Mechanisms of Clinical and Experimental Proteinuria:
Analysis using Theoretical Models of Macromolecular Transport

by

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Abstract

Previous experimental studies have revealed that under normal conditions, the glomerular capillary wall restricts the passage of polyanions more than that of neutral molecules. Similarly the filtration of macromolecules is restricted on the basis of molecular size. In a variety of clinical disorders associated with the leakage of large quantities of proteins across the glomerular capillary (proteinuria), there is evidence of defects both in glomerular charge and size selectivity leading to an increased permeability to circulating macromolecules.

An existing theoretical model of glomerular charge and size selectivity was applied to the human disorder, minimal change nephropathy. It was demonstrated that proteinuria in this disorder results from a reduction in the fixed negative charge density of the glomerular capillary wall with no demonstrable defect in size selectivity. An alternativie model for glomerular charge selectivity was developed. It was found that for molecules of similar configuration this model yields consistent estimates of membrane charge, and has several theoretical advantages over the existing model.

In contrast to MCN, in a variety of diseases including diabetic nephropathy, glomerulonephritis, amyloidosis, and focal sclerosis, proteinuria was shown to be the result of defects in both the size and charge selective properties of the glomerular capillary wall. A novel theoretical model which allows for continuous distributions of "pores" in the idealized glomerular capillary wall was developed and implemented for the analysis of these and other proteinuric disorders.

An experimental model of proteinuria in rats resulting from infusion of a polycation (HDM) was studied. Dramatically increased urinary excretion of plasma proteins albumin and IgG was completely reversed by infusion of a polyanion. Using the theoretical model developed here, proteinuria in this disorder was related to abnormalities in both charge and size selectivity induced through neutralization of glomerular polyanion by HDM.. These results suggest that neutralization of glomerular fixed negative charge may be the primary event in the pathogenesis of a variety of proteinuric disorders, since if sufficiently severe, depletion of glomerular negative charge may lead to defects in size selectivity.

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