Transplant Int (1992) 5 [Suppl 1]: S587–S588

TRANSPLANT
International

Chronic rejection of rat aortic allografts: effect of inhibition of the thromboxane cascade

A. Mennander[1], J. Ustinov[1], T. Paavonen[1,2], A. Räisänen[1], and P. Häyry[1]

[1] Transplantation Laboratory, Fourth Department of Surgery and [2] Department of Pathology, University of Helsinki, Helsinki, Finland

Abstract. Non-immunosuppressed rat aortic allografts from DA ($RT1^{av1}$) to WF ($RT1^{u}$) strain develop, after a short reversible acute rejection episode, chronic arteriosclerotic changes in the vascular wall, which are indistinguishable from those seen in human allografts during chronic rejection [1]. Incubation of the aortic wall segments in vitro and immunochemical assays demonstrated that the allografts synthesized increased amounts of TxB2, but not 6-keto-$PGF_{1\alpha}$ or LTB4, compared to syngenic or normal aortas. The two major cellular components of the vascular wall, intima and adventitia, were incubated separately after microdissection. TxB2 was produced in the adventitia, whereas most of the 6-keto-$PGF_{1}\alpha$ was synthesized in the intima. Administration of a specific TxA2 receptor inhibitor to the recipient rat reduced significantly the proliferation of adventitial inflammatory cells and the intimal smooth muscle cells. Nevertheless, it only delayed but did not inhibit the overall sclerosis of the intima.

Key words: Chronic rejection – GR 32191B – Rat aortic transplants

Materials and methods

Aortic allografts were exchanged form DA ($RT1^{av1}$) to WF ($RT1^{u}$) strain, or for control, to DA strain. A group of rats was treated with a thromboxane A2 receptor inhibitor, GR 32191B, at the rate of 1.0 mg/kg per day. The recipients received a bolus of 250 mCi of ^{3}H-TdR by i.v. injection 3 h prior to sacrifice. The grafts were removed at various times, and were processed for histology, autoradiograms, immunohistochemistry or biochemical determinations [1].

Results and discussion

Morphologically, both types of grafts underwent an acute adventitial inflammatory episode, which subsided. The inflammation was more intense in the allografts, where the inflammatory cells also displayed the activation markers IL-2 receptor and Class II. The intima of the allograft, but not of syngeneic graft, developed an intimal proliferative lesions (arteriosclerosis) characteristic to chronic rejection. The cells in the media were lost in allografts, but preserved in syngeneic grafts.

The vascular wall components, adventitia (media lacking any nuclei) and intima were incubated either separately or together in vitro, and the prostanoids were quantitated by RIA. There was a significantly increased synthesis of TxB2 in the allografts, lacking in syngeneic grafts, but only a small increase in the synthesis of 6-keto-$PGF_{1\alpha}$ and no increase in the synthesis LTB4. The TxB2 synthesis occured mainly in the inflammatory component in the adventitia and 6-keto-$PGF_{1\alpha}$ synthesis in the intima.

Administration of a TxB2 receptor blocker, GR 32191B, did not inhibit the arteriosclerotic changes; nevertheless it delayed them for 1 month compared to the controls.

The incorporation of ^{3}H-TdR to proliferative adventitial and intimal cells was detected by autoradiography. These proliferative responses were significantly inhibited by the administration of GR 32191B. Since the adventitial cells were mainly LCA-positive white cells, and the intimal cells mainly α-smooth muscle actin positive smooth muscle cells, the administration of GR32191B was found to have an inhibitory effect on the proliferation on both of these cell types.

Taken together, the ^{3}H-TdR incorporation studies showed that the adventitial and the intimal proliferative responses were both downregulated by the administration of GR 32191B. Nevertheless, there was only a delay, but no definite inhibition of the generation of the arterio-

Offprint requests to: Ari Mennander, Transplantation Laboratory, University of Helsinki, Haartmaninkatu 3, SF 00290 Helsinki, Finland, Telefax: + 358-0-411227, Phone: + 358-0-434-6596

Grants: Supported by grants from the Academy of Finland, the Sigrid Juselius Foundation, the Finnish Cancer Society, the University of Helsinki, Helsinki, and Farmos Pharmaceuticals, Turku, Finland

sclerotic changes in the transplant as a consequence of the administration of GR 32191B. We concluded that lipid mediators of inflammation, particularly TxB2, were involved in the arteriosclerotic process of chronic rejection. However, this pathway, if blocked, may be bypassed by other, yet unidentified mediatory pathways.

Reference

1. Mennander A, Tiisala S, Halttunen J, Yilmaz S, Paavonen T, Häyry P (1990) Chronic Rejection in rat aortic allografts: an experimental model for transplant arteriosclerosis. Arteriosclerosis Thomb 11: 671–680