ENHANCED PROSTACYCLIN SYNTHESIS IN ACUTE HUMAN KIDNEY TRANSPLANT REJECTION

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Summary

In acute and chronic kidney transplant rejection renal cortical and medullary tissue samples were examined for their prostacyclin (PGI₂) generation by bioassay and compared with normal tissue. In acute rejection PGI₂ formation was significantly enhanced, particularly in the cortex. In chronic rejection the PGI₂ formation was comparable with control tissue. Since PGI₂ is a very potent platelet aggregation inhibitor and vasodilator, it is concluded that the increase in PGI₂ generation in acute rejection might be a self protecting mechanism which is, however, overwhelmed in irreversible rejection.

Introduction

The original work of Moncada and co-workers demonstrated the very potent antiaggregatory and vasodilating effects of prostaglandin I₂ (PGI₂), also called prostacyclin [1]. The protective function of PGI₂ in the vascular wall and its key role in balancing homeostasis is now widely accepted. The generation of PGI₂ in the kidneys of man has been reported [2]. McGiff and Wong suggested a compartmentalisation of prostaglandins (PGs) in the kidney, assuming that PGI₂ is mainly formed in renal vascular tissue, whereas other PGs, as PGE₂ and PGF₂α, are synthesised in the urinary tissues [3]. The renal effects of PGI₂ seem to be vasodilation, increase in blood flow, stimulation of renin release and regulation of the excretory function [4].

Under pathological conditions the PGs may play an important role. In experimental renal ischaemia and in systemic lupus erythematosus the renal PG production was found to be significantly increased [5, 6]. Anderson et al described elevated plasma PGE levels in a patient during and after acute kidney transplant rejection [7]. Recently, we reported a temporary stimulation in PGI₂ formation in the early stages of atherosclerosis suggesting that this may be a self protection phenomenon against mural platelet thrombus formation [8]. Since during kidney
transplant rejection there are two PG synthesis stimulating factors — vascular injury and ischaemia — our interest was focused onto the question whether transplant rejections are accompanied by changes of PGI₂ production.

Material and methods

We studied the kidneys of each of eight patients with acute irreversible and chronic irreversible rejection respectively (Table I). Acute rejection was defined as beginning acutely within three months after transplantation with typical symptoms, fever, swelling and tenderness of the transplant, and sudden plasma creatinine increase; chronic rejection started after three months without these symptoms and was diagnosed by an insidious plasma creatinine increase. All patients but one had suffered from chronic glomerulonephritis as primary renal disease, all received cadaver transplants. Because of clinical and angiographical evidence of irreversible rejection the transplants were surgically removed 12 ± 5 days (group 1) and 6 ± 3 days (group 2) respectively after loss of transplant function. Excluded from the study were transplants showing hydronephrosis, necrosis or extensive thrombosis. The third group, which served as control, consisted of eight patients, who underwent nephrectomy for malignant kidney tumors. Immediately after nephrectomy tissue samples from cortex and medulla were excised, frozen and stored in liquid nitrogen. In the malignant disease kidneys, tissue samples were withdrawn from histologically controlled uninvolved, normal areas. The tissue samples were assayed for their PGI₂ generation using Moncada’s bioassay [1]. The PGI₂ concentration was calculated by comparison with standards of synthetic PGI₂ (generously provided by Dr JE Pike, Upjohn Co., Kalamazoo, Michigan).

In another part of this study the plasma levels of 6-oxo-PGF₁α, the stable hydrolysis-product of PGI₂, were estimated by radioimmuno-assay in each of three patients showing acute rejection, chronic rejection and normal transplant function respectively [9, 10].

<table>
<thead>
<tr>
<th>Type of rejection</th>
<th>Patients with irreversible rejection</th>
<th>Transplant survival time</th>
<th>PGI₂-Release ng/g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Sex</td>
<td>Mean age ± SEM</td>
</tr>
<tr>
<td>Acute</td>
<td>8</td>
<td>3/5</td>
<td>34.6 ± 2.0</td>
</tr>
<tr>
<td>Chronic</td>
<td>8</td>
<td>4/4</td>
<td>29.0 ± 4.9</td>
</tr>
<tr>
<td>Controls</td>
<td>8</td>
<td>4/4</td>
<td>43.0 ± 4.7</td>
</tr>
</tbody>
</table>
Results and Discussion

The results of PGI$_2$ formation in renal tissue samples are summarised in Table 1. There was no significant difference between control kidneys and those with chronic rejection in the amounts of PGI$_2$ released, but in acute rejection release was increased significantly in both cortex and medulla (p < 0.005 and p < 0.025 respectively). These data indicate that during acute rejection PGI$_2$ release is enhanced. This might be caused by hypoxia, which is a feature of rejection. Other contributing factors could be vascular lesions including parietal thromboses and tissue damage, which could increase the supply of precursors for PG synthesis [11]. One enhancing factor which was demonstrated in vascular tissue is the uraemia itself, which stimulates PGI$_2$ formation by so far unidentified mechanisms [12, 13]. We suggest that the increased PGI$_2$ generation in acute rejection is a self protecting mechanism. It may be of major importance in safeguarding the organ, probably controlling rejection episodes. In addition, it might be of benefit during the repair processes of reversible rejections. In irreversible rejection this mechanism seems to be overwhelmed by the severe immunological attack. In chronic rejection the phenomenon of enhanced PGI$_2$ formation could not be demonstrated. It might be possible that this rather slowly advancing process causes an exhaustion of this mechanism.

The estimation of plasma 6-oxo-PGF$_{1\alpha}$ levels showed markedly elevated values before and during acute rejection episodes, rising from the normal range (≤ 70 pg/ml) to spikes of nearly 200 pg/ml (see Figure 1). Elevations of lower degree

![Graph](image)

Figure 1. Elevated plasma levels of 6-oxo-PGF$_{1\alpha}$ observed before and during an acute rejection episode which ended in transplant rupture

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were rarely observed in chronic rejection and could not be demonstrated in patients with good and stable transplant function. The origin of increased 6-oxo-PGF\textsubscript{1\alpha} levels in acute rejection is not clear. It might be that the transplant contributes to its formation. On the other hand it could be possible that the PGI\textsubscript{2}-synthesis in the whole vascular system, especially in the lung, is stimulated by platelet aggregates, immune complexes, angiotensin II and other nonspecific factors in acute rejection.

A very important role could be played by thromboxane A\textsubscript{2} (TXA\textsubscript{2}) in acute rejection. TXA\textsubscript{2} promotes platelet aggregation and vasoconstriction. It is known that kidneys can synthesise TXA\textsubscript{2} under pathological conditions [14]. We presume that the production of TXA\textsubscript{2} is enhanced in acute rejection too.

Recently Moncada showed that experimental hyperacute rejection can be prevented by the administration of synthetic PGI\textsubscript{2} [15]. Instead of thrombosing, these renal transplants produced urine normally as long as the PGI\textsubscript{2}-infusion was running. The future will show if PGI\textsubscript{2} is able to prevent acute rejections in human renal transplantation too.

**Acknowledgments**

We acknowledge the help of numerous colleagues, notably, Professor Dr S Rummelhardt, Dr K Klein and Dr G Syre.

**References**

1. Moncada S, Higgs EA, Vane JR. *Lancet* 1977; i: 18
7. Anderson CB, Newton WT, Jaffe BM. *Transplantation* 1975; 19: 527

**Open Discussion**

REMUZZI (Bergamo) Have you thought of the possibility that platelet activation, which is known to occur in chronic rejection can account for your results? You
know that beta thromboglobulin, a selective inhibitor of PGI₂, seems to be released by these platelets; have you tried to correlate PGI₂ with plasma BTG levels?

LEITHNER We have only made some tests with beta thromboglobulin. I think the interaction between the thromboxane production in platelets and transplant and the PGI₂ formation of the transplant may be the striking feature.

CHAN (London) We had the opportunity of using PGI₂ in the treatment of a patient with chronic rejection and we obtained quite satisfactory results, being able to improve his creatinine clearance from below 10ml per min to 15ml per min. Unfortunately this improvement in renal function only persisted for a week after the last PGI₂ infusion and within two weeks after stopping the drug, his creatinine clearance went back to his pre-treatment level.

LEITHNER Yes, I think that is the crucial point. It may be that in treatment with PGI₂ the early effect may be good but it is also possible that the rejection will recur if you stop infusion. Perhaps in acute rejection you can get a state of better immunological tolerance during prolonged infusion for two or three weeks.

REMUZZI In relation to your suggestion of a balance between prostacyclin and thromboxane in transplant rejection. I would like to mention a preliminary result we obtained in two patients with chronic rejection studied at Guy's Hospital. We were so far unable to demonstrate any increase in plasma level of thromboxane B₂ (measured by radioimmunoassay).

LEITHNER That is a very interesting comment and I wonder that you could not find elevated thromboxane B₂ levels in chronic rejection because, I think, if beta-thromboglobulin is elevated, thromboxane B₂ should be elevated too. But I think a lot of further work has to be done in this field.

SALTIS (Cardiff) In terms of therapy would not using imidazole to block the PGE pathway, diverting prostaglandin synthesis to PGI₂ seem a more satisfactory approach? There does not appear to be a safe non-toxic imidazole derivate.

LEITHNER I think it should be worthwhile to test all these compounds in renal transplantation.

SALTIS (Cardiff) In Cardiff we are at present investigating a gut flora-produced metabolite of niridizole, termed TC1, which appears to be a potent immuno-suppressive agent without any known toxic effect so far.

RAWER (Giessen) What do you think is the main protective effect of prostacyclin? Is it the inhibition of platelet aggregation or is it the dilatation of the vessels?

LEITHNER The main protective effect of prostacyclin is surely the inhibition of platelet aggregation. I am sorry that Moncada is not here, because his experiments on hyperacute rejection are really fascinating. The transplants produced urine and decreased plasma creatinine in uraemic animals and this was mainly caused by platelet aggregation inhibition.