**Analysis of Glomerular Permselectivity in the Rat Using Theoretical Models of Hindered Transport**

by

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**Abstract**

Changes in glomerular permselectivity are the physiological basis for proteinuria, which typically accompanies chronic kidney disease. Traditionally changes in the size-restrictive properties of the glomerular barrier have been quantified by measuring the fractional clearance ($\Theta$) of exogenous infused dextrans and interpreting the results using the hindered transport theory for uncharged, solid spheres in cylindrical pores. The observed values for $\Theta$ for dextran in normal rats and healthy humans are unexpectedly large, however, given the normal absence of proteinuria. Recent *in vitro* diffusion studies show that dextran's hindered transport behavior is better represented by a random coil with attractive pore/solute iteractions, while Ficoll follows the predictions for a neutral solid sphere. Thus Ficoll sieving data should provide a better indication of the size-selective properties of the glomerular capillary wall. In one of the studies for this thesis, healthy Munich-Wistar rats were infused with either $^3$H-dextran or $^3$H-Ficoll. Plasma and urine samples were fractionated on gel chromatography columns which had been calibrated with narrowly-sized dextran and Ficoll standards. While values of $\Theta$ for Ficoll were similar to those measured for nearly-neutral proteins, dextran values were significantly higher at all molecular sizes. On this basis, the glomerular capillary wall is shown to be considerably more size-restrictive than had been previously determined. The random coil model was applied to the dextran data, and the attractive energy required to explain the dextran/Ficoll discrepancies *in vivo* was nearly the same as that required *in vitro*. Thus is appears that dextran's enhanced transport is nearly independent of the medium through which it travels.

The implications of the more size-restrictive barrier were examined in a second experimental protocol, in which $^3$H-Ficoll was infused into four groups of fawn-hooded (FH) rats: a two-kidney (2K) control group, an uninephrectomized (UNX), a UNX group treated with the angiotensin converting enzyme inhibitor enalapril (ENA), and a UNX group treated with the nitrous oxide inhibitor NAME. The UNX and NAME groups had significantly higher glomerular filtration pressures ($\overline{\Delta P}$) and more proteinuria than the 2K and ENA groups, but the membrane pore size parameters of the four groups were essentially the same. The extent of albumininuria correlated strongly with $\overline{\Delta P}$, while the total rate of excretion of non-albumin proteins did not. Because albumin is negatively charged, these findings imply that albuminuria in FH rats results from a specific defect in glomerular charge-, rather than size-selectivity induced by chronic glomerular

hypertension. Finally to examine the potential for using fractional clearances to estimate filtration pressures in the clinical setting, the mathematical model was modified to make $\overline{\Delta P}$ an adjustable parameter, and fitted values were compared with those actually measured in the FH rats. The fitted and measured $\overline{\Delta P}$ did not show significant correlation, suggesting that $\Theta$ may not be sufficiently sensitive to $\overline{\Delta P}$ to allow such estimations.

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