Competition between Albumin and Beta-2-Microglobulin for Renal Tubular Uptake: Brush Border and/or Lysosomes?

H.		Nguyen-Simonnet.
C.		Vincent
J.P.		Revillard

Unité de Recherche en Néphro-Urologie, Transplantation et Immunologie Clinique, INSERM U.80, CNRS UA1177, UCBL, Hôpital E.-Herriot, Lyon, France

J.P. Revillard, Hôpital E.-Herriot-INSERM U.80, F-69437 Lyon Cédex 3 (France)

Dear Sir,

We were most interested in the recent paper by Bernard et al. [1] showing that low- and high-molecular-weight protein can compete for renal uptake. These authors challenged the current opinion that tubular protein reabsorption is achieved through distinct pathways for small and large molecules. Their data showed that injection of 1 g/kg of bovine serum albumin in rats, which resulted in an estimated concentration of 6–13 $\mu\text{g/ml}$ in glomerular ultrafiltrate (assuming a sieving coefficient of 10^{-3} to 5×10^{-4}) induced an increased excretion of human β_2 -microglobulin ($\beta_2\text{m}$) (336-fold), rat $\beta_2\text{m}$ (10-fold) and retinol-binding protein (4-fold). Human serum albumin, at comparable concentrations in the ultrafiltrate, merely induced a 4-fold increase in human $\beta_2\text{m}$ excretion. Human $\beta_2\text{m}$ injected at 16 mg/kg, a dose which increases $\beta_2\text{m}$ levels in glomerular filtrate by a factor of 10–15, resulted in a 4-fold increase of albumin excretion.

Our own studies [2] using injections of 0.2–150 mg/kg of human $\beta_2\text{m}$ in rats demonstrated a possible increase in albumin excretion but mainly the occurrence of several low-molecular-weight proteins in the urine. Intravenous infusion of arginine in humans was reported to induce a rapid increase of urinary excretion of albumin and a much greater increase of $\beta_2\text{m}$ [3].

Considering the relatively high concentration of low-molecular-weight proteins in primitive urine, as compared to that of albumin, the data from these studies do not exclude the hypothesis of a common reabsorption pathway. However, as pointed out by Bernard et al. [1], the postulated higher affinity of bovine versus human serum albumins for a tubular binding site is surprising in view of the great similarities in the amino acid composition, net charge and size of the two molecules. Furthermore, in selective glomerular proteinuria there is usually no substantial increase of low-molecular-weight proteins despite a major elevation of the albumin filtered load [4].

Tubular reabsorption of proteins is a complex process in which several subsequent interrelated steps can be distinguished: binding to a putative brush border acceptor site, endocytosis, cellular transport of endocytic vesicles, fusion with lysosomes and proteolysis [5, 6]. Kinetic studies of $\beta_2\text{m}$ reabsorption in the rat demonstrated tubular uptake within 5 min, and increase in tubular reabsorption between 10 and 20 min after $\beta_2\text{m}$ injection [2]. Degradation reached a maximum between 30 and 60 min after injection [2, 7]. After infusion of 150 mg/kg of $\beta_2\text{m}$, urinary excretion of some rat low molecular-weight-proteins and albumin did not reach its maximum

before 30 min, a time at which the β_2 m concentration in glomerular ultrafiltrate was already much lower than during the first period. Only a few low-molecular-weight proteins appeared in the urine during the first 10-min period [2]. Thus, sequential measurements of uptake, degradation and protein excretion in urine already suggested that at least two levels of competition could be distinguished. It may be postulated that the saturation of endocytosis and transport, or that of lysosomal degradation, may result in apparent binding competition between proteins which actually bind to distinct brush border sites. Induction of tubular proteinuria by various substances which interfere with lysosomal activity, as, for instance, aminoglycosides, support this view. Experiments in animals will prove inadequate to dissect the various levels at which several proteins may interfere with each other for their renal tubular reabsorption. Experiments of competitive binding to brush border microvesicles now in progress in

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our laboratory will determine whether low- and high-molecular-weight proteins do actually compete for the same brush border binding structure.

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