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Release of urokinase plasminogen activator receptor during urosepsis and endotoxemia

To the Editor: In the June 2001 issue of *Kidney International*, Florquin et al clearly show a strong and early upregulation of urokinase plasminogen activator receptor (uPAR) in renal tubular epithelial cells during pyelonephritis and an increase in both blood and urine levels of soluble uPAR during endotoxemia [1]. The authors quoted only one study about uPAR expression in the kidney that indicated that uPAR was found in all segments of the tubular epithelium in normal renal tissue [2]. However, in accordance to Florquin et al we have previously reported that uPAR is barely detectable in the normal human kidney by immunohistochemistry and in situ hybridization [3]. In contrast, in acute tubular necrosis, whether isolated or associated to glomerular diseases or thrombotic microangiopathy, we found that uPAR was up-regulated in tubular epithelial cells, especially in cells detaching from the basement membrane and in desquamated cells in the tubular lumen [3]. Recently, we also demonstrated an up-regulation of uPAR in tubular lesions associated to nephrotoxic nephritis in the rat [4]. These results suggest that uPAR may play a role in the pathogenesis of acute renal failure related to acute tubular necrosis, either by focalizing uPA activity at the cell surface and promoting cell detachment from the basement membrane, or by facilitating cell migration and recovery of tubular integrity. Experimental models of acute tubular necrosis in uPAR knockout animals would be helpful to determine if uPAR plays a pathogenic role and whether it is deleterious or beneficial for the kidney.

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Reduced content of α subunit of Gq protein content in monocytes of Bartter and Gitelman syndromes: Relationship with vascular hyporeactivity

To the Editor: The clinical picture of Bartter and Gitelman syndromes reflects functional defects in kidney transporters that lead to hypokalemia, volume depletion, as well as activation of the renin-angiotensin-aldosterone system. In addition, patients with Bartter and Gitelman syndromes present with normotension/hypotension, reduced peripheral resistance, and hyporesponsiveness to pressors [1]. We recently provided a mechanistic explanation for the decreased vascular reactivity characteristic of Bartter and Gitelman syndromes by demonstrating that there is a defective coupling of the agonist receptor to phospholipase C, at the level of the Gα subunit of the Gq-binding protein. Protein kinase C activity is therefore reduced, thereby inducing vascular hyporeactivity [2]. As the reduced expression of the Gαq was based on mRNA level [2], a direct demonstration of a correspondent decrease in the abundance of Gαq protein was required to further strengthen the existence of a defect in the intracellular biochemical sequence of events that leads to vascular hyporeactivity in Bartter and Gitelman syndromes [3].

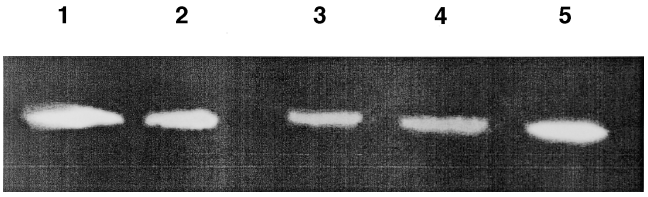

Fig. 1. Western blot of Gαq protein expression in monocytes of healthy controls (lanes 1 and 5) and of patients with Bartter and Gitelman syndromes (lanes 2, 3, and 4).

We also report here the evaluation of Gαq protein content in the same cohort of patients with Bartter and Gitelman syndromes ($N = 9$, two Bartter and seven Gitelman) using Western blotting.

Proteins from monocytes were processed for Western blot analysis essentially as described by Hepler, Kozasa, and Gilman [4] with the use of chemiluminescence for detecting the primary antibody (polyclonal rabbit anti-Gαq, Santa Cruz Biotechnologies, Santa Cruz, CA, USA) used at 1 to 2000 dilution. Exposed films were digitized by scanning densitometry and protein levels were compared to that of healthy controls ($N = 10$) monocytes using National Institutes of Health imaging software. A few examples are reported in Figure 1. The results demonstrate that patients with Bartter and Gitelman syndromes had significantly reduced levels of Gαq protein: 60 ± 12 vs. 107 ± 8 densitometric units; $P < 0.001$ (Student t test).

The decrease in the abundance of Gαq protein strengthens the defect in the intracellular signaling that reduces vascular reactivity of Bartter and Gitelman syndromes. The next step will be to establish whether the reduction of Gαq is a result of decreased production or increased degradation, as well as to evaluate the molecular basis for these changes.

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Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease

To the Editor: In their excellent review on peroxisome proliferator-activated receptors (PPARs), Dr. Guan and Dr. Breyer indicate that fibrates bind to and activate PPARα, but they do not mention any renal adverse event associated with the modulation of PPAR activity [1]. We would like to emphasize the fact that fibrates may lead to renal dysfunction. Indeed, an analysis of 27 patients from our institution who developed an impairment of renal function during fibrate therapy and a literature review of 24 papers that reported data on 2676 patients taking fibrates lead us to conclude that therapy with fenofibrate, bezafibrate, and ciprofibrate may induce renal dysfunction [2]. This side effect was observed in patients with either native kidneys or kidney transplants and among those with either normal or impaired renal function at baseline [2]. Interestingly, gemfibrozil was devoid of this side effect [2]. A recent prospective study in hyperlipemic patients with normal renal function confirmed that fenofibrate, but not gemfibrozil, induced a significant rise of serum creatinine level [3]. Of note, hyperhomocysteinemia was associated with fenofibrate-induced increase in creatinine level [3].

On pathophysiological ground, the activation of PPARα results in a down-regulation of the expression of cyclooxygenase 2 (COX-2) and a reduction in the production of vasodilatory prostaglandins [4]. These events may obviously account for fibrate nephrotoxicity.

How should these data influence the nephrologist's practice? First, we believe that fenofibrate, bezafibrate, and ciprofibrate should not be prescribed to patients with renal dysfunction. Second, hyperhomocysteinemia may counteract the benefits expected from the lipid-lowering action of these fibrates. This is consistent with trials showing that gemfibrozil is the only fibrate that allowed for significant reductions of cardiac events in both primary and secondary prevention trials.

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