NADPH oxidase subunits (NOX-1, p22phox, Rac-1) and tacrolimus-induced nephrotoxicity in a rat renal transplant model

Sir,

As Editor-in-Chief of Nephrology Dialysis Transplantation, we would like to draw your attention to the recent publication by Khanna and Pieper in the February issue of the journal [1], describing the results of their examination of tacrolimus-induced nephrotoxicity in a rodent renal transplant model. We read this paper with interest; however, we were really stunned by the complete absence of any citations whatsoever of our work directly addressing this very same system, particularly as it was in a much more relevant system such as human subjects.

We have, in fact, previously shown increased reactive oxygen species production in kidney and heart transplant patients treated with cyclosporin [2]. The same patients also showed upregulation of the nitric oxide system, as suggested by increased endothelial nitric oxide synthase (eNOS) gene expression and nitrite/nitrate levels, which suggested that the increased nitric oxide production is degraded by conversion to peroxynitrite, resulting from the reaction of nitric oxide with superoxide.

In a follow-up study [3], we examined the effects of cyclosporin and tacrolimus on cellular markers of oxidative stress and endothelial dysfunction in kidney transplant patients with post-transplant hypertension, as well as the effect of the angiotensin-converting enzyme (ACE) inhibitor ramipril on cellular markers of oxidative stress and endothelial dysfunction. This study measured the monocyte gene expression of p22phox, a NADPH/NAD oxidase system subunit, transforming growth factor-β (TGF-β), heme oxygenase-1 (HO-1) and eNOS, at baseline and after 2 months of treatment with ramipril. We reported that cyclosporin and tacrolimus induce a comparable oxidative stress in kidney transplant patients with post-transplant hypertension and that ramipril normalizes blood pressure and reduces the oxidative stress induced by both drugs.

In another study, in kidney transplant patients with cyclosporin-induced post-transplant hypertension, we also evaluated the effect of carvedilol, an α1-β blocker with strong antioxidant activity, on the cyclosporin-induced mononuclear gene expression of p22phox, TGF-β, HO-1 and eNOS [4]. Carvedilol reduced blood pressure and increased plasma antioxidant power and HO-1 mRNA and reduced 3-nitrotyrosine and TGF-β mRNA levels.

Of key importance, directly and indisputably applicable to the findings reported by Khanna and Pieper, were our observations that in our post-transplant hypertensive patients, ramipril and carvedilol reduced both p22phox and TGF-β gene expression.

The overwhelming degree of overlap is readily apparent when you compare their concluding paragraph: “Collectively, our studies demonstrate that TGF-β and O$_2^\text{-}$ participate in the events leading to renal damage. Therefore, a strategy to inhibit TGF-β and/or O$_2^\text{-}$ would assist in the prolongation of graft survival without unwanted side effects of TAC for transplant recipients.” with that of our studies: “The results of the current study demonstrate that at the cellular level cyclosporin or tacrolimus treatments induce a comparable oxidative stress that could contribute to the post-transplant hypertension frequently observed in transplant patients. These data strengthen our previous observations on the role of oxidative stress in calcineurin inhibitor mediated post-transplant hypertension and endothelial dysfunction. Furthermore, they show that inhibition of angiotensin II-mediated effects with the ACE inhibitor ramipril may potentiate protective mechanisms against long-term complications of chronic cyclosporin or tacrolimus treatment, such as oxidative stress-induced endothelial dysfunction, fibrogenesis, and chronic rejection.”

“In conclusion, carvedilol reduces the oxidative stress and corrects the altered cellular signaling mediated by oxidative stress in CsA-induced post-transplant hypertension. Therefore, it may prevent long-term complications, such as endothelial dysfunction, fibrogenesis and post-transplant nephropathy by decreasing NO degradation and production of TGF-β, a key fibrogenic cytokine, and by activating HO-1 production.”

Given this, it is obvious that the authors should have cited our work, and this further suggests that a reiteration of the authors’ duty to ensure that relevant work is properly cited/credited may be useful. What other measures may be necessary or useful we leave to your discretion. One of these possibilities would be to publish this e-mail as Letter to the Editor.

Conflict of interest statement. None declared.

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