Podocyte Melanocortin 1 Receptor Mediated Signaling
A potential new target for patients with kidney diseases

Avhandlingen baseras på följande arbeten:

I. **Effects of Melanocortin 1 Receptor Agonists in Experimental Nephropathies**

II. **Melanocortin 1 Receptor Agonist Protects Podocytes Through Catalase and RhoA Activation**

III. **Melanocortin 1 Receptor Activation Influences Podocyte Cytoskeletal Dynamics**
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A potential new target for patients with kidney diseases

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Abstract

Treatment of patients with nephrotic syndrome (NS) is currently unspecific and directed at ameliorating the symptoms rather than eliminating the cause. NS is actually a multitude of glomerular diseases characterized by poorly understood disease mechanisms and symptoms that include proteinuria, hypoalbuminemia and edema. Originally described in the 1950s, treatment of NS with adrenocorticotropic hormone (ACTH) was rediscovered lately and its potentially beneficial effects on proteinuria and glomerular function have been studied in patients with different nephrotic diseases.

Our research group has shown that the effects of ACTH treatment are mediated through cells in the glomerulus. Thus, the melanocortin 1 receptor (MC1R) was found to be colocalizing with the podocyte marker synaptopodin. Treatment with MC1R specific agonists had beneficial effects in an experimental model of membranous nephropathy, Passive Heymann Nephritis (PHN). The aims of this thesis have therefore been to examine the intracellular signaling pathways and beneficial mechanisms following MC1R stimulation both in vitro and in vivo.

The hypothesis is that MC1R stimulation activates a number of beneficial effects in podocytes and stabilizes the actin cytoskeleton. To study these mechanisms, we performed experiments with MC1R selective agonists in the in vivo models of nephrotic syndrome; PHN and adriamycin nephropathy (AN). MC1R stimulation had ameliorating effects in the PHN model, but not in the AN model. In addition, we did in vitro experiments in order to analyze the intracellular effects induced by MC1R stimulation, and to perform a large-scale pathway analysis. MC1R stimulation induced a number of protective effects in podocytes, including increased catalase activity, decreased oxidative stress and protection against apoptosis. Furthermore, MC1R stimulation affected the actin cytoskeleton by inducing RhoA activity and increasing stress fiber formation. Subsequently, the MC1R stimulation had protective effects in both the puromycin and protamine sulfate in vitro models.

We conclude that MC1R stimulation has beneficial effects in different models of NS through activation of endogenous protective pathways and by stabilizing of the actin cytoskeleton. Building on these results, we believe that it is possible to create new, specific drugs with minimal side effects to treat patients with nephrotic syndromes in the future.

Keywords: Podocyte, Melanocortin 1 Receptor, actin cytoskeleton, nephrotic syndrome, adrenocorticotropic hormone, oxidative stress, βPIX, RhoA

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