on the 5th day after their decentralization [8]. Activity of the lymphoid tissue of the mice undergoing these operations (donors) was determined by the method in [10], based on determination of the proliferative activity of splenic lymphocytes of the donor mice by counting the number of colony-forming units (CFU) in the spleen of lethally irradiated recipient mice. For this purpose, a suspension of splenic lymphocytes obtained from donor mice of one of the experimental groups at different times of observation was injected into the caudal vein of lethally irradiated recipient mice. Material for injection was taken 24 h after the operation and monthly thereafter until the 10th month inclusive. At each time point from five to 10 donor mice were sacrificed and the mixed lymphocyte suspension obtained from them was injected into recipient mice in a dose of 10^{10} lymphocytes. The recipient mice were irradiated with gamma-rays on the "Stebel'-3A" apparatus, in a dose of 9 Gy (900 R). Spleen cells were injected into these animals 24 h after irradiation. The recipient mice were killed 8 days later and the number of colonies formed was counted. The number of animals at each time of observation was 15-20. The numerical results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Functional activity of the splenic lymphocytes in the group of mice undergoing the mock operation and in the group of mice with denervation and delymphatization of the kidneys was found to undergo long-term fluctuating changes (Fig. 1). The fact will be noted that periods of rising activity of lymphocytes in these two groups of experiments coincided, but with an increase in the time after the operation, activity of the splenic lymphocytes of the donor mice decreased. It was also noted that functional activity of splenic lymphocytes of mice with denervated and delymphatized kidneys was 2 to 3 times higher ($p < 0.01$) throughout the period of observation than in animals undergoing the mock operation, and this difference persisted until the end of observation (10 months).

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TABLE 1. Characteristics of Experiments

Group of experiments	Number of animals	
	donors	recipients
Transplantation of lymphocytes from spleen of mice with denervated and delymphatized kidneys into irradiated recipients (principal group)	80	220
Transplantation of lymphocytes from spleen of mice undergoing laparotomy into irradiated recipients (control of operative trauma)	60	160
Transplantation of lymphocytes from spleen of intact mice into irradiated recipients (control of initial level of lymphocyte activity)	53	170
Irradiated mice without transplantation of lymphocytes (irradiation control)		45
Total	193	525

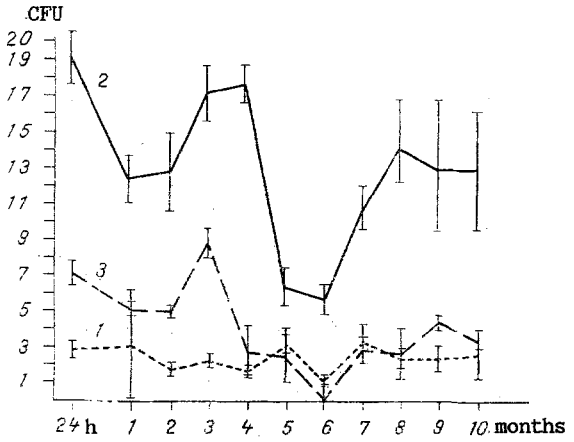

Fig. 1. Trend of functional activity of lymphocytes of intact mice (1), of mice with denervation and delymphatization of the kidneys (2), and in mice undergoing laparotomy (3). Abscissa, times of observation; ordinate, proliferative activity of splenic lymphocytes of donor mice.

Since activity of the splenic lymphocytes of mice of the control group was significantly higher ($p < 0.05$) for 4 months than that of intact animals (group 3), but activity of the lymphocytes of mice of the experimental group was significantly higher ($p < 0.01$) throughout the period of observation, we suggested that the lymphocyte activity discovered may have been due to processes of reparative regeneration of tissues which, in animals undergoing the mock operation, reached the level of physiological regeneration by the 4th month (normalization of activity of splenic lymphocytes), whereas in mice with denervation and delymphatization trauma to the kidneys, they remained at a high level right until the end of observation.

Peaks of intensification of lymphocyte activity, which occurred in the present experiments 24 h, 3-4 months, and 8-10 months after denervation and delymphatization, are in agreement with available data on periodic intensification of reparative regeneration processes in the organs in neurodystrophy [2]. It can be concluded from analysis of the facts that during transplantation of the kidneys, which always accompanies denervation and delymphatization of the organ, especially after transplantation into the hetero-position, not only histoincompatibility antigens may play the role of activator of the recipient's immune system, but also antigens arising in the course of development of the dystrophic process [3, 5, 6, 7]. It is logical to suppose that the high level of regeneration information of the lymphoid cells in the early postoperative period guarantees adaptation to the unchanged transplant, hypertrophy of individual cells, and functional compensation (without any signs of sclerosis) [1].

In the later periods transmission of regeneration information by lymphoid cells takes place in response to dysfunction of the dystrophic nephrons, which induces their replacement by connective tissue [6].

We know that the intensity of responses of different systems of the body, including the immune system, depends on biological activity of the stimulus [4]. In this connection it can be postulated that during autotransplantation, release of antigen from cells damaged by denervation—delymphatization induces only local compensatory—adaptive reactions in the organ, leading to its gradual sclerosis. This process may follow a protracted course without any manifest clinical symptoms [6].

During allografting a similar response of the immune system takes place to hypertrophy, dystrophy, and death of the nephrons under the influence of denervation and delymphatization factors. The difference, however, is that the biological activity of the kidney antigen, entering the recipient's body under these circumstances, is significantly higher than during autografting. That is why it gives rise to great activation of the recipient's immune system with the formation of a clinical picture of acute rejection crises and chronic rejection nephropathy. Similar mechanisms are probably involved also during rejection of kidneys transplanted from HLA-identical twins [9].

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