Critical concentration of 'unbound' cadmium in the rabbit renal cortex

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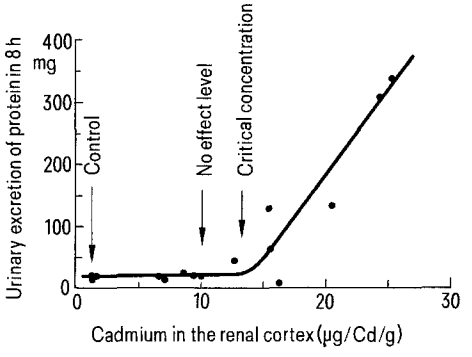
Summary. Critical concentration of 'unbound' cadmium in the rabbit renal cortex was around 13 μg Cd/g, which was far lower than the critical concentration of 'total' cadmium in the renal cortex, 200–300 μg Cd/g, and a little lower than the critical concentration of non-MT-Cd in the renal cortex, 35–60 μg Cd/g, respectively. The above result may suggest that it is necessary to identify the chemical form of 'active' cadmium in the renal cortex.

Key words. Active cadmium; cadmium; critical concentration; metallothionein; proteinuria; rabbit; renal cortex; renal dysfunction.

Environmental pollution with cadmium has become a serious concern, and a large number of residents in cadmium-polluted areas have undergone medical examination in Japan as well as in Europe[1–3]. One-third on the cadmium taken into the body accumulates in the kidneys, the critical organ[4], and cadmium has been thought to induce renal dysfunctions when cadmium in the renal cortex exceeds a certain level, the critical concentration[4]. The WHO/FAO Joint Committee estimated the critical concentration of cadmium in the human renal cortex as being 200 μg/g[5]. However, because metallothionein, the low mol. wt metal-binding protein, has been thought to detoxify cadmium by its binding to cadmium[6,7], questions may be raised about whether it is appropriate to determine the critical concentration of 'total cadmium' in the renal cortex or not. Cadmium not bound to metallothionein (non-MT-Cd) may cause nephropathy in animals and humans exposed to cadmium[8–10]. Therefore, it is necessary to estimate the critical concentration of non-MT-Cd in the renal cortex. In our previous experiments, renal dysfunctions appeared in rabbits and monkeys exposed to cadmium for a long period when non-MT-Cd in the renal cortex reached 35–60 μg Cd/g[8–10]. However, not all of the non-MT-Cd will necessarily always be 'active' in inducing renal dysfunction. Non-MT-Cd includes higher mol. wt cadmium, low mol. wt cadmium, and/or 'unbound' cadmium[10]. Therefore, it is necessary to identify the chemical form of 'active' cadmium in the renal cortex in future studies.

In our first approach to the investigation of 'active' cadmium, we estimated the critical concentration of 'active' cadmium in rabbit renal cortex by exposing renal tubular cells to 'unbound' cadmium in vivo. Fifteen male rabbits of the Japanese white strain weighing 2.8 kg were each given a single i.v. injection of cadmium chloride at a dose level of 0, 0.25, 0.5 or 1.0 mg Cd/kg simultaneously with excessive mercaptoethanol (0.35 mmoles/kg) to prevent cadmium from binding to plasma proteins and to enable cadmium to be freely filtered at the glomeruli[11]. Cadmium concentration in the renal cortex may be instantly elevated after cadmium administration, and 'unbound' cadmium may affect renal tubular cells until cadmium is detoxified by its binding to induced-metallothionein[6,7]. Animals were autopsied by bleeding 8 h after cadmium administration, because 1) cadmium-induced metallothionein synthesis and was detoxified itself by induced metallothionein in 8 h after cadmium administration, and 2) the retention time for cadmium-induced renal dysfunction was shown by our preliminary experiment to be around 8 h. Protein and amino acid in 8-h urine samples were determined by the Tsuchiya-Biuret method[12], and the trinitrobenzene sulfonic acid method[13], respectively. Cadmium in the renal cortex was determined by atomic absorption spectrophotometry after wet ashing with nitric acid and sulfuric acid.

As seen in the figure, urinary excretion of protein was elevated when the renal cadmium level exceeded 13 μg Cd/g. The level at which no effect was seen was 10 μg Cd/g for all rabbits. No elevations were observed in urinary excretion of amino acid in this experiment, even though the preliminary experiment indicated that urinary excretion of amino acid in 24 h is elevated, probably due to a longer retention time for cadmium-induced aminoaciduria. The above result may indicate that the critical concentration of 'unbound' cadmium in the renal cortex was around 13 μg Cd/g.



Relationships of urinary excretion of protein and cadmium in the renal cortex of 15 rabbits that were each given a single i.v. injection of cadmium chloride at various levels simultaneously with excessive mercaptoethanol, 8 h after cadmium injection.

Gieske and Foulkes[11] reported that renal tubular functions were depressed in rabbits by i.v. injecting cadmium chloride simultaneously with excessive mercaptoethanol, and that the cadmium-induced renal dysfunction in their experiment was similar to that in rabbits chronically exposed to cadmium.

The estimated critical concentration of 'unbound' cadmium in the present experiment was similar to but slightly lower than the critical concentration of non-MT-Cd in animals that were given cadmium for a long period[8,9]. Non-MT-Cd includes higher mol. wt cadmium, low mol. wt cadmium, and/or 'unbound' cadmium[10]. This may be the reason why the critical concentration of 'unbound' cadmium in the present experiment is slightly lower than the critical concentration of non-MT-Cd in animals exposed to cadmium for a long period[8,9].

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