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Effect of 15-deoxyspergualin on allograft arterio-sclerosis and growth factor synthesis in the rat

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Abstract Chronic rejection is a major cause for late graft loss. Typical vascular changes in the grafts are adventitial inflammation, disappearance of myocytes in the media and thickening of the intimal layer. We investigated the effect of a new immunosuppressive drug, 15-deoxyspergualin (DSG), on chronic rejection using our rat aortic allograft model. At the dose of 1.0 mg/kg per day, DSG significantly reduced all histopathological parameters of chronic rejection, thus, inhibiting the generation of allograft arteriosclerosis. Growth factor synthesis in the grafts was determined by reverse transcription reaction with oligo dT primers and semiquantitated by polymerase chain reaction. The expression of several growth factors, PDGF-BB, IGF-1, EGF an TGF-β, was suppressed to 16–60% of the non-treated allograft level. This indicated that DSG may work via suppression of growth factor synthesis and, thus, inhibits the generation of chronic rejection.

Key words DSG · Chronic rejection
Rat · Allograft
Growth factor inhibition

Introduction

15-Deoxyspergualin (DSG) is a new immunosuppressive drug that is believed to work predominantly via macrophage/monocyte suppression [3, 4]. There is also evidence of suppression of T and B cells [6, 7]. The final mechanism of action of DSG still remains unknown. In this study we investigated the vascular wall changes in chronic rejection using the rat aortic allograft model.

Materials and methods

Aortic transplantantations

A segment of the donor's thoracic aorta (DA rat strain) was used as a transplant and was sutured into a heterotopic position below the renal arteries in the recipient's abdominal cavity (WF rat strain) [5].

Medication

The rats were given 15-deoxyspergualin (Takara Shuzo Co. Ltd., Kyoto, Japan) i.p. at doses of 1.0 mg and 0.3 mg/kg per day for 3 months, after which time the rats were sacrified.

Quantitation of histology

Morphological changes were quantitated according to standard morphometric principles and expressed as point score units (psu) [1].

Determination of mRNA expression of growth factors

Total RNA from aortic grafts was extracted using the quanide-isothiocyanite method [2]. Reverse transcription reaction with oligo dT primers and polymerase chain reaction with GAPDH standard were used to quantitate the intensity of growth factors by densitometry.

Results

Dosages of 1.0 and 0.3 mg/kg per day of DSG significantly reduced the adventitial inflammation from 5.5 to 4.1–4.3 psu ($P < 0.05$). DSG at a dose of 1.0 mg/kg per day inhibited media necrosis from 0.6 to 2.0 psu ($P < 0.01$), intimal thickness from 2.9 to 0.8 psu ($P < 0.01$) and intimal cellularity from 2.0 to 1.4 psu. The dose of 0.3 mg/kg per day was ineffective.

At a dose of 1.0 mg/kg per day, DSG reduced the mRNA synthesis of platelet derived growth factor-BB to 23%, insulin-like growth factor-1 to 16%, epidermal growth factor to 60% and transforming growth factor-b to 33% of the non-treated allograft level.

DSG was effective in preventing the vascular changes of chronic rejection in the allograft. As the expression of several growth factors previously linked with allograft arteriosclerosis was concomitantly reduced, our results suggested that growth factors are necessary effector molecules in the generation of allograft arteriosclerosis.

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References

1. Aherne WA, Dunnill MS (1982) Morphometry. Edward Arnold, London, p 205
2. Davis LG, Dibner MD, Battney JF (1986) Basic methods in molecular biology. Elsevier New York, p 388
3. Dickneite G, Schorlemmer HU, Sedlacek HH (1987) Decrease of mononuclear phagocyte cell functions and prolongation of graft survival in experimental transplantation by (+)-15-deoxyspergualin. Int J Immunopharmacol 9:559
4. Dickneite G, Schorlemmer HU, Sedlacek HH, Falk W, Ulrichs K, Müller-Ruchholtz W (1987) Suppression of macrophage function and prolongation of graft by guanidinie-like structure, 15-deoxyspergualin. Transplant Proc 19:1301
5. Mennander A, Tiisala S, Halttunen J, Yilmaz S, Paavonen T (1991) Chronic rejection in aortic allografts: an experimental model for transplant arteriosclerosis. Arteriosclerosis Thromb 11:671
6. Morikawa K, Oseko F, Morikawa S (1992) The suppressive effect of deoxyspergualin on the differentiation of human B lymphocytes maturing into immunoglobulin-producing cells. Transplantation 54:526–531
7. Yoshikawa Y, Uchida H, Kuroda H, Nakamura T, Obayashi A, Fuji A, Takeuchi T (1988) In vivo effect of deoxyspergualin (NKT-01) on lymphocyte activation in response to alloantigens. J Antibiot 41:1675–1680