Pharmacological Melanocortin 5 Receptor Activation Attenuates Glomerular Injury and Proteinuria in Rats with Puromycin Aminonucleoside Nephrosis

Bohan Chen[1], Zubia Alam[1], Yan Ge[1], Lance Dworkin[1], Rujun Gong[1]

[1]Division of Nephrology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: lance.dworkin@utoledo.edu

Published: 05 May 2023

Background: Clinical evidence indicates that the melanocortin peptide ACTH is effective in inducing remission of nephrotic glomerulopathies like minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), including those resistant to steroids. This suggests that a steroid-independent melancortinergic mechanism may contribute. However, the type of melanocortin receptor (MCR) that conveys this beneficial effect as well as the underlying mechanisms remain controversial. Burgeoning evidence suggests that MC5R is expressed in glomeruli and may be involved in glomerular pathobiology. This study aims to test the effectiveness of a novel highly selective MC5R agonist (MC5R-A) in puromycin aminonucleoside (PAN) nephrosis.

Methods: Rats were injured with a tail vein injection of PAN, and 5 days later, were randomized to daily MC5RA or vehicle treatment.

Results: Upon PAN injury, rats developed evident proteinuria on day 5, denoting an established nephrotic glomerulopathy. Following vehicle treatment, proteinuria continued to persist on day 14 with prominent histologic signs of podocytopathy, marked by ultrastructural glomerular lesions, including extensive podocyte foot process effacement. Concomitantly, there was loss of podocyte homeostatic markers, such as synaptopodin and podocin, and de novo expression of the podocyte injury marker desmin. Treatment with MC5R-A attenuated urine protein excretion and mitigated the loss of podocyte marker proteins, resulting in improved podocyte ultrastructural changes. In vitro in cultured podocytes, MC5R-A prevented the PAN-induced disruption of actin cytoskeleton integrity and apoptosis. MC5R-A treatment in PAN-injured podocytes also reinstated inhibitory phosphorylation and thus averted hyperactivity of GSK3β, a convergent point of multiple podocytopathic pathways.

Conclusion: Collectively, pharmacologic activation of MC5R by using the highly selective small-molecule agonist is likely a promising therapeutic strategy to improve proteinuria and glomerular injury in protenuric nephropathies.

https://dx.doi.org/10.46570/utjms.vol11-2023-765