Podocyte Melanocortin 1 Receptor Mediated Signaling

A potential new target for patients with kidney diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Europa, Konferenscentrum Wallenberg, Medicinaregatan 20 C, Göteborg
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av **Johannes Elvin**

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Avhandlingen baseras på följande arbeten:

I. **Effects of Melanocortin 1 Receptor Agonists in Experimental Nephropathies**
Lindskog Jonsson A, Granqvist A, **Elvin J**, Johansson ME, Haraldsson B, Nyström J (2014). PLoS ONE 9(1): e87816. doi:10.1371/journal.pone.0087816

II. **Melanocortin 1 Receptor Agonist Protects Podocytes Through Catalase and RhoA Activation**
Elvin J, Buvall L, Lassén E, Bergwall L, Lindskog Jonsson A, Granqvist A, Nyström J, Haraldsson B. *Manuscript under revision.*

III. **Melanocortin 1 Receptor Activation Influences Podocyte Cytoskeletal Dynamics**
Elvin J, Bergwall L, Sihlbom C, Olsson BM, Wallentin H, Haraldsson B, Nyström J, Buvall L. *In manuscript.*

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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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