Renal Handling of Human $\beta_2$-Microglobulin in Normal and Cadmium-Poisoned Rats

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Abstract. The renal handling of human $\beta_2$-microglobulin ($\beta_2$-m) was investigated in normal rat and in rat with cadmium-induced renal damage. Cadmium was administered either in drinking water at a concentration of 100 ppm for up to 16 months or by i. p. injection of 1 mg Cd/kg, five times a week for up to 4 months. When renal dysfunction has developed, namely after 2 and 10 months of the i. p. and oral treatment respectively, unlabelled human $\beta_2$-m was injected intravenously and its disappearance in serum and its urinary excretion were studied by means of a sensitive immunoassay. In serum, the level of $\beta_2$-m drops by about 90% during the 10 first min, then declines more slowly with a half life around 20 min. Serum disappearance curves of $\beta_2$-m in normal and cadmium-treated rats did not differ markedly.

The amount of $\beta_2$-m recovered in urine during the 4 h following the injection averaged 0.03% of the injected dose in normal rats. It increased on the average to 10% in rats treated i. p. with 1 mg Cd/kg for 3 months. However, in rats given 100 ppm Cd per os for 10 months, this amount averaged only 0.14%. A similar value was observed 5 months later, although at that stage, the critical level of cadmium in kidney cortex had been reached for 6–7 months. These data which were in accordance with the disturbances of the other renal parameters measured in cadmium-treated rats indicate that:

1) human $\beta_2$-m is reabsorbed by rat kidney at a similar rate as by human kidney;
2) if the occurrence of cadmium tubulopathy is concomitant with the saturation of cadmium-binding sites in kidney, its severity depends greatly on the rate at which cadmium reaches the saturated kidneys.

Key words: $\beta_2$-Microglobulin – Cadmium – Kidney – Tubular proteinuria

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Introduction

Cadmium (Cd) is a widespread environmental and occupational cumulative pollutant. Its biological half-life in the human organism exceeds 10 years. The kidney is the main site of deposition and usually also the first organ to exhibit signs of adverse effects. Human and animal data so far available suggest that the risk of renal dysfunction during cadmium exposure occurs when the concentration of Cd in kidney cortex reaches a critical value of 200 ppm (Friberg et al. 1974; Roels et al. 1981). Cd nephropathy is characterized by various signs of tubular and glomerular dysfunction (Lauwerys et al. 1979). However, the most striking toxic effect of Cd is an increased urinary excretion of low molecular weight proteins resulting from a depressed tubular reabsorption. Among these proteins, $\beta_2$-microglobulin ($\beta_2$-m) has been the most extensively studied and its determination in urine is currently used as a sensitive test for the early detection of Cd-induced proteinuria.

Investigations on the renal metabolism of $\beta_2$-m and other low molecular weight proteins have demonstrated that these proteins are freely filtered through the glomeruli but are reabsorbed and catabolized by the proximal tubular cells (Maack et al. 1979). In the majority of these studies, the injected protein was radiolabelled and its fate in the organism was followed up by measuring the trichloroacetic acid – precipitable radioactivity. In the study of Bernier and Conrad (1969) on the catabolism of human $\beta_2$-microglobulin by rat kidney, unlabelled protein was injected and its concentration was determined in biological fluids by an immunochemical method. However, Bernier and Conrad (1969) measured $\beta_2$-m by radial immunodiffusion and because of the low sensitivity of this technique, they were unable to detect $\beta_2$-m in the urine of normal rats even following injection of 2 mg of protein.

Recently, we have developed a nonisotopic method for the determination of human $\beta_2$-m, which is about 10 times more sensitive than immunoassays (Bernard et al. 1981a) so far described for this protein. This high sensitivity (the detection limit is 0.1 $\mu$g/l) allows us to measure the concentration of human $\beta_2$-m in normal rat urine following the i.v. injection of less than 0.1 mg of protein.

We have examined the renal handling of human $\beta_2$-m in normal rat and in rats with renal damage induced by chronic Cd poisoning. Two different modes of Cd administration were chosen: the repeated i. p. injection of a relatively high dose of cadmium, a protocol commonly used for the study of cadmium nephrotoxicity (Friberg et al. 1974) and also a long term oral administration of Cd in drinking water, this second model being more representative of human exposure to this heavy metal.

Materials and Methods

Cadmium Treatment. Female Sprague-Dawley rats (100–150 g; 8 weeks old) were administered CdCl$_2$ either in deionized drinking water at a concentration of 100 ppm Cd for up to 16 months or by i. p. injection of 1 mg Cd/kg 5 times a week for up to 4 months. Control animals were given deionized drinking water or were injected with physiological saline.