



Biochemistry

The concentrations of major and trace elements in rat kidney: Aging effects and mutual relationships

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ABSTRACT

The concentrations of 26 major to trace elements in rat kidneys aging from 5 to 113 weeks old were determined. The rats investigated were the same rats used previously reported to have 29 elements in bones (femurs). The samples were decomposed by high purity nitric acid and hydrogen peroxide. Eight elements (Na, Mg, Si, P, K, Ca, Fe and Zn) were determined using inductively coupled plasma atomic emission spectrometry (ICP-AES) and 18 elements (Mn, Co, Ni, Cu, As, Se, Rb, Sr, Mo, Cd, Sn, Sb, Cs, Ba, Tl, Pb, Bi and U) were determined using inductively coupled plasma mass spectrometry (ICP-MS). The aging effects on the concentrations of these elements and mutual elemental relationships were investigated. Analysis of variance (ANOVA) for age variations indicated that the concentrations of P, K, Mn and Mo were almost constant across the age of rats ($p > 0.3$). The concentration of many elements such as Na, Mg, Ca, Fe, Co, Cu, Zn, As, Se, Cd, Sn, Sb, Tl, Pb and Bi, showed significant increasing trends ($p < 0.01$) with different patterns. Rubidium, Cs, Pb and Bi showed significant age variations but not monotonic trends. Silicon, Ni, Sr, Ba and U showed large concentration scatterings without any significant trends ($p > 0.01$). The metabolism of these elements may not be well established in the kidney. Many toxic elements such as As, Cd, Sn, Pb and Bi showed a narrow concentration range among age-matched rats. The kidney may have established metabolic mechanisms to confine or accumulate these toxic elements even though their concentrations are very low (e.g., 10 ng g^{-1} of Cd). These elements also closely coupled with Fe. A cluster analysis was performed using an elemental correlation matrix and indicated that these elements, including Fe, formed a cluster. However, another cluster analysis using “an aging effect eliminated” elemental correlation showed different clustering in which the Fe, Cd cluster disappeared.

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Introduction

The kidney plays a key role in the regulation of homeostasis in an animal body [1]. Kidneys eliminate toxic substances and waste products from the body, regulate electrolytes, maintain the acid–base balance in body fluid and blood pressure, and produce hormones, such as erythropoietin and calcitriol, and the enzyme renin.

The kidney contains relatively higher concentrations of trace elements such as Co, Zn and Se (essential elements), and Cd and Pb (non-essential elements) compare to other organs [2–4]. Since Cd is a nephrotoxic element that causes Itai-itai disease [5], many researchers have studied Cd concentrations in kidneys using various types of animals. The concentrations of Cd and its metal binding protein metallothionein (MT) in the kidney were also comparatively analyzed with those of Cu, Zn and Fe and their corresponding MTs [6–9].

Many experiments were performed under a high level of Cd administration (order of $\sim \text{mg Cd kg}^{-1} \text{ body wt}$) [10–13]. Kuriwaki et al. [10] suggested that Cd exposure to rats of $1\text{--}10 \text{ mg kg}^{-1} \text{ day}^{-1}$ could inhibit Zn, Fe and possibly Cu, Ca, Na and K transportation from the placenta to fetus. Schroeder and Nason [14] reported interactions of trace metals (Cd, Ni, Zn, Cr, Cu and Mn) in rat tissues and

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claimed that Cd administration induced increases in the concentrations of Zn, Mn and Cu in kidneys. The functions of MT and Cd toxicity have been extensively reviewed in [8,15]. In addition, As has been reported to accumulate in the kidneys of cattle and swine [16,17]. Although some researchers regard As as an essential element [18], inorganic As is highly toxic and carcinogenic to humans [19]. Because kidneys are the major organ for As elimination, renal cells are exposed to a large portion of absorbed As.

From ecological and environmental perspectives, there are also many reports on the concentration of trace elements in the animal kidney due to its accumulation of many toxic elements [3,20–26]. Nriagu et al. [20] reported levels of As, Cd, Pb, Cu, Se and Zn in bovine kidneys and livers in Jamaica. Their data indicated that many cattle seemed to have Cu and Zn deficiencies. However some cattle showed elevated Cd levels. They suggested that the consumption of large quantities of these organs could be hazardous to the health of Jamaicans. Spierenburg et al. [26] reported Cd, Pb, Zn, Cu levels in the livers and kidneys of cattle from farms located close to zinc refinery plants in the Netherlands. They found significantly higher levels of Cd (10 times higher) and Pb (2 times higher) both in livers and kidneys compare to those of the control animal group.

The mechanism of interactions among these trace elements is not well understood. In studies on these interactions, experimental animals were either administered large amounts of toxic elements or reared under the conditions deficient of the essential elements. In addition, the rearing periods of the animals were usually short, making it difficult to trace the effects of aging. Thus it is important to obtain the reference values of elemental concentrations in the organs of animals reared under normal and healthy conditions for a longer period of time. However, it is hard to find out such reference values. Gélinas et al. measured the concentrations of 33 elements in 10 different rat organs (Sprague Dawley rat) using ICP-MS [2], and claimed that some elements closely correlated with one specific tissue. For example, As, Ba and Fe correlated with erythrocytes; B and Pb correlated with liver; and Ni, Co, Hg, Tl and Cd correlated with kidney. Unfortunately, they did not observe aging variations among the concentrations of these elements. Béliveau et al. performed extensive analyses of trace elements in Sprague Dawley rat kidney but did not collect any aging data [27]. Uchino et al. studied aging and sex effects on 7 elements in Sprague Dawley rat organs [28]. They bred both male and female rats (Sprague Dawley) from birth to 364 days old. They found significant increases in the concentrations of Cu, Hg and Cd in the male and female rat kidneys from the age of weaning to 127 days old. They also observed significant sex differences among the concentrations of Fe, Cu and Zn. However, only 7 elements were studied and elemental correlations were not discussed.

In the present study, we determined the concentrations of 26 elements in the kidneys of Wistar rats, which were also used to measure the concentrations of 29 elements in bone (femur) [29], to investigate the effects of aging on these elements and mutual elemental correlations. Eight elements (Na, Mg, Si, P, K, Ca, Fe and Zn) were measured by inductively coupled plasma atomic emission spectrometry (ICP-AES) and 18 elements (Mn, Co, Ni, Cu, As, Se, Rb, Sr, Mo, Cd, Sn, Sb, Cs, Ba, Tl, Pb, Bi and U) were determined by inductively coupled plasma mass spectrometry (ICP-MS) with collision/reaction cell technologies.

A cluster analysis of the elements was performed using a correlation matrix to investigate the similarities of elemental behaviors in kidneys. We also investigated the aging effects of individual elements in kidney using the analysis of variations (ANOVA). These data provide a basic knowledge of the mutual elemental correlations and aging variations in healthy rat kidneys. Detailed discussions about elemental correlations and aging

variations of individual elements in rat bones were previously reported [29].

Experimental

Samples

Detailed descriptions of sampling and analytical methods were previously described in [29], therefore we present brief descriptions for sampling and analytical methods in here. Female Wistar rats of 4 weeks old were purchased from CLEA Japan, Inc. and were reared from 4 (Aug. 19, 1993) to 113 weeks (Sept. 21, 1995). The rats were fed a rodent diet (CE-2, CLEA Japan, Inc.) and tap water ad libitum. The rearing period covered from the weaning to the average lifetime of rats (~2 years). Rats that were deeply anesthetized with ethyl ether + chloroform (1 + 1) were sequentially dissected over time (5, 9, 13, 17, 21, 25, 33, 42, 50, 59, 68, 77, 85, 95, 105 and 113 weeks; total 16 times). Five rats were dissected at a time with the exception of 4 rats at 113 weeks. After the femoral artery was cut and drained, following 18 organs and tissues were extracted and were refrigerated at -25°C : brain, skin, stomach, small intestine, large intestine, cecum, liver, pancreas, lung, heart, muscle, kidneys, spleen, thymus (from 13 to 33 weeks old), fat, bone (femur), serum and hair. Kidney samples were cleaned with high purity water (Milli-Q, Millipore Japan, Japan) to remove blood stain. A total of 79 samples ($5 \times 15 + 4 = 79$) were collected. In addition, samples of feces, urine, rodent diet, tap water were kept and analyzed as references. All the experiments performed on animals were completed according to the Guide for the Care and Use of Laboratory Animals and approved by the Committee of Animal Experiments, Kitasato University.

Sample preparation and element analysis

Samples (~0.15 g, wet) were split from frozen organs using a ceramic knife on a class 10 clean bench, and then transferred into 30 mL Teflon tubes. The samples were decomposed by the addition of 5 mL of ultra high purity HNO_3 and 1 mL of H_2O_2 (TamaPure AA 100, Tama Chemicals, Japan) while gently heated up to 180°C on a graphite heating block (Digi PREP Jr., SCP Science, Canada). The samples were then dried up and the same process was repeated 2 or 3 times. The samples were dissolved and diluted with 3% HNO_3 by a factor of 1000. Certified Reference Material of bovine liver (SRM 1577b, NIST, USA) was decomposed using the same procedure. Although we measured the concentration of elements in wet sample mass, we determined the water contents in kidneys of specific ages (5, 21, 68 and 113 weeks). Four samples were collected for the each specific age and dried using a freeze-dry method. The water contents were calculated from both wet and dried masses. We obtained water content of kidney to be 71, 74, 70 and 68% for 5, 21, 68 and 113-week-old rats, respectively.

To determine the element concentrations, inductively coupled plasma atomic emission spectrometry (ICP-AES, Vista AX, Varian, USA) and inductively coupled plasma mass spectrometry (ICP-MS, PQ-ExCell-S, Thermo Scientific, Germany) were used. The detailed methods for element analysis were described in [29]. We tried to determine 33 elements (Li, B, Na, Mg, Al, Si, P, K, Ca, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Rb, Sr, Mo, Ag, Cd, Sn, Sb, Cs, Ba, W, Tl, Pb, Bi and U) in 18 organs. However, when the numbers of the data for each element were reduced to $N < 25$, because of the raw data were either below the quantification limits, below the procedure blanks, high background of the instruments or interference problems, we omitted whole the data. In the case of kidney, Li, B, Al, V, Cr, Ag and W data were omitted.

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