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Zeroing in on the albumin glomerular sieving coefficient

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Running title: Glomerular barrier

Increased urinary albumin excretion is a hallmark of kidney disease. Drugs that interfere with the renin-angiotensin system reduce proteinuria and slow the progression of renal disease in patients (4). The cause of increased albuminuria induced by angiotensin is generally thought to be increased glomerular filtration of albumin (1).

In a recent issue of this journal, Schiessl and Castrop (8) reported a multiphoton microscopy study of the effects of angiotensin II on the glomerular sieving of albumin in the rat. The authors' main findings were *1*) the glomerular sieving coefficient (GSC) for albumin is normally extremely low, *2*) intravenous angiotensin II infusion results in an acute increase in albumin GSC, *3*) the effects of angiotensin II on the albumin GSC are largely independent of the renal artery blood pressure, *4*) angiotensin type 1 (AT_1) receptor stimulation increases the albumin GSC, and *5*) angiotensin type 2 (AT_2) receptor stimulation decreases the albumin GSC.

The use of multiphoton (two-photon) microscopy to measure glomerular sieving is appealing because of its directness. GSC is equal to the fluorescence intensity (concentration) of the molecular species in the urinary space of Bowman's capsule divided by the fluorescence intensity of the molecule in glomerular capillary plasma. Striking images can be obtained (3, 5-9), and quantitative measurements of fluorescence intensities are straightforward.

The first study (5) to use multiphoton microscopy to determine the albumin GSC created considerable controversy, since the reported value was 0.034, 25-50

times higher than previous values obtained by kidney micropuncture (10). Russo et al. (5) suggested that massive amounts of albumin are normally filtered and that the tubules reabsorb most of the filtered albumin intact. These ideas run counter to the traditional view that little albumin is filtered and that most of the filtered albumin is degraded in proximal tubule cells during reabsorption (2). The high values reported by Russo et al. appear to result from technical problems, such as the physiological state of their animals and their failure to recognize the problem of out-of-focus fluorescence (9). When these issues were addressed, albumin GSCs averaging 0.002 or 0.004 were found in Munich-Wistar rats of both sexes (9). Such low values are consistent with several meticulous studies (2).

Schiessl and Castrop (8) reported an albumin GSC of 0.0005 under baseline conditions in young, female Munich-Wistar Frömter rats, similar to results from the Peti-Peterdi laboratory (3, 6). In these three multiphoton studies, large negative offsets were applied to external photodetectors; possibly this might have led to an underestimate of albumin GSC (7). It would have been helpful if these authors had reported the instrument calibration (fluorescence intensity versus concentration plot) (7, 9), or if they had used internal photodetectors or non-filtered reference molecules to correct for out-of-focus fluorescence (9).

A very low GSC indicates that the glomerular filtration barrier severely restricts the filtration of albumin. The albumin GSC depends on the permeability of the glomerular barrier, glomerular filtration rate (GFR), and plasma flow (2). As GFR falls to zero, albumin GSC rises and approaches a limiting value of 1.00 (2).

Interpretation of changes in albumin GSC induced by drugs or disease, therefore, should take into account both the properties of the glomerular barrier and glomerular hemodynamics. In the Schiessl and Castrop study (8), the 3-fold increase in albumin GSC produced by angiotensin II exceeded the ~40% fall in single nephron GFR, indicating that the amount of albumin filtered through the glomerular barrier was indeed increased. The acute increase in albumin GSC in response to angiotensin II administration appears to be mediated by AT_1 receptors, since a specific antagonist, losartan, blocked this change. AT_2 receptors appeared to have the opposite effect on the albumin GSC. Schiessl and Castrop concluded that angiotensin changes the albumin GSC mainly by a direct effect on the filtration barrier.

This study of angiotensin's action on glomerular sieving of albumin is important because it sheds light on the antiproteinuric effect of blocking the renin-angiotensin system (4). Whether, as the authors suggest, a specific AT_1 receptor blocker would be better than a converting enzyme inhibitor (which would result in decreased stimulation of both AT_1 and AT_2 receptors) can be settled only by rigorous clinical trials. As a model for future studies of glomerular sieving of macromolecules, the Schiessl and Castrop study (8) illustrates the advantages of the two-photon microscope as a research tool. Investigators are learning more about how to use the two-photon microscope to quantify biological processes, and it looks as if we are zeroing in on an accurate albumin GSC.

DISCLOSURES

The authors declare no conflicts of interest, financial or otherwise.

References

1. **Eisenbach GM, Van Liew JB, Boylan JW.** Effect of angiotensin on the filtration of protein in the rat kidney: a micropuncture study. *Kidney Int* 8: 80-87, 1975.
2. **Haraldsson B, Nyström J, Deen WM**. Properties of the glomerular barrier and mechanisms of proteinuria. *Physiol Rev* 88: 451-487, 2008.
3. **Nakano D, Kobori H, Burford JL, Gevorgyan H, Seidel S, Hitomi H, Nishiyama A, Peti-Peterdi J**. Multiphoton imaging of the glomerular permeability of angiotensinogen. *J Am Soc Nephrol* 23: 1847-1856, 2012.
4. **Ruggenenti P, Cravedi P, Remuzzi G**. Mechanisms and treatment of CKD. *J Am Soc Nephrol* 23: 1917-1928, 2012.
5. **Russo LM, Sandoval RM, McKee M, Osicka TM, Collins AB, Brown D, Molitoris BA, Comper WD**. The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: retrieval is disrupted in nephrotic states. *Kidney Int* 71: 504-513, 2007.
6. **Salmon AHJ, Ferguson JK, Burford JL, Gevorgyan H, Nakano D, Harper SJ, Bates DO, Peti-Peterdi J**. Loss of the endothelial glycocalyx links albuminuria and vascular dysfunction. *J Am Soc Nephrol* 23: 1339-1350, 2012.
7. **Sandoval RM, Wang E, Molitoris BA**. Finding the bottom and using it. Offsets and sensitivity in the detection of low intensity values in vivo with 2-photon microscopy. *IntraVital* 2: e23674-1-9, 2013.
8. **Schiessl IM, Castrop H**. Angiotensin II AT_2 receptor activation attenuates AT_1 receptor-induced increases in the glomerular filtration of albumin: a

multiphoton microscopy study. *Am J Physiol Renal Physiol* 305:F1189-F1200, 2013.

9. **Tanner GA**. Glomerular sieving coefficient of serum albumin in the rat: a two-photon microscopy study. *Am J Physiol Renal Physiol* 296: F1258-F1265, 2009.

10. **Tojo A, Endou H**. Intrarenal handling of proteins in rats using fractional micropuncture technique. *Am J Physiol Renal Physiol* 263: F601-F606, 1992.