Off the Beaten Renin–Angiotensin–Aldosterone System Pathway: New Perspectives on Antiproteinuric Therapy

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CKD is a major public health problem in the developed and the developing world. The degree of proteinuria associated with renal failure is a generally well accepted marker of disease severity. Agents with direct antiproteinuric effects are highly desirable therapeutic strategies for slowing, or even halting, progressive loss of kidney function. We review progress on therapies acting further downstream of the renin–angiotensin–aldosterone system pathway (e.g., transforming growth factor-beta antagonism, endothelin antagonism) and on those acting independent of the renin–angiotensin–aldosterone system pathway. In all, we discuss 26 therapeutic targets or compounds and 2 lifestyle changes (dietary modification and weight loss) that have been used clinically for diabetic or nondiabetic kidney disease. These therapies include endogenous molecules (estrogens, isotretinoin), biologic antagonists (monoclonal antibodies, soluble receptors), and small molecules. Where mechanistic data are available, these therapies have been shown to exert favorable effects on glomerular cell phenotype. In some cases, recent work has indicated surprising new molecular pathways for some therapies, such as direct effects on the podocyte by glucocorticoids, rituximab, and erythropoietin. It is hoped that recent advances in the basic science of kidney injury will prompt development of more effective pharmaceutical and biologic therapies for proteinuria.

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Key Words: Proteinuria, Albuminuria, Podocyte, Glomerulus, Diabetes, Novel therapies

Overview of Non-Renin–Angiotensin–Aldosterone System Agents

Looking beyond renin–angiotensin–aldosterone pathway inhibitors, which are addressed elsewhere in this issue, there are diverse antiproteinuric therapies. Several recent reviews have recently been written on novel agents used for slowing the progression of CKD.[1,2] We will highlight novel mechanisms for established antiproteinuric therapies, as well as progress on the development of new antiproteinuric agents. Some of these agents may work by stabilizing or normalizing podocyte phenotype.[2-6] Most molecular entities have pleiotropic effects, and, collectively these therapies also have anti-inflammatory, immunosuppressive, antifibrotic, and cytoprotective properties. Given the complexity of kidney injury and repair, it is seldom possible to disentangle these effects in vivo. We will focus in this brief overview on antiproteinuric effects, particularly on publications in the past 5 years. A summary of these agents and their proposed cell targets and mechanisms of action is presented in Table 1.

Glucocorticoids

Glucocorticoids have efficacy in both inflammatory and noninflammatory glomerular disease, suggesting complex modes of action. In human podocytes and rodent adriamycin nephrosis, dexamethasone was shown to restore suppressed nephrin and reduced vascular endothelial growth factor (VEGF) proteins.[7,8] Nephrin is an integral component of the slit diaphragm structure; when reduced in quantity, as in nephrotic syndrome, it causes disruption of the glomerular barrier. VEGF is involved in angiogenesis regulation. Fuji and colleagues found in cells expressing nephrin, that the stress of glucose deprivation induces endoplasmic reticulum (ER) stress and subsequent underglycosylation of nephrin and retention in the ER.[9] Dexamethasone was shown to restore nephrin release, apparently by stimulating mitochondrial ATP generation, but it could not improve nephrin processing in another form of ER stress (calcium imbalance), raising questions about the generalizability of the findings. In cultured mouse podocytes, it was shown that dexamethasone administered either before or after the toxin puromycin aminonucleoside prevented or reversed actin depolymerization and increased RhoA activity, which promotes stress fiber assembly.[10] Although it is unclear how these activities relate to in vivo conditions, it is conceivable that dexamethasone might have favorable effects on disordered podocyte structure.

Adrenocorticotropic Hormone

Adrenocorticotropic hormone (ACTH), also known as corticotropin, is derived from the pituitary peptide proopiomelanocortin. ACTH is further processed into alpha-melanocyte-stimulating hormone (MSH) and corticotropin-like intermediate lobe peptide. A synthetic, active form of ACTH known as cosyntropin (synacthen) consists of the first 24 amino-acid residues of the hormone. Beginning in the 1950s, ACTH was widely used for nephrotic syndrome, but was later supplanted by synthetic glucocorticoids. More recently, an open-label trial in 23 subjects with diverse glomerular disease showed benefit,[11] and a randomized controlled trial by Ponticelli and colleagues showed similar efficacy for cytotoxic

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Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.
1548-5595/$36.00
doi:10.1053/j.ackd.2011.06.002

therapy versus ACTH in membranous nephropathy.[12] Beyond stimulating adrenal production of cortisol, ACTH may be acting by other mechanisms. ACTH specifically binds one of the MSH receptors, which is expressed on all 3 glomerular cell types, with highest expression by podocytes. In Heymann nephritis, a rat model of membranous nephropathy, MSH and an MSH agonist peptide both reduced proteinuria.[13]

Calcineurin Inhibitors

The observation that cyclosporine reduces proteinuria in nonimmune-mediated renal disease has prompted a search for additional mechanisms of action. Two recent observations may explain the role of cyclosporine in proteinuric disease. First, cyclosporine blocks the calcineurin-mediated dephosphorylation of synaptopodin, and this action protects synaptopodin from cathepsin L-mediated degradation; because synaptopodin is an actin-binding protein, it therefore helps maintain the integrity of the actin cytoskeleton.[14] Second, cyclosporine downregulates expression of transient receptor potential channel, subfamily 6 (TRPC6) in adriamycin nephropathy, the animal model of focal glomerulosclerosis. TRPC6 gain-of-function mutations cause focal segmental glomerulosclerosis (FSGS) and TRPC is upregulated by angiotensin II, thus downregulation of TRPC-6 may contribute to the antiproteinuric effect of cyclosporine.[15]

Mycophenolate

Mycophenolate has been widely used for proteinuric diseases, but their antiproteinuric mechanisms have remained poorly defined. Apart from possible effects on systemic immunity, there is evidence of reduced interstitial mononuclear cell accumulation (but not reduced proteinuria) in the rat 5/6 renal ablation model,[16] and reduced proteinuria and glomerular and tubular injury in the obese Zucker rat model.[17] Few randomized controlled trials have addressed the use of mycophenolate in primary glomerular disease[18]; the recently completed, but unpublished, FSGS controlled trial suggested similar efficacy between the cyclosporine arm and the mycophenolate plus intermittent oral dexamethasone pulse.

Rituximab

A serendipitous observation that rituximab anti-CD20 therapy used for post-transplant lymphoproliferative disease was associated with remission of recurrent FSGS has led to widespread use of this agent for recurrent and native kidney FSGS. In general, response rates have been variable, with the most beneficial effects in case series of glucocorticoid-sensitive children with nephrotic syndrome as a result of native kidney FSGS and minimal change disease.[19,20] In 10 children on long-term cyclosporine therapy for steroid-dependent minimal change disease, a single infusion of rituximab was associated with decreased relapse rates and steroid use at a mean follow-up of 17 months.[20] The salutary effect in podocytopathies has been puzzling because B cells have not been implicated in pathogenesis. Recently, it has been shown that in cultured podocytes, recurrent FSGS serum disrupts the actin–myosin cytoskeleton and reduces activity of acid sphingomyelinase. Rituximab binds sphingomyelinase-like-phosphodiesterase-3b-precursor and restores acid sphingomyelinase activity, and this cytoprotective effect may explain the remittive potential.[21]

Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) have anti-inflammatory effects and may decrease proteinuria. Garman and colleagues showed that in rat diabetic nephropathy, canola oil (rich in omega-3 PUFAs) attenuated albuminuria, glomerulosclerosis, tubulointerstitial fibrosis, hypertension, and inflammation.[22] The degree of reduction in nephrin and nestin normally associated with diabetic nephropathy was reduced when treated with canola. Transforming growth factor-beta (TGF-β) immunostaining in mesangial cells improved after canola supplementation. Omega-3 PUFAs may affect previously noted TGF-β-related injury of podocytes in glomerular diseases. In addition, markers of inflammation, such as MCP-1, and CD68-positive cells were also attenuated by canola oil, which would point to an additional anti-inflammatory mechanism. In cultured mesangial cells, docosahexaenoic acid, an omega-3 PUFA, suppressed proliferation and growth of cultured mesangial cells. In rodent acute mesangial proliferative glomerulonephritis, omega-3 PUFAs significantly reduced proteinuria and mesangial cell proliferation and matrix expansion.[23]

A recent meta-analysis of 17 trials (10 of them randomized controlled trials) examined omega-3 PUFA effects on proteinuria. It involved 626 patients with glomerular diseases that included immunoglobulin A (IgA) nephropathy, diabetic nephropathy, lupus nephritis, and mixed etiologies.[24] The doses used ranged considerably (by 8-fold) and the median follow-up was 9 months. The estimated pooled effect size was −19% (95% CI: −34%, −4%; $P = .01$). Although the effect size was modest, this therapy is well-tolerated and merits continued consideration.

Tumor Necrosis Factor Antagonism

Chronic inflammation and cytokines such as tumor necrosis factor (TNF; the cytokine formerly known as TNFα) have been implicated in diabetic nephropathy and may contribute to other glomerulopathies. Several approaches to block TNF activity are available, including anti-TNF monoclonal antibodies (infliximab, adalimumab) and a soluble TNF receptor (etanercept). TNF antagonism may have direct effects on glomerular cells.