Lysophospholipase D activity exists in the urine to catalyse the formation of lysophosphatidic acid

Sir,

Lysophosphatidic acid (LPA) has been suggested to be involved in the pathogenesis of a number of disease states, including cancer and atherosclerosis, through its induction of a wide range of (patho)physiological events, such as cellular survival, proliferation, migration, change in morphology and extracellular matrix deposition [1,2]. These actions of LPA are believed to be mediated via specific cell-surface G protein-coupled receptors and the downstream intracellular signalling pathways [1,2]. The important role of LPA is also true in the field of kidney and bladder diseases; it has been shown that glomerular mesangial cells express LPA receptors of the endothelial differentiation gene family and that this bioactive lipid stimulates mesangial cell proliferation (by itself or synergistically with platelet derived growth factor) and contraction, and plays a role in the pathogenesis of glomerular diseases [3,4]. LPA also has profound effects on the proximal tubular epithelial cells [5,6], while LPA signalling and functions may be important in human bladder carcinoma cells [7]. Accordingly, it would be important to determine whether LPA can be produced/detected in the urine samples of patients.

Although the mechanisms by which cellular responses to LPA are elicited have been clarified through a series of studies on LPA receptors and related intracellular signalings, it was not until the discovery of lysophospholipase D (lysoPLD) [2,8] that the molecular mechanism of extracellular LPA production came to be understood. LysoPLD is identical to autotaxin, a tumour cell motility-stimulating factor, originally isolated from melanoma-cell supernatants, and hydrolyses lysophosphatidylcholine (LPC) to produce LPA, serving as the main pathway for the generation of this bioactive lipid [2,8]. In this letter, we discuss the results of our investigation of whether lysoPLD activity can be detected in the urine and whether, therefore, LPA can be formed in the urine.

The urine samples used in this study were residual samples of those obtained for routine laboratory analyses (for clinical purposes) and were mainly proteinuria samples; informed consent was obtained from all the subjects for the use of their residual urine samples for this study. We first examined the samples for lysoPLD activity, by measuring the amount of choline released following the addition of LPC as the substrate, as previously described [2]. The lipase activities in the normal and proteinuria samples were 0.06 ± 0.02 nmol/ml/min (mean ± SD, n = 4) and 0.23 ± 0.18 nmol/ml/min (mean ± SD, n = 12), respectively. The activities were correlated well with the lysoPLD antigen levels as assessed by western blot analysis (data not shown). Furthermore, there was also a good correlation between the lysoPLD activity and the urinary protein concentration (Figure 1).

Presumably, lysoPLD also leaks into the urine like the other protein components (mainly albumin) in the presence of kidney damage. We then examined the urine samples for the presence of LPA and attempted to determine whether LPA can actually be produced in the urine samples with the addition of LPC as a substrate; the concentration of LPA was determined by an enzymatic cycling assay [9]. LPA was detected in the urine samples in concentrations ranging from 0.02 to 0.86 μM; this result, however, may not be reliable quantitatively; the values changed with just mere changes in the incubation time. Addition of LPC markedly resulted in the production of LPA (Figure 2A), suggesting the existence of lysoPLD activity in the urine. Furthermore, addition of ethylenediamine tetraacetic acid (EDTA) to the samples suppressed the increase of the LPA concentrations (data not shown), confirming the requirement of Co2+ for the activity of lysoPLD.
the lysoPLD activity [8,9]. The increase of the LPA concentration (upon LPC addition) was correlated well with the lysoPLD activity in the urine samples (Figure 2B).

Our present results suggesting that lysoPLD activity exists in the urine and that LPA can be formed in the urine may be important from the perspective of the reported results of a number of studies on the effects of exogenous LPA on renal systems. Sphingosine 1-phosphate is the major sphingosine-based lysophospholipid, structurally similar to LPA. Recent evidence has implicated this sphingolipid mediator in the (patho)physiology of kidney diseases [10]. Lysophospholipid, a relatively new family of bioactive lipids, may play important and hitherto unexpected roles in the pathophysiology of kidney diseases, and further studies must be conducted in this field.

Conflict of interest statement. None declared.

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Efficient treatment of crescentic glomerulonephritis associated with hepatitis B virus with lamivudin in a case referred with acute renal failure

Sir,

Glomerulonephritis (GN) associated with hepatitis B virus (HBV) and concomitant acute renal failure (ARF), though rare, has been previously reported [1]. In recent years, lamivudine has been used frequently in GN cases related HBV due to its few side effects and ease of use [2,3].

Case. A 40-year-old female patient referred to our clinic with nausea, vomiting, oedema in the lower extremities and reduced urine amount. Laboratory findings were: urea: 212.2 mg/dl, creatinine: 9.4 mg/dl, albumin: 29 g/l. AST: 29 g/l, ALT: 414 U/l, ALT: 261 U/l and 3206 mg/day proteinuria. C3, C4 and C1q were normal. Antinuclear antibodies (ANA), pANCA, cANCA, and glomerular basement membrane antibody were detected as negative. Serological tests revealed; HbsAg (+), HBcAg (+), AntiHbs (–), AntiHbc (–), AntiHbe IgM (–) and HBV DNA was detected to be 5.81 x 10^5 copies/ml. A renal biopsy had shown global sclerosis (7 of the 10 glomeruli), crescent formation and mesangial proliferation with IgA and C3 deposits in the glomeruli. Monoclonal antibodies gave positive results with HbsAg in the glomeruli. Treatment was planned with interferon-α (IFN-α). Because of an anaphylactic reaction observed after the first dose, IFN-α therapy was stopped, and the patient was followed-up with lamivudine treatment and haemodialysis 3 days a week. Thirty-six weeks after the onset of 30 therapy, HBV DNA levels were 454 copies/ml, creatinine levels were 1.5 mg/dl, and the proteinuria level was 334 mg/day. Though in low titers, Anti-HBs antibody turned positive. Renal biopsy was repeated in this period. Global sclerosis (6 of the 14 glomeruli), mild or moderate mesangial proliferation with IgA deposits were observed in the glomeruli. Monoclonal antibodies were detected as negative with HbsAg. Patient was still in the 20th month of the therapy and levels of creatinine were observed as 1.9 mg/dl.

Comment. Antiviral therapy has taken first place in the treatment of HBV-related GN [1]. Our case is the first adult case demonstrating crescentic GN and ARF secondary to HBV, in which an efficient improvement in renal functions, if for short duration, was obtained with lamivudine therapy. Taking into consideration other data in the literature, we thought that lamivudine might be an alternative for its advantages, particularly in developing countries and in cases where IFN-α cannot be used due to its side effects.

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