Cyclooxygenase-2 (COX-2) and the kidney: current status and potential perspectives

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Introduction

Prostaglandins are important mediators of renal physiology and disease. The main enzyme which governs the synthesis of prostaglandins is cyclooxygenase (COX), also called prostaglandin endoperoxide synthase (PGS). Until recently it was assumed that only one cyclooxygenase gene and protein exists, an enzyme which is now called cyclooxygenase-1 (COX-1) or the 'constitutive' isomorph. Between 1989 and 1991 however, several groups reported evidence for the existence of a mitogen- and endotoxin-inducible cyclooxygenase, a second isomorph of cyclooxygenase. This so-called 'inducible' enzyme was named cyclooxygenase-2 (COX-2) [1,2]. The terms 'constitutive' and 'inducible' are actually inadequate since COX-2 is also constitutively expressed in some organ systems including the kidney [3-5], and there is evidence that COX-1 mRNA expression can be regulated under certain circumstances [1,2]. COX-2 products have been found to be important also in kidney development and cell differentiation [6,7].

COX-2 expression in renal cells

Soon after the discovery of COX-2 in fibroblasts and monocytes/macrophages the expression and regulation of this isomorph was studied in rat mesangial cells in culture. A rapid and transient induction of COX-2 in mesangial cells is induced by serotonin, thromboxane A2 [8], interleukin 1-β [9-11], bacterial endotoxin (lipopolysaccharide, LPS) [9], phorbol esters (phorbol 12-myristate 13-acetate, PMA) [10-12], and endothelin-1 [13,14]. The COX-2 expression is mediated through multiple signalling pathways involving protein kinases A and C, tyrosine kinases, and bacterial endotoxin (lipopolysaccharide, LPS), depending on the cell type studied and the stimulus applied [1,2]. Independent of the stimulatory agents of COX-2 induction, glucocorticoids (i.e. cortisol, dexamethasone) inhibit COX-2 protein and COX-2 mRNA expression both by transcriptional and post-transcriptional mechanisms [8,11]. Similarly cyclosporin A, has been shown to reduce IL1-β [9] and serotonin [8] mediated COX-2 expression in rat mesangial cells by post-transcriptional regulation. Recent interest has focused on the interaction of the cyclooxygenase and nitric oxide (NO) pathways and studies in cultured mesangial cells show that prostaglandin E2 downregulates iNOS induction [15], whereas NO can potentiate IL1-β induced COX-2 expression [16].

COX-2 expression in the kidney

The first evidence that low levels of COX-2 mRNA are detectable in normal kidney tissue was presented in 1993 [3,17]. Studies in rats using in situ hybridization and immunohistochemistry demonstrated that expression of COX-2 is localized to medullary interstitial cells, macula densa cells, and to adjacent epithelial cells of the nearby cortical thick ascending limb [5]. In contrast to rats, in human kidneys expression of COX-2 protein was localized to endothelial and smooth muscle cells of arteries and veins and intraglomerularly to podocytes, whereas no COX-2 expression was found in the macula densa [18].

Functional role of COX-2 in the kidney

Although the importance of prostaglandins in kidney physiology and pathophysiology is well known, the contribution of COX-2 to the production of prostaglandins in the diverse physiologic and pathophysiologic states has not yet been elucidated.

Evidence for a very important role of COX-2 in kidney development comes from studies generating COX-2 deficient mice. Among other pathologic alterations, COX-2 null mice developed severe renal abnormalities [6,7]. Only few functioning nephrons with immature, small glomeruli and dysplastic tubules grew in underdeveloped mesenchymal tissue. The observed abnormalities were not detectable in the first days after birth but increased with age of the animals. This implicates the importance of COX-2 in the postnatal development of the kidneys.

Studies in a rat model of renal ablation in our
laboratories showed an enhanced COX-2 expression in the early days after renal ablation and seem to point to a role of COX-2 products in proliferation, since inhibition of COX-2 leads to enhanced proliferation of glomerular cells [19]. To investigate a possible role of COX-2 products in the mediation of inflammatory cell recruitment, we used a model of mesangio proliferative glomerulonephritis in rats. A transiently enhanced COX-2 expression was found in the early phase of this disease. Selective inhibition of COX-2, however, did not alter the inflammatory cell recruitment, whereas unselective inhibition of COX-1 and COX-2 lead to an enhanced and sustained influx of monocytes/macrophages into the glomeruli [20]. This does not suggest that COX-2 has a major role in the mediation of inflammatory cell recruitment in this disease.

Studies in the rat revealed that chronic Na⁺-depletion increases COX-2 immunoreactivity in the macula densa and adjacent thick ascending limb, suggesting a role for COX-2 in the regulation of renin release, possibly mediated by changes in prostaglandin production. Further evidence that COX-2 is a source of prostaglandins in the response to sodium changes derives from a recent study where treatment with a selective COX-2 inhibitor reduced the increased renin content and renin mRNA in chronically Na⁺-depleted mice [21]. Importantly, the COX-2 inhibitor was without an effect on renal renin content in mice fed a normal sodium diet. The blood pressure was not altered by treatment with the COX-2 inhibitor in mice on a low-sodium diet. Although these studies suggest a role for COX-2 in the regulation of salt, volume, and blood pressure homeostasis, the exact physiological role of COX-2 remains to be established.

The signalling pathways involved in the in vivo regulation of COX-2 expression have been investigated in different animal models. In a rat model of anti-GBM glomerulonephritis the enhanced expression of COX-2 was inhibited by a protein tyrosine kinase inhibitor, both at a transcriptional and a post-transcriptional level [22]. In vivo studies in a rabbit model of ureteral obstruction [23] and in LPS-treated rats [24] revealed that endogenous iNOS products and exogenously added NO further stimulate enhanced COX-2 in renal inflammation. Since inhibition of endogenous production of NO reduced the production of prostanoids in LPS-treated rats [24], inhibitors of iNOS might possibly exert anti-inflammatory properties through inhibition of NO but also PG production. Further investigations using selective iNOS and COX-2 inhibitors will help to clarify the interaction between the two pathways.

Role in human kidneys and perspective

The discovery of molecular differences between COX-1 and COX-2 allows the development of pharmacological agents selectively inhibiting COX-1 or COX-2 and selective inhibitors of COX-2 are now available. Because NSAID administration in the treatment of pain and inflammation risks the development of acute haemodynamic renal failure or analgesic nephropathy, the chronic use of NSAIDs in renal disease is not desirable. Selective COX-2 inhibitors might be an alternative in the treatment of inflammation and pain and recent results in experimental glomerulonephritis in rats suggest that selective inhibition of COX-2 might reduce nephrotoxic side effects in renal inflammation. However, since to date the exact physiological role of COX-2 is still unclear and the role of COX-1 and COX-2 in human kidneys seems to differ from animals, there is no current evidence justifying the use of COX-2 inhibitors in renal disease.

References

Renal nuclear medicine: can it survive the millennium?

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The reflex use of nuclear medicine investigations by nephrologists reflects its relative safety but fails to take account of either the value or the comparative expense of these tests. This editorial re-examines the contribution of isotopic renography to clinical management.

Assessment of renal function and structure

Isotopic renograms can provide information about dynamic function and structure depending on the handling of the radioisotopes which are either filtered at the glomerulus, (EDTA and DTPA), or extracted and secreted by the tubule, (HIP, MAG3 and DMSA).

Both EDTA and the modern formulations of DTPA, which are minimally protein-bound, can be used to measure glomerular filtration rate (GFR) [1]. The accuracy improves as the number of plasma samples and the duration of the sampling period is increased, although DTPA is less reliable than EDTA when the GFR is less than 30 ml/min. DTPA renography should routinely measure GFR as well as providing a dynamic image and split function.

The 99technetium labels, usually DTPA or MAG3, provide the best dynamic images, with MAG3 preferred in renal insufficiency. Renal structure is best defined by 99technetium-DMSA (a static tracer) with computer enhancement able to generate tomographic and three-dimensional images although in the future, it may be possible to produce simultaneous high quality structural and dynamic imaging using MAG3 [4]. The calculation of divided function from either static or dynamic images is equally accurate. The DMSA renogram is more sensitive than the intravenous urogram in the detection of cortical scars [5,6]. Using DMSA renography, a relationship between the severity of reflux and the degree of cortical scarring has been demonstrated [7] and this technique is widely used to differentiate between upper and lower urinary tract infection in infants, in whom physical signs and blood tests are often unhelpful [8]. Unfortunately, the specificity of the DMSA renogram is poor and it fails to differentiate between cortical abnormalities secondary to acute inflammation, reflux nephropathy, duplex moieties, cysts, dysplasia or infarction.

Radiological techniques, which provide simultaneous structural and functional information, are fast emerging. Iohexol, a low osmolality iodinated radiographic contrast agent, can measure GFR and provide dynamic and structural information [2,3] when combined with simultaneous urography or computerized tomography, although X-ray doses may limit its use. Soon, contrast ultrasonography will provide improved images of the renal vasculature to complement conventional ultrasound and Doppler studies; and, functional magnetic resonance imaging will provide all the information required in a single test at a price which is cheaper than the cost of the two nuclear medicine investigations currently required.