The Role of Melanocortin 1 Receptor in Kidney Disease

Avhandlingen baseras på följande arbeten:

I. **Melanocortin 1 receptor agonists reduce proteinuria**

II. **Effects of melanocortin 1 receptor agonists in experimental nephropathies**
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    Manuscript

III. **Melanocortin 1 receptor function and signaling in podocytes**
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The Role of Melanocortin 1 Receptor in Kidney Disease

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Abstract

Nephrotic syndrome is a term describing a group of poorly understood glomerular diseases that are responsible for a steadily increasing number of patients requiring active uremic care. Characteristic symptoms of nephrotic syndrome are proteinuria, hypoalbuminemia, hyperlipidemia and peripheral edema, and treatment of these symptoms, rather than their cause, is currently the only option available to the clinician. While the mechanisms underlying these diseases remain elusive, a number of studies have lately revisited adrenocorticotropic hormone (ACTH) as a potential treatment option since it has been shown to reduce proteinuria and improve glomerular function. Thus, the aim of this thesis has been to elucidate the mechanisms behind this treatment strategy.

The hypothesis is that ACTH mediates its effect by a kidney specific receptor. The gene expression of all ACTH receptors, melanocortin receptors (MCR) 1-5, was therefore investigated. MC1R gene expression was detected in kidney tissue, including cells specific for the glomerular filtration barrier (endothelial cells, podocytes and mesangial cells). MC1R protein was also detected and found to be co-localized with synaptopodin, a podocyte specific marker. In order to assess the relevance of MC1R in disease, selective agonists were used in experimental nephrotic models. MC1R agonists ameliorated the disease in a rat model resembling membranous nephropathy, and reduced proteinuria, improved morphology and reduced oxidative stress. MC1R agonists did not reduce proteinuria in a model resembling focal segmental glomerulosclerosis, suggesting different mechanistic pathways. Signaling pathways were investigated by stimulating podocytes with a selective MC1R agonist. Several known intracellular pathways were activated, including cAMP, phosphorylation of ERK1/2 and activation of catalase, an anti-oxidative enzyme. MC1R stimulation may also have a protective effect in nephrotoxin-induced rearrangement of the actin cytoskeleton.

In conclusion, this thesis has provided new data on the mechanisms behind the beneficial effects of ACTH treatment in nephrotic patients. MC1R, expressed in podocytes, likely mediates these effects. The results presented herein will pave the way for new, more specific and possibly curative treatment options, without severe side effects, for nephrotic patients.

Keywords: nephrotic syndrome, proteinuria, adrenocorticotropic hormone, melanocortin 1 receptor, podocytes


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