PROSTAGLANDINS SYNTHESIS AND RECEPTORS IN THE PATHOGENESIS OF VARIOUS KIDNEY DISEASES

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ABSTRACT

In terms of global mortality and morbidity, chronic kidney disease ranks first among equals. Despite recent advances in our knowledge of disease processes, conventional methods of treatment have proven unable to halt the spread of most chronic conditions. Research efforts are concentrated on pinpointing the precise mechanisms at play so that more potent therapy alternatives might be discovered. Many renal disease processes are regulated by prostaglandin E2 via its four EP receptors; as a result, EP receptors may become useful therapeutic targets for nephrotic syndrome and other kidney diseases. The kidney contains a very variable distribution of PGs, synthases, and receptors.

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I. INTRODUCTION

For three months or longer, impaired kidney function and/or damage constitutes Chronic Kidney Disease (CKD). Globally, hypertension and diabetes are the primary causes, and treatment seeks to stop kidney failure and reduce its effects. Together with cardiovascular disease, diabetes-related nephropathy is a leading cause of death and disability in North America, where it is responsible for 30–40% of all cases of ESRD requiring renal replacement therapy. CKD is progressive, its course can vary widely, and its specific pathophysiology is unknown despite intensive study. Diseases can begin in any one of the kidney's three functional areas; vascular, glomerular, or tubular events all have a role. Multiple factors contribute to the progressive loss of renal function seen in diabetic kidneys. Current intervention tactics that focus on hyperglycemia and blood pressure management can postpone renal damage, but they cannot prevent the disease's progression; thus, a number of complementary treatments to the traditional suppression of the renin-angiotensin-aldosterone system (RAAS) are being examined.

Initial hyperfiltration with preferential vasodilatation of the afferent arteriole is followed by a decline in renal function, hypertrophy of the glomerulus and tubular structures, podocyte injury, expansion of the mesangial matrix leading to glomerular sclerosis, tubulointerstitial fibrosis, and tubular lesions and atrophy in patients with diabetic nephropathy. Glucose is the primary element, although there are numerous others to consider. Changes in growth responses (proliferation, hypertrophy, and senescence),

cell death (apoptosis, necrosis), fibrosis (epithelial-myofibro blast trans differentiation), and transport systems are only some of the harmful pathways that have been identified.

In normal kidneys, the cortex produces mostly PGE2 and PGI2, with very little TXA2. The renal medulla principally manufactures PGE2, and its synthetic capacity is around 20 times that of the cortex. PGE2 production by the kidneys is commonly indicated by its presence in the urine. Vasodilator effects on the kidney are produced by intrarenal infusions of PGE2 and PGI2, leading to an increase in renal blood flow. Furthermore, PGs block chloride transport in the thick ascending loop of Henle and have natriuretic effects. Epithelial and mesangial cells in the glomerulus have the potential to generate PGI2 and PGE2. Because of their anatomical location, the kidneys play a vital role in regulating systemic and renal blood flow, respectively. Renal cortex-derived prostaglandin I2 (PGI2) and prostaglandin E2 (PGE2) promote renin secretion. PGI2 generated by COX-2 in mesangial cells may directly trigger renin secretion due to the overexpression of COX-2 in the macula densa following salt deprivation.

II. PGI2 IN KIDNEY DISEASES

One of the main COXs pathway products, prostacyclin (PGI2), is well recognized for controlling renal hemodynamics, tubular transport, and renin release. Atypical cytochrome p450 enzyme prostacyclin synthase (PGIS) produces prostacyclin (PGI) from prostaglandin H (PGH), which is produced by COXs from arachidonic acid. It is disappointing that the precise cellular location of PGIS protein has not yet been discovered, despite the fact that the inner medullary tubules and medullary interstitial cells exhibit considerable PGIS mRNA expression.Similar to PGES, studies of PGIS were conducted using kidney disease models and mice lacking the PGIS gene. Previous studies shown that PGIS deficiency caused renal fibrosis, which was accompanied by renal hemodynamics that were noticeably out of control, tubular atrophy, surface abnormalities, and cysts. Additionally, overexpression of PGIS supported renal defense against AKI brought on by endotoxemia. MnTBAP, a synthetic form of superoxide dismutase (SOD), might stop the decline in PGI2 synthase activity in uremic mice. It was proposed that oxidative stress, which was linked to the development of end-stage renal disease (ESRD), may act as a mediator for the malfunction of the PGI2-generating pathway. In addition to renal cases, PGI2 is well recognized for its positive benefits in the case of stroke, thrombosis, atherosclerosis, and myocardial infarction, which may indirectly impact the advancement of kidney disorders. PGI2 has been linked to cell destiny, fibrotic response, and renal growth, according to a prior study. Numerous research have recently focused on Beraprost Sodium (BPS) to understand the function of PGI2 in renal disorders. BPS, a prostacyclin analogue, is a vasoactive chemical that may widen renal arteries to boost renal blood flow, decrease TXA2 production, stop platelet aggregation, and prevent the development of immunological complexes. Additionally, it was claimed that BPS might lower proteinuria by preventing glomerular thrombosis. Some clinical studies also produced comparable findings. Additionally, BPS enhanced renal function in a diabetic kidney condition caused by STZ, presumably by reducing oxidative stress and inflammation.

The IP receptor found on cell surfaces mediates several of PGI2's renal activities. It is disputed across species where the IP receptor is located in renal cells. Mesangial cells, interstitial cells, the vasculature, and tubular epithelial cells (proximal tubule, mTAL, and collecting duct) in mouse kidney were found to contain IP. The IP receptor was found in podocytes in human kidney. This may have pointed to distinct IP receptor functions in various nephron regions. It has been discovered that the IP receptor is essential for preserving renal hemodynamics, tubule transport, renin secretion, and minimizing renal fibrosis and inflammation. According to a recent study, prostaglandin I2 receptor agonism reduced albuminuria and protected beta-cell function through nephrin-dependent processes. ONO1301, a new nonprostanoid IP agonist, was tested in models of type 1 diabetic nephropathy and UUO, and it shown

a therapeutic impact on treating diabetic nephropathy by stimulating hepatocyte growth factor (HGF), which acts as a TGF- β inhibitor. ONO-1301 also reduced mesangial matrix buildup, inflammation, and oxidative stress through an IP receptor-mediated mechanism, which improved the renal lesions in type 2 diabetes. Interestingly, PGIS knockout animals showed more glomerular, vascular, and interstitial abnormalities than IP-knockout mice, indicating that other receptors in addition to IP may have contributed to these abnormalities. Peroxisome proliferator-activated receptor α (PPAR α) or peroxisome proliferator-activated receptor δ (PPAR δ) activation was thought to protect tubular cells against apoptosis in AKI, according to a large body of research up to this point. Additionally, recent research has focused particularly on the cyclic vasoactive peptide known as urotensinII, which has the potential to stimulate PGI2 synthesis in NRK-52E cells treated with gentamicin and protect renal cells through a PPAR α -dependent mechanism. Additionally, researchers discovered that via stimulating the PGI2/PPAR α signal pathway, L-carnitine might shield renal tubular epithelial cells in an experimental animal model caused by carboplatin. Together, CKD and AKI are two different forms of renal disorders in which PGI2, a key COXs product, plays a significant role via interacting with its receptors and the downstream signals.

III. PGD2 IN KIDNEY DISEASES

The neurophysiological processes that prostaglandin D2 is known to affect include the regulation of body temperature, the release of hormones, and the sleep-wake cycle. Renal artery flow, urine output, creatinine clearance, and salt and potassium excretion were all dose-dependently elevated in the kidney after intrarenal infusion of PGD2. Prostaglandin D synthase (PGDS) converts PGD2 through the typical pathway of PGs production, much as it does with other kinds of PGs. There are two different forms of PGDS: hematopoietic prostaglandin D synthase (H-PGDS) and lipocalin type prostaglandin synthase (L-PGDS), also known as beta trace protein (BTP). Regarding cellular or tissue distribution and functional importance, they are distinct from one another. L-PGDS is primarily found in inflammatory cells, particularly mast cells and antigen-presenting cells. Under various circumstances, H-PGDS exhibits both pro-inflammatory and anti-inflammatory effects. L-PGDS, which is fundamentally distinct from H-PGDS, may be found in many tissues, including the kidney, lung, heart, and brain. L-PGDS has recently caused widespread concern as a biomarker in large population-based research cohorts. Numerous studies have shown that L-PGDS has become a more effective intracellular measure of GFR than blood creatinine level. During kidney injuries, L-PGDS has been shown to serve as a marker for proximal tubule damage in addition to reflecting the glomerular filtration rate. L-PGDS is becoming into a significant predictor of the outcome in renal disorders due to its sensitivity in assessing GFR decline. It captures the dangers brought on by pathophysiologic or renal function decline. As a result, it could provide a chance for early detection and treatment for renal disease patients.

As a PGD2 synthase and a lipophilic ligand-binding protein after being secreted, L-PGDS is often thought of as a multifunctional protein. Numerous experiment models have examined the protective effects of L-PGDS, particularly in the cardiovascular and renal systems. The scope of this evaluation does not include information on L-PGDS's effects on the cardiovascular system. We concentrated on the roles of L-PGDS in the kidney in this review. It has been unequivocally shown that kidney obstruction dramatically increases L-PGDS expression in the tubular epithelium. L-PGDSKO mice greatly reduced the tubulointerstitial fibrosis brought on by UUO, emphasizing the crucial role L-PGDS plays in renal fibrosis. Other researchers, however, demonstrated that L-PGDS KO mice exhibited glomerular hypertrophy, fibrosis, thickening of the basement membrane, and elevated TGF-β deposition.Adriamycin-induced nephropathy in mice and the function of L-PGDS in early stage diabetic nephropathy in rats provided further evidence that PGD2 may

have a role in chronic kidney disorders. The variety of adverse renal effects revealed that L-PGDS had diverse functions in the kidneys that were subjected to various stressors.

The DP1 receptor and DP2 receptor (also known as CRTH2) are two receptors with which PGD2 interacts. PGD2 activates the DPs, which causes a rise in cAMP levels. The DP1 receptor is expressed more extensively and seems to have a variety of roles. Contrarily, the DP2 receptor, which functions as a chemo-attractant receptor homologous molecule, is mostly found in inflammatory cell types like Th2 cells. The functions of DP1 in platelet aggregation, mucin production, and cutaneous and pulmonary venous vasodilation have been investigated. The DP2 receptor, which is physically distinct from the DP1 receptor and is a member of the chemokine receptor family, aids in the production of Th2 cytokines such IL-4, IL-5, and IL-13. The study of PGD2 receptors in the kidney has lagged behind that of the respiratory system. However, research suggests that CRTH2 may contribute to the development of inflammation and tubulointerstitial fibrosis. Researchers showed that interstitial collagen deposition, collagen I gene expression, and soluble collagen content were dramatically decreased in CRTH2-KO UUO mice. CRTH2 was stopped by creating CRTH2-KO mice or utilizing CRTH2 antagonist (CAY10471). They also discovered that PGD2 collaborated with CRTH2 to activate Th2 cells, which in turn generated IL-4 and IL-13 to facilitate fibrosis. A prior research also revealed that PGD2 may have a role in kidney disorders irrespective of the DP receptor. Particularly the 15d-PGJ2, which is regarded as a natural endogenous ligand of PPAR, PGD2 may be converted to physiologically active J-series cyclopentonePGs. In several organs, activation of PPAR γ might successfully block TGF-induced profibrotic effects. Thus, PGD2 may prevent fibrosis by activating PPAR γ and inhibiting the transcription of AP-1 and NF-κβtranscription factors via the end product 15d-PGJ2. In addition, when HK-2 cells were treated with a combination of IFN-γ and TNF-α 15d-PGJ2 was able to reduce the production of CXCL9, CXCL10, and CXCL11. Together, the data suggested the significance of the PGD2-generating cascade in the pathophysiology of kidney disorders, despite the fact that the activities of PGD2 in the renal system are not completely known.

IV. PGF2α IN KIDNEY DISEASES

Another important colooxygenase-mediated arachidonate metabolite in the kidney is PGF2α . PGF2α may be produced from PGH2 by PGF synthase or by PGE9 ketoreductase, which converts PGE2α to PGF2α enzymatically. The G protein-coupled transmembrane receptors, FPA and FPB, mediate the cellular actions of PGF2α. It has been discovered that FP receptors are involved in the transformation of kidney fibroblasts by contributing to the rise of intracellular Ca2+ in response to PGF2α in renal cells. The kidney is where the FP receptors are often found. The main cells of the collecting duct, the distal convoluted tubule, and the podocytes of the glomeruli were found to have high expression levels of FPs, whereas the thick ascending limb had lower levels. PGF2α , in contrast to other PGs, is little understood in renal disorders. Previous investigations have shown that PGF2α activates FP receptors in the cortical collecting duct, which results in natriuresis and diuresis. Because FPA and FPB in the PKC and Rho pathways are activated differently, PGF2α blockedbasolateral 40 pS K channels at high doses and stimulated these channels at low concentrations. Additionally, cortical collecting ducts' arginine vasopressin-stimulated water permeability may be inhibited by FP activation without an increase in intracellular Ca2+. It has been shown in animals that FP KO mice have a slight impairment in controlling renal medullary osmolality under water deprivation, as well as modest polyuria and polydipsia. Despite compensatory enhancements of AT1 receptors and an enhanced hypertensive response to AngII infusion, this study also showed that FP deletion decreased blood pressure through inactivating RAS. In a model of renovascular hypertensive rats (RHR), ROS was thought to be an initiator that stimulates endothelial COX-2 to produce PGF2α and contribute to endothelial dysfunction in rabbit

arteries. A new understanding of renal-related hypertension is provided by treatment with celecoxib or tempol, which decreased blood pressure, improved renal blood flow, and restored endothelial function in renovascular hypertension rats. Regarding PGF2α's function in oxidative stress, it has been shown that the amount of PGF2α synthesis changes significantly during an inflammatory reaction. Increased serum concentrations of the oxidative stress markers 8-isoprostane and PGF2α were linked to the GFR and kidney volume in a study done on patients with autosomal dominant polycystic kidney disease (ADPKD), suggesting a connection between PGF2α and renal function during the growth of cystic kidney. In this investigation, PGF2α was also shown to raise the blood levels of MMP-1 and MMP-9. There must be additional undiscovered roles in the renal incidences given the quantity of PGF2α and its receptors in the kidney.

V. CONCLUSION

The prevalence of chronic kidney disease is increasing. The hunt for better alternatives/additives to the standard RAAS therapies continues to fail, despite massive attempts to identify alternative medicines that would more specifically target different parts of kidney disease and halt its progression. The pathogenesis of some renal illnesses, such as chronic kidney disease and acute kidney injury, also involves PGs. The therapy of kidney illnesses may benefit from strategies that target any part of the cyclooxygenase (COX), prostaglandin (PG) synthesis, PG, or receptor cascade. A number of recent studies have shed light on the PGs system in kidney pathology, and while there are still many open questions, they do pave the way for more thorough research in the future.

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