PROLONGATION OF RAT HEART ALLOGRAFT SURVIVAL BY 15-DEOXYSPERGUALIN

Sir:

15-Deoxyspergualin (15-DS) is a derivative of spergualin which was discovered in culture filtrates of a bacterial strain BMG162-aF2[1]. Spergualin was first shown to exhibit antitumor activity[2], and later it was shown that both spergualin and 15-DS were able to suppress the rejection of skin allograft in the mouse resulting in prolongation of the graft survival period[3]. The mode of rejection of the skin allograft was considered to be different from that of vascularized organ allografts such as the kidney, heart or liver[4]. Therefore, we tested the effect of 15-DS on cardiac allograft survival in the rat.

Male rats of the inbred WKA ($RT1^k$) strain were used as recipients, and male rats of the inbred F344 ($RT1^{lv1}$) were used as donors. They were obtained from commercial sources (WKA: Shizuoka Laboratory Animal Center, F344: Charles River, Tokyo) and kept under specific pathogen-free conditions in our animal facility. The rats were 10~16 weeks old and weighed 250 g.

Heterotopic cardiac allografting was performed by cuff anastomosis of the donor aorta and pulmonary artery to the recipient's common carotid artery and external jugular vein, respectively, according to the method described elsewhere[5]. In the experimental model, the donor venae cavae and pulmonary vein were ligated. The grafts were palpated daily and rejection was determined at the time of cessation of heart beats. This was confirmed by histological examination when necessary. The graft survival period was designated from the day of transplantation to 1 day before rejection. The recipient rats were administered various doses of 15-DS intramuscularly from the day of transplantation for 11 days, and then discontinued.

All of the heart allografts of the untreated recipient rats were rejected within 8 days after transplantation and the median graft survival time was 6 days. Treatment of recipient rats with 3.0 or 10.0 mg/kg of 15-DS prolonged graft survival time of all the grafts indefinitely, and the prolongation was statistically significant ($P<0.01$). The results clearly showed that 15-DS suppressed the rejection of the vascularized organ and brought about prolongation of the graft survival time, as previously demonstrated in the murine skin allotransplantation[3]. Heterotopic cardiac allotransplantation has been adopted as an appropriate model for evaluating anti-rejection agents. Cyclosporine, which is now widely used for treatment and prevention of rejection in clinical organ transplantation was also tested for its ability to suppress the rejection in rat heart allografting and was confirmed to be effective in the initial study[6]. The results shown here indicate that 15-DS is promising as a new immunosuppressive agent in organ transplantation.

Table 1. Effect of 15-deoxyspergualin on the graft survival time in heterotopic cardiac allotransplantation of the rat.

Daily dose of 15-DS[a] (mg/kg)	No. of animals	Graft survival days	Median	*P* value[c]
—	10	2, 5, 6, 6, 6, 6, 7, 7, 7, 8	6	
0.5	8	6, 6, 6, 6, 8, 8, 42, >100	7	ns
1.0	8	4, 9, 10, 14, 32, 46, 58, >100	23	ns
3.0	8	>23[b], >90, >90, >90, >100, >100, >100, >100	>95	$P<0.01$
10.0	8	>70, >80, >80, >80, >80, >100, >100, >100	>80	$P<0.01$

[a] 15-Deoxyspergualin was injected intramuscularly from the day of transplantation for 11 days and then discontinued.

[b] Sacrificed with a living graft.

[c] Calculated using Mann-Whitney U-test.

>: The graft continues to survive on the day indicated.

ns: Not significant.

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