Deficiency of melanocortin 5 receptor exacerbates proteinuria and podocytopathy after glomerular injury

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Background: Converging evidence suggests that therapeutic targeting of nonsteroidogenic melanocortinergic pathways represents a novel strategy for treating proteinuric glomerulopathies. However, the type of melanocortin receptor (MCR) mediating this beneficial effect remains controversial and uncertain. MC5R is one such receptor that is expressed in glomerular cells. This study examined the possible effect of MC5R knockout (KO) in nephrotoxic serum (NTS)-elicited podocytopathy.

Methods: NTS nephritis was induced in MC5R KO mice and wild-type (WT) littermates. Additional WT mice received treatment with a highly selective MC5R agonist or vehicle before NTS injury. Proteinuria, podocyte injury and glomerular damage were evaluated.

Results: Despite no discernible phenotype under physiological conditions, KO mice sustained exacerbated glomerulopathy early in the heterologous phase of NTS nephritis, as shown by heavier albuminuria. This was associated with worsened glomerular pathology, which was characterized by glomerular hypercellularity, swelling of glomerular endothelial cells, and fibrinoid necrosis of glomerular capillary tufts. In parallel, KO mice exhibited more severe podocytopenia than WT mice after NTS injury, as evidenced by reduced numbers of WT-1 positive cells in glomeruli, as well as worsened podocyte injury, marked by loss of glomerular expression of podocyte homeostatic proteins such as podocin and synaptopodin. Conversely, to test if activation of MC5R signaling is sufficient to protect against NTS-elicited podocytopathy, WT mice with NTS nephritis were subjected to MC5R agonism by using a peptidomimetic selective agonist. This resulted in an attenuated proteinuria and an improved podocyte injury, shown by preserved expression of podocyte marker proteins. However, glomerular depositions of the glomerular basement membrane-reactive heterologous rabbit IgG and the C5b-9 membrane attack complex along the glomerular capillary loops were found to be comparable in the WT and KO groups after NTS insult.

Conclusion: MC5R-mediated melanocortinergic signaling protects against proteinuria and podocytopathy upon glomerular injury and may be harnessed as an actionable target for treating proteinuric glomerulopathies.

