A spoonful of sugar helps the proteinuria go down?*

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Summary

This paper describes kidney defects in knock-in mice homozygous for the M712T mutation in the gene encoding for uridine diphospho-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase (GNE/MNK). In humans, this genetic defect causes hereditary inclusion body myopathy (HIBM), an autosomal recessive neuromuscular disorder characterized by adult onset, slowly progressive muscle weakness and atrophy. GNE/MNK is ubiquitously expressed and catalyses the first two rate-limiting steps in the biosynthesis of 5-N-acetylenuraminic acid (sialic acid). HIBM is thought to result from hyposialylation of muscle glycoproteins. The aim of the study was to generate a model of HIBM, in which the hypothesis that supplementation with free sialic acid could ameliorate the muscle disease could be tested. Unexpectedly, M712T homozygotes did not survive beyond Day 3 post-partum. At this point no myopathic features were detectable, but there was evidence of significant glomerular pathology (haematuria, proteinuria, podocyte foot process effacement and abnormalities of glomerular development (absence of podocalyxin and neutralization with polycation causes this cytoskeleton to the apical membrane [9]). Desialylation of the barrier function of the glomerulus. Removal of glomerular sialic acid by infusion of sialidase and neutralization of surface sialic acid using polycations such as protamine sulphate, results in proteinuria and podocyte foot process effacement [1,2]. Puromycin aminonucleoside administration results in foot process effacement and reduction of glomerular sialic acid content [3,4]. Interestingly, this is specifically due to a reduction in sialic acid, rather than loss of sialoglycoproteins [4]. Furthermore, the infusion of sialic acid-rich alpha-1-acid glycoprotein in this model prevents proteinuria and podocyte foot process effacement, presumably through sialylation of critical glomerular proteins [5]. Human proteinuric renal diseases such as minimal change disease are also associated with reduced glomerular sialic acid content [6], and in some studies with reduced red blood cell sialic acid content, suggesting a more widespread defect of sialylation [7].

Podocalyxin, the major glomerular sialoglycoprotein [8], is found on glomerular endothelial cells and on the apical surface of podocytes, where it interacts with the ezrin/NHERF2/actin protein complex and links the actin cytoskeleton to the apical membrane [9]. Desialylation of podocalyxin or neutralization with polycation causes this protein complex to break down, and results in foot process effacement and proteinuria [9]. Mice with a targeted deletion of podocalyxin die within 24 h of birth, with profound abnormalities of glomerular development (absence of podocyte processes and slit-diaphragms), and extrarenal manifestations such as omphaloceles and hernias [10]. Interestingly, in contrast to mice with the M712T mutation,
podocalyxin knock-out mice do not have abnormalities of the GBM. This suggests that reduced sialylation of other proteins may account for the GBM changes. Podocytes are linked to the GBM through a number of sialylated anchoring molecules such as αIβ3 integrin and αIβ-dystroglycans [11,12]. These molecules facilitate crosstalk between the GBM and the podocytes and determine podocyte structure and possibly also the composition of the GBM. Altered sialylation of these molecules or other anchoring proteins may account for the observed GBM changes, through altered signalling and dysregulation of GBM synthesis.

It is possible that additional factors contributed to the M712T phenotype, since GNE/MNK also enhances the activity of the sialyltransferases, GM3 synthase and GD3 synthase, thereby increasing synthesis of the gangliosides GM3 and GD3 [13]. These are expressed in podocytes, contribute to the charge characteristics of the filtration barrier and are reduced in response to puromycin aminonucleoside and diabetes-induced injury [14–16].

Taken together however, these data highlight the importance of sialic acid to the normal structure and function of the glomerular filtration barrier, and indicate that the renal abnormalities observed in this paper were probably due to impaired sialic acid synthesis.

Given the findings in this mouse model, the absence of renal disease in patients with HIBM needs to be explained. The inter-species differences in sialic acid utilization (Neu5Gc in mice and Neu5Ac in humans) and protein glycosylation patterns may provide some insight but are unlikely to be the whole explanation [17]. There may be some specific consequence of the way this model was generated, since in a separate study, mice with a targeted deletion of GNE/MNK rescued with a GNE transgene expressing the V572L mutation (found in Japanese patients with HIBM) developed myopathic features similar to that seen with HIBM, but had no evidence of disease of other internal organs, although the kidneys were not examined in detail [18]. The M712T and V572L mutations result in similar phenotypes in humans, therefore, the significant disparity in mouse phenotypes raises concerns that factors other than sialylation may be involved in the M712T model.

How could this affect my clinical work?

Perhaps the most exciting aspect of this paper is the observation that dietary supplementation with MannNAc, a cell-permeable precursor of sialic acid, extended survival of M712T homozygous mice, improved the renal histology, increased sialylation of podocalyxin and increased both GNE/MNK protein expression and Gne epimerase activities. This raises the question of whether similar strategies could have a therapeutic use in patients with proteinuric disease. There is some experimental precedent for therapeutically restoring the charge characteristics of the glomerular filtration barrier in humans. Administration of the anionic glycosaminoglycan, sulodexide, has been shown to reduce albumin excretion in patients with both micro- and macro-albuminuric diabetic nephropathy [19]. Although the mechanism of this effect is unknown, it is postulated that it is at least in part mediated by correction of the glomerular charge defect.

If the sialylation defect observed in experimental models of proteinuric disease and human proteinuric disease is the result of acquired defects in the sialic acid synthetic pathway, supplementation with MannNAc may be therapeutically beneficial and this hypothesis warrants further investigation.

Take home message

Sialic acid supplementation may be therapeutically helpful in proteinuric glomerular diseases characterized by hypo-sialylation.

Conflict of interest statement. None declared.

References


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