Leveraging Melanocortin Pathways to Treat Glomerular Diseases

Rujun Gong

The melanocortin system is a neuroimmunoendocrine hormone system that constitutes the fulcrum in the homeostatic control of a diverse array of physiological functions, including melanogenesis, inflammation, immunomodulation, adrenocortical steroidogenesis, hemodynamics, natriuresis, energy homeostasis, sexual function, and exocrine secretion. The kidney is a quintessential effector organ of the melanocortin hormone system with melanocortin receptors abundantly expressed by multiple kidney parenchymal cells, including podocytes, mesangial cells, glomerular endothelial cells, and renal tubular cells. Converging evidence unequivocally demonstrates that the melanocortin-based therapy using the melanocortin peptide adrenocorticotropic hormone (ACTH) is prominently effective in inducing remission of steroid-resistant nephrotic syndrome caused by various glomerular diseases, including membranous nephropathy, minimal change disease and focal segmental glomerulosclerosis, suggesting a steroidogenic-independent mechanism. Mechanistically, ACTH and other synthetic melanocortin analogues possess potent proteinuria-reducing and renoprotective activities that could be attributable to direct protection of glomerular cells and systemic immunomodulation. Thus, leveraging melanocortin signaling pathways using ACTH or novel synthetic melanocortin analogues represents a promising and pragmatic therapeutic strategy for glomerular diseases. This review article introduces the biophysiology of the melanocortin hormone system with an emphasis on the kidney as a target organ, discusses the existing data on melanocortin therapy for glomerular diseases, and elucidates the potential mechanisms of action.

Key Words: Glomerulopathy, Nephrotic syndrome, Melanocortin, Adrenocorticotropic hormone, Podocyte

Glomerular disease is the third leading cause of end-stage kidney failure in the United States.[1] Treatment of glomerular disease depends on its cause and type, but it is currently limited largely to the use of blockades of the renin-angiotensin-aldosterone system and immunosuppressants, including glucocorticoids, alkylating agents, calcineurin inhibitors, antimetabolites, and more.[2-4] However, these treatments are of limited utility with unsatisfying therapeutic efficacy. Indeed, although 95% of children[5] and 50% to 75% of adults[6] with minimal change disease (MCD) achieve complete remission of proteinuria after an 8-week course of prednisone therapy, more than 70% of all patients who are initially prednisone responsive go on to experience relapses of the nephrotic syndrome, and almost half of them show frequent relapses or steroid dependence and require further immunosuppression.[5,6] For other glomerular diseases such as idiopathic membranous nephropathy (iMN)[7,8] and focal segmental glomerulosclerosis (FSGS),[9] initial immunosuppressive treatments usually have much lower response rates than for MCD, and additional immunosupressants are essential to induce remission. In actuality, neither the target cells nor the mechanism of action of these immunosuppressants for glomerular disease has been clearly understood.[4] Most of these therapeutic strategies were borrowed from transplant immunosuppressive regimens and thus are believed to be effective in glomerular diseases also via immunosuppression; however, some such as cyclosporine A[10] are found to function, at least in part, through nonimmune mechanisms[10] whereas some others, such as levamisole,[11] might be effective via immune stimulatory mechanisms. Furthermore, a considerable number of patients suffer from the complications of overimmunosuppression, including opportunistic infection, neoplasia formation, and growth retardation.[2,3] Therefore, it is imperative to develop novel and more effective therapeutic modalities with minor side effects to satisfactorily ameliorate glomerular injury and induce remission of proteinuria in patients with refractory glomerular diseases. Recently, a plethora of evidence suggests that melanocortins possess potent antiproteinuric and renoprotective activities and might serve in this role.[12-17]

Melanocortin System: A Multitasking Neuroimmunnoendocrine Hormone System

The melanocortin system is a set of hormonal, neuropeptidergic, and immune signaling pathways that play an integral role in the homeostatic control of a diverse array of physiological functions, including melanogenesis, inflammation, immunomodulation, adrenocortical steroidogenesis, hemodynamics, natriuresis, energy homeostasis, sexual function, and exocrine secretion.[17] The melanocortin hormone system comprises multiple components, including the 5 guanine protein-coupled melanocortin

From Division of Kidney Disease and Hypertension, Department of Medicine, Rhode Island Hospital, Brown University School of Medicine, Providence, RI.

Financial Disclosure: R.G. received research grants and speaker honoraria from Questcor and served on scientific advisory boards for Questcor.

Address correspondence to Rujun Gong, MD, PhD, Division of Kidney Disease and Hypertension, Department of Medicine, Rhode Island Hospital, Brown University School of Medicine, 593 Eddy Street, Providence, RI 02903. E-mail: Rujun_Gong@Brown.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2013.09.004

receptors (MCRs); peptide ligands derived from the proopiomelanocortin preprohormone precursor; and endogenous antagonists, agouti signaling protein, and agouti-related protein (Table 1).[18,19]

The endogenous agonist ligands of the melanocortin hormone system, also known as melanocortins, are a group of hormonal neuropeptides that include adrenocorticotropic hormone (ACTH) and the different forms of melanocyte-stimulating hormone (MSH). Melanocortin peptides are produced by corticotrophs in the anterior lobe of pituitary gland, constituting 15% to 20% of the cells in the anterior lobe of the pituitary gland.[20] Melanocortins are synthesized from the precursor peptide preproopiomelanocortin, which is encoded by a single-copy gene on chromosome 2p23.3 that is over 8 kb in length.[20] The removal of the signal peptide during translation produces the 267-amino-acid polypeptide proopiomelanocortin (POMC), which undergoes a series of post-translational modifications such as phosphorylation and glycosylation before it is proteolytically cleaved by prohormone convertase (PC) enzymes PC1 and PC2 to yield a chemically and biogenetically related family of polypeptides with varying physiological activities, including endorphin, lipotropins, and melanocortins[20] (ACTH and α-, β-, and γ-MSH) (Fig 1A).

Plasma melanocortins have a diurnal variation in normal subjects[21,22] and can be induced by physical or psychological stress via hypophysiotropic hormones including corticotropin-releasing hormone and arginine vasopressin secreted by the hypothalamus. Conversely, melanocortin synthesis and release are negatively controlled by slow/intermediate or fast feedbacks by many substances secreted within the hypothalamic-pituitary-adrenal axis. Glucocorticoids (cortisol in human) secreted from the adrenal cortex in response to ACTH stimulation generate a negative feedback.[21] Thus, patients treated with a high dose of synthetic glucocorticoids for a long period are likely to have a very low plasma level of melanocortins and develop a clinical constellation of symptoms that highly mimic the phenotypes of POMC deficiency syndrome, a rare genetic disease, including hyperphagia, central obesity, pale skin, and adrenal insufficiency.[23]

The melanocortins exert their biological functions by binding to and activating the cognate MCRs with different affinity.[24] So far, 5 MCRs have been cloned and characterized. All of the 5 MCRs are highly conservative across different species and share many homologs.[19,25] The MCRs are all members of the rhodopsin family (class A) of 7-transmembrane guanine protein-coupled receptors, which intracellularly mediate their effects mainly by activating adenylate cyclase, leading to stimulation of the cyclic AMP (cAMP)-dependent cell signaling pathways.[24] The 5 MCRs have distinct tissue distribution, convey signaling of different melanocortins, and mediate varying biological effects.[24]

MC1 R exhibits high affinity for ACTH and most MSH. It is highly expressed in melanocytes and is the principal MCR in the skin, where it mediates pigmentation as 1 of the major biological functions of most melanocortin peptides.[19,25] MC1 R is also widely expressed in other organ systems, including adrenals, lung, lymph nodes, ovary, testis, brain, placenta, spleen, and uterus.[19,25] It is also present in vascular endothelial cells and immune-competent cells including leukocytes, dendritic cells, and macrophages, suggesting a role of MC1 R in the regulation of inflammatory reaction and immune response.[19,25] Indeed, α-MSH[26] or ACTH[27] treatment has been shown to prevent acute and chronic inflammation in animal models of multiple diseases, including acute kidney inflammation[27] and injury.[26,28] Direct evidence of the important role of MC1 R in inflammation and immunomodulation was recently shown in mice with a nonfunctional MC1 R.[29] These mice demonstrated a dramatic exacerbation of experimental inflammation,[29] confirming a general anti-inflammatory effect of the MC1 R signaling pathway.

MC2 R is the primary and exclusive receptor for ACTH that is expressed mainly in the adrenal gland and binds to ACTH with strong affinity but does not bind to the MSH peptides.[19,25] Activation of MC2 R initiates a cascade of events affecting multiple steps in steroidogenesis and growth of adrenal cortex. Of note, although MC2 R is predominantly expressed in adrenal cortex, recent studies indicate that it is also present in some other tissues including adipocytes, where MC2 R mediates stress-induced lipolysis via central ACTH release.[19,25]

MC3 R and MC4 R regulate energy expenditure.[19,25] MC3 R is expressed in the brain, predominantly in the arcuate nucleus in the hypothalamus and limbic system and in a few regions of the brain stem, as well as in the periphery, where it has been found in the placenta

CLINICAL SUMMARY

- The melanocortin system is a set of hormonal, neuropeptidergic, and immune signaling pathways that play an integral role in the homeostatic control of a diverse array of physiological functions, including inflammation, immunomodulation, and adrenocortical steroidogenesis.
- The kidney is a quintessential effector organ of the melanocortin hormone system with melanocortin receptors abundantly expressed by multiple kidney parenchymal cells, including podocytes, mesangial cells, glomerular endothelial cells, and renal tubular epithelial cells.
- Converging clinical and experimental evidence suggests that the melanocortin-based therapy using ACTH and other melanocortin analogues confers potent proteinuria-reducing and kidney protective effects in various glomerular diseases possibly through both direct protection of glomerular cells and systemic immunomodulation.