ACTH action on podocytes: mystery solved?

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PODOCYTES are the key target cell for injury in proteinuric kidney disorders such as focal segmental glomerulosclerosis (FSGS), minimal change disease, and membranous nephropathy. Sadly, advances in elucidating the molecular architectural details of the podocyte actin cytoskeleton, cell body, and intervening slit diaphragm have not yet translated into targeted therapeutic agents for clinical use. For over 60 yr, nephrologists have been treating glomerular diseases with repurposed, nonspecific immunosuppressive drugs, such as steroids and alkylating agents. Clinical responses have been variable with wide side effect profiles, further highlighting the need for the development of agents with a clear mechanistic rationale for their use.

Quite often, the podocyte-specific rationale for using these agents is deciphered years after their widespread use becomes commonplace. For example, the B cell-depleting antibody Rituximab was initially used to treat patients with membranous nephropathy by reducing anti-phospholipase A2 receptor autoantibody titers (10a). More recently, Rituximab has been shown also to stabilize sphingomyelinsase-like phosphodiesterase 3b protein expressed on podocyte cell membranes, possibly explaining its efficacy in treating recurrent FSGS posttransplant (7). Similarly, dexamethasone stabilizes the podocyte actin cytoskeleton in response to puromycin aminonucleoside-mediated injury (10), and cyclosporine prevents the degradation of the actin-bundling protein synaptopodin by calcineurin-mediated dephosphorylation (6). Direct protective effects on podocytes have also been reported for other immunomodulatory drugs, including levamisole and mycophenolate mofetil (11).

According to recent findings, adrenocorticoid hormone (ACTH) could be added to the list. ACTH is an endogenous peptide hormone and agonist for all melanocortin receptors [melanocortin receptor 1 (MC1R) through melanocortin receptor 5], with only melanocortin receptor 2 specifically binding ACTH. In the 1950s and early 1960s, ACTH was widely used to treat childhood nephrotic syndrome. At that time, ~50% of these unfortunate patients died of infectious episodes related to massive proteinuria (the other half of those not developing spontaneous remission eventually died in renal failure). ACTH was used to improve nephrotic syndrome through a mechanism that was thought to be mediated by ACTH steroidogenic effects. After half a century, Berg et al. (1) found that ACTH lowered the urinary albumin excretion by 90% and increased the glomerular filtration rate by 25% in 14 patients with membranous nephropathy, a disease that is refractory to steroid treatment. A series of subsequent studies, including a randomized study, converged to demonstrate that ACTH therapy induces remission of proteinuria in patients with nephrotic syndrome of different etiologies who were refractory to glucocorticoid and/or immunosuppressive therapies, suggesting that ACTH has antiproteinuric and renoprotective effects that are not entirely explained by its steroidogenic activity (4, 9).

Yet, despite recently renewed interest in its use, the exact mechanism underlying this antiproteinuric action has remained largely unknown and the precise pathobiology underlying the function of ACTH as a renoprotective agent in patients with nephropathies remained obscure.

The present work by Elvin et al. (5) sheds new light on the possible mechanism of action of ACTH in glomerular diseases. In a previous study (8), the same group showed that MC1R is present and colocalized with the podocyte marker synaptopodin in human kidneys. In that study, treatment with different MC1R agonists (ACTH and α-melanocyte-stimulating hormone) and MS05 reduced proteinuria, improved glomerular morphology, and reduced oxidative stress markers in urine in rats with passive Heymann nephritis, a model of membranous nephropathy (8).

In the present study, they showed that puromycin increased both gene and protein expression of MC1R in cultured murine podocytes (5). MC1R activation by specific agonists in puromycin-treated podocytes induced a protective signaling cascade that led to increased intracellular cAMP levels, enhanced catalase activity, and decreased oxidative stress. They showed that MC1R agonists decreased the activity of the RhoA inhibitor p190RhoGAP, which explains the resulting RhoA-mediated stabilization of stress fibers in response to puromycin treatment in the presence of MC1R agonists. Finally, using complementary cell survival assays, the authors demonstrated that treatment with both MC1R agonists MCIR-a (a synthetic compound) and MS05 (a peptide) protected podocytes from puromycin-induced cell death (5). The study is not without limitations. The endogenous expression level of MC1R in the podocyte cell line used was low. As a result, the authors overexpressed MC1R to detect the beneficial effects of MC1R agonists. They also relied exclusively on puromycin as a podocyte injury model. These approaches are a source of caution in interpreting the potential clinical utility of these agents. Still, particularly coupled with their prior human and in vivo passive Heymann nephritis data, these findings represent a major step forward in our understanding of the nephroprotective effects of MC1R activation.

The MC1R-dependent action of ACTH on podocytes does not rule out the existence of concurrent immune effects that could contribute to proteinuria reduction in glomerular diseases. Indeed, ACTH has been shown to exert direct anti-inflammatory and immunomodulatory functions on T and B lymphocytes, including a reduction of proinflammatory cytokines, nitric oxide, adhesion molecules, and production of anti-inflammatory IL-10 (3). Studies in RAG knockout mice lacking T and B cells will be important to distinguish the
immune-independent nephroprotective effects of ACTH in models of proteinuric glomerular diseases.

This study did not specifically evaluate ACTH as a therapeutic agent but could in part explain its action on podocytes in the treatment of nephrotic disorders. Unlike the agonists MC1R-a and MS05, ACTH is not specific for MC1R, raising the concern for significant offtarget effects such as Cushingoid features with its use. Since the expression profile and distribution of melanocortin receptor subtypes in podocytes and the kidney in general remains unclear, it is also still possible that action through MC1R may not fully explain the efficacy of ACTH in some proteinuric disorders. Nonetheless, the present study provides a mechanistic rationale for MC1R agonist use and may fuel further investigations aimed at leveraging the melanocortin pathway to treat glomerular disease.

DISCLOSURES

K. N. Campbell has served as a consultant for Mallinckrodt Pharmaceuticals.

AUTHOR CONTRIBUTIONS

P.C. and K.C. drafted manuscript; P.C. and K.C. edited and revised manuscript; K.C. approved final version of manuscript.

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