Filtration of Macromolecules by Renal Glomerular Capillaries

by

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Abstract

The overall goal of this thesis was to understand the biophysical basis for glomerular filtration, the impairment of which characterizes most forms of kidney disease. The permselectivity of the glomerular capillary wall *in vivo* is usually assessed by measuring sieving coefficients (Θ) of tracer solutes, and relating these data to the intrinsic properties of the barrier using a mathematical model. Membrane models based on the concept of equivalent cylindrical pores have traditionally been used for that purpose, but they do not reflect the real ultrastructure of the capillary wall, which consists of three layers: a fenestrated endothelium, a glomerular basement membrane (GBM), and epithelial cells spanned by slit diaphragms. We first showed that pore models could not be used to estimate the mean transmural hydraulic pressure difference ($\overline{\Delta P}$) from macromolecular sieving data, due to the effect of random measurement errors and uncertainties in the models.

A novel "ultrastructural" model was developed to relate the sieving coefficients of neutral macromolecules to the structural characteristics of the individual layers of the glomerular capillary wall. To characterize solute transport across each layer, we first measured diffusion rates of Ficoll across intact and cell-free glomerular capillaries isolated from the rat, using confocal microscopy. The contribution of the GBM to the mass transfer resistance of the barrier varied between 10 and 30% of the total, depending on molecular size. Diffusional hindrance coefficients for GBM were determined from the data, as well as ultrastructural parameters related to the slit diaphragms. We also measured Ficoll sieving coefficients for isolated rat GBM, and determined diffusional and convective hindrance coefficients as a function of solute size and $\overline{\Delta P}$. The dependence of the Darcy permeability of GBM on $\overline{\Delta P}$ was examined, and the results were interpreted assuming that the GBM consists of a random fibrous network with two populations of fibers of distinct sizes.

The ultrastructural model was then extended to permit simulations of glomerular filtration *in vivo*, and predictions of sieving coefficients. The simulations indicated that basement membrane thickness and the spacing of the epithelial slits, one or both of which change in certain glomerular diseases, have relatively little effect on glomerular permselectivity. The main determinants were found to be the diffusional and convective hindrance coefficients in the GBM and the parameters which describe the structure of the epithelial slit diaphragm. This new approach has the potential to provide a much better

understanding of the physical basis for the functional impairments seen in glomerular disease.

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