Kidney and Liver Metallothioneins in Rats after Administration of an Organic Compound*

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Intubation of rats with α-mercapto-β-(2-furyl)acrylic acid (MFA) for 5 days at 50 mg/kg caused a 7-fold increase in kidney copper concentration, a 2-fold increase in kidney zinc concentration, and a 20% increase in liver zinc concentration. The proteins which bound the increased metals were purified and identified as metallothioneins by their amino acid compositions. Two isoforms were isolated from each organ. Renal thioneins appeared identical to counterpart hepatic apoproteins, but the former bound Cu and Zn in a 2:1 mole ratio and the latter bound only Zn. Kidney contained over 10 times more metallothionein per g of tissue than did liver. In rats previously administered MFA, injection of cadmium sulfate resulted in rapid displacement of liver metallothionein-bound Zn by Cd under conditions where minimal metallothionein was found in Cd-dosed animals not administered MFA. We conclude that MFA induces metallothionein biosynthesis in kidney and liver of normal rats; this is a novel effect for an organic compound.

Metallothioneins are cysteine-rich, metal-binding proteins and have been investigated principally in mammalian liver, kidney, and intestine, although they may be found in other mammalian organs and in nonmammalian species (1, 2). Their biosynthesis is induced in adrenalectomized rats by the synthetic glucocorticoid dexamethasone (3), in normal rats by stresses such as bacterial infection (4), food restriction (5), CCl₄ intoxication (6), and surgical intervention (7, 8), but most potently by administration of cadmium, zinc, mercury, or copper salts (5, 9–15).

Administration to rats of α-mercapto-β-arylacrylic acids, for example, the furyl compound MFA, was reported (16) to cause the appearance in liver cytosol of a zinc-binding species which co-eluted with metallothionein on size exclusion chromatography. The possibility that MFA induces metallothionein biosynthesis was examined more thoroughly in the present investigation. MFA was found to provoke the synthesis of copper- and zinc-binding thioneins in rat kidney and zinc-binding thioneins in liver. Cadmium ion was able to be incorporated in vivo into MFA-induced metallothioneins.

EXPERIMENTAL PROCEDURES AND RESULTS

Induction of metallothionein biosynthesis in rats by the administration of MFA was proposed in a previous report (16); however, comparison by size exclusion chromatography, which was the basis for that suggestion, is considered inadequate for characterization of metallothionein (2). The novel effects of administration of this organic compound compelled us to undertake the fuller investigation reported here. Most rigorously, a putative metallothionein could be identified by primary amino acid sequence analysis. In the absence of that information, other criteria have been established (2): Metallothioneins have a high metal content, a cysteine content of 33 mol %, with a single methionine residue per molecule and lack aromatic amino acids and histidine. The kidney and liver metalloproteins isolated from MFA-dosed rats satisfy these criteria and thus may be identified as metallothioneins. Two metallothionein isoforms were obtained from each organ in very roughly equal amount. Although the kidney species contained copper and zinc in a 2:1 mole ratio and the liver species contained only zinc, corresponding isoforms in kidney and liver appeared identical to one another in amino acid composition and to liver metallothionein isoforms induced in rats by the administration of cadmium sulfate.

Upon fractionation of tissues of MFA-dosed rats, 57% of the increased kidney Cu, 52% of the increased kidney Zn, and 47% of the increased liver Zn were recovered in metallothionein fractions. (The liver figure takes into account the cadmium sulfate added during the fractionation scheme.) In our isolation of metallothionein from cadmium-exposed rats, 46% of the whole liver cadmium was recovered in the two isoforms. These similar per cent recoveries of Cd and of excess Cu and Zn, in view of the conclusion of Minkel et al. (23) that greater than 95% of liver cadmium is bound to metallothionein in rats administered CdCl₂ in their drinking water, suggests that most of the increased metal in kidney and liver of MFA-dosed rats is metallothionein-bound.

Three cysteine thiols are found per metal ion in cadmium and zinc metallothioneins of rat liver (5, 13, 30), whereas the thiol/metal ratio is lower in copper-containing metallothioneins (14). We observed thiol/metal ratios of about unity for all MFA-induced metallothioneins. However, except for the L-II preparation, more cysteine was recovered (as the S-

* Portions of this paper (including “Experimental Procedures,” “Results,” Figs. 1–6, and Tables 1–III) are presented in miniprint at the end of this paper. Miniprint is easily read with the aid of a standard magnifying glass. Full size photocopies are available from the Journal of Biological Chemistry, 9650 Rockville Pike, Bethesda, MD 20814. Request Document No. 83M-2629, cite the authors, and include a check or money order for $6.00 per set of photocopies. Full size photocopies are also included in the microfilm edition of the Journal that is available from Waverly Press.

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3658
carboximidomethyl derivative) after purification of the derivatized polypeptides than had been measured before reduction and alkylation. We conclude that the thiol/metal ratio was low in our material because of thiol oxidation during purification. Metallothioneins, particularly those containing copper, are susceptible to such oxidation (4, 13, 14, 20). Based on specific activity and recovery of $^{14}C$-carboximidomethylated polypeptides, we estimate a ratio of 7 mol of Zn/mol of MFA-induced liver metallothionein and a ratio of 10 mol of Cu plus Zn/mol of MFA-induced kidney metallothionein. These are indirect estimates, but they are consistent with data for the metal content of known metallothioneins (2, 12, 13, 15, 30, 35, 36). The yield of 27.8 μmol of metallothionein-associated cysteine from 54 g of kidney, compared to 7.2 μmol from 175 g of liver, indicates that the amount of metallothionein per g of tissue was over 10-fold higher in kidney of MFA-dosed rats than in liver.

Cadmium sulfate was added to the initial supernatant during fractionation of MFA-induced liver metalloproteins to demonstrate in vitro replacement of zinc by cadmium ions, one of the earliest noted properties of metallothioneins (2). Replacement of Zn by Cd occurred in vivo as well. After intraperitoneal administration of cadmium sulfate, both control and MFA-dosed rats accumulated equivalent concentrations of Cd in liver over a 2-h period. However, over one-third of the total liver cadmium was associated with, and apparently saturated, the metallothionein fraction in MFA-dosed rats, whereas in control rats, cadmium associated with particulate fractions and high molecular weight cytosol species. Actinomycin D effectively inhibits metallothionein biosynthesis in liver when administered to rats $1/2$ to 4 h prior to administration of the inducer metal (28). In the experiments reported here, control rats and one group of MFA-dosed rats were given the antibiotic, in order to demonstrate that hepatic metallothionein involved in metal exchange was present in consequence of previous administration of MFA and was not newly synthesized. MFA-dosed rats not administered the antibiotic differed only slightly in the parameters of metal metabolism which were measured, suggesting that protein synthesis permitted over the 2-h exposure to cadmium had modest effects. The rats not administered actinomycin D (group 3) cleared more Cd from plasma and from high molecular weight species in liver cytosol, compared to the inhibitor-treated groups. In other studies of cadmium-exposed rats, where protein synthesis was blocked, or when observations were made during the 2- to 3-h period before significant metallothionein synthesis had occurred, Cd was taken up by the liver, but its distribution in the cytosol was among high molecular weight species (28, 37-39); all or almost all of the cytosol Cd was found in the metallothionein fraction after biosynthesis was permitted. In rat kidney, in contrast, most of the cytosol Cd was associated with the metallothionein fraction within 1 h after cadmium administration (37, 38) and renal metallothionein biosynthesis was not inhibited by actinomycin D (37). It may be that the 3-fold greater accumulation of Cd in the kidney in the MFA-dosed groups was due not only to exchange into pre-existing Cu, Zn-thionein, but also to metallothionein biosynthesis. In any event, the consistency of many of our observations with those in the literature demonstrate that the participation of metallothionein in trace metal metabolism may be successfully studied in MFA-treated animals.

An explanation for the long lasting elevation of plasma zinc concentration in MFA-dosed rats has been proposed (34). Less obvious are mechanisms by which MFA causes accumulation of copper and zinc in kidney and of zinc in liver and metallothionein synthesis in both tissues. However, comparison with other metallothionein inducers is informative. Following dexamethasone administration to adrenalectomized rats (3), bacterial infection (4), food restriction (5), stresses such as cold exposure, exercise or CCl4 intoxication (6), partial hepatectomy (7), or sham operation (8), zinc-binding metallothioneins are synthesized in liver, while total liver zinc is increased or unchanged. Plasma zinc concentration usually decreases. Kidney was examined in only one of these studies (6); there was little or no effect on metals or metallothionein content of this organ. On the other hand, when Cd, Cu, Hg, or Zn salts are injected to rats, a different, but reasonably consistent, pattern of responses occurs (5, 10-15, 28, 30-32, 35-44): zinc and the inducer metal accumulate in liver, zinc, copper, and the inducer metal accumulate in kidney and in these organs, metallothioneins are synthesized which bind the accumulated metals. Plasma concentration of the inducer metal must rise, if only transitorily before clearance of the metal into other tissues. Plasma zinc and copper concentrations, when these are not the inducer metal, neither consistently increase nor decrease (38). Elevated plasma zinc concentration in zinc-injected animals is proposed (41) as a key stimulus for hepatic zinc-thionein synthesis. Pertinent differences in organ specificity exist among the inducer metals. Copper and zinc salts provoke metallothionein biosynthesis to a considerably greater extent in liver than in kidney (32, 42, 43). Induction of hepatic metallothionein biosynthesis by mercury may be indirect or may require more metal than suffices to induce renal metallothionein (15, 31, 40, 44) and in cadmium-injected rats, liver contains a greater amount of metallothionein-bound Cd than does kidney (11, 31, 37-40, 42).

The effects of MFA administration to rats do not duplicate exactly those of physiological stress nor metal administration, but resemble more the response to the latter stimuli than to the former. In particular, MFA shares with mercury, among the metal inducers, a predominant effect on kidney metallothionein biosynthesis. There also may be a cause and effect relationship between high plasma zinc concentration and hepatic zinc-thionein synthesis in MFA-dosed rats, as described in the scheme of Richards and Cousins (41). We have not investigated the status of intestinal metallothionein, although since MFA is active when administered by intubation, this obviously would be interesting. However, we have demonstrated that MFA is an antidote to mercuric chloride intoxication in rats, apparently due to enhanced deposition of mercury in kidney metallothionein (45). MFA does not alter zinc absorption nor zinc or copper balances in rats, although clearly redistribution of these metals occurs within the animals (34).

Metallothionein is involved in the metabolism of both essential and toxic trace elements and may have other roles which are speculative at present (2). Because the administration of MFA leads to synthesis of these metal-binding proteins in the absence of exogenously supplied metals, it will be useful in further study of physiological roles of metallothionein.

REFERENCES

6. Oh, S. H., Deagen, J. T., Whanger, P. D., and Weswig, P. H.
Supplementary materials to ‘Kidney and liver metallothioneins in rats after administration of an organomercurial’, Geert Croux and Philip J. Lachmann

Metallothionein induction by MFA

Metallothionein Induction by MFA

RESULTS

Characterization of metallothioneins isolated by MFA

(Copper and zinc concentrations of pooled kidney from rats administered MFA were 65 and 62 g/g, respectively. Compared to concentrations of 5.5 g/g and 22 g/g in kidneys of normal animals. Concentrations of 4.9 g/g and 38 g/g were found in pooled livers of the MFA-treated rats, compared to control values of 3.6 g/g and 32 g/g, respectively. Thus, there were 9-fold and 5-fold increases in kidney copper and zinc concentrations, respectively, and a 2-fold increase in liver zinc (128% of control), but no increase in liver copper in the MFA-treated animals. Organ weights of liver and kidney did not differ between vehicle- and MFA-treated rats.)

Low-MW metallothioneins were purified by 40-50% lead acetate precipitation, of kidney and liver Cu-protein, as determined by lead acetate precipitation and by chromatographic procedures. The metal content of these proteins was determined by microwave digestion of aliquots of known volume. Copper and zinc were measured by flame atomic absorption spectrophotometry. The metal concentrations of the purified metallothioneins were determined by atomic absorption spectrophotometry.

TABLE I

<table>
<thead>
<tr>
<th>Fraction Number</th>
<th>Copper</th>
<th>Zinc</th>
<th>Relative Protein Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-111</td>
<td>1.5</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>K-111</td>
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<td>K-111</td>
<td>199</td>
<td>2.3</td>
<td>1.7</td>
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</table>

Fig. 1. Ion-exchange chromatography of low-MW metallothioneins from kidney of MFA-treated rats. Further explanation is given in the legend to Fig. 2. Cationic (solid circle), zinc (open circle), salt gradient (dotted line) and relative protein concentration (measured by fluorometry, E2 is shown.)

Table I: Recovery of copper and zinc and lead-ion precipitable nitrogen in purification of metallothioneins from 10 g of liver tissue from MFA-treated rats

<table>
<thead>
<tr>
<th>Purification Step</th>
<th>Copper (μM)</th>
<th>Zinc (μM)</th>
<th>Lead-Ion Precipitable Nitrogen (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenate</td>
<td>10.9</td>
<td>300.8</td>
<td>375.9 x 10^-6</td>
</tr>
<tr>
<td>Initial supernatant</td>
<td>210</td>
<td>6.8</td>
<td>76.1 x 10^-3</td>
</tr>
<tr>
<td>[20K]SO4 supernatant</td>
<td>20.4</td>
<td>5.2</td>
<td>13.8 x 10^-3</td>
</tr>
<tr>
<td>Sepharose 6-10 pool</td>
<td>499</td>
<td>10.4</td>
<td>13.4 x 10^-3</td>
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<tr>
<td>DEAE-Sepharose pool</td>
<td>49.9</td>
<td>9.3</td>
<td>10.9 x 10^-3</td>
</tr>
</tbody>
</table>

For purposes of comparison, two metallothioneins were isolated from livers of copper-fed rats. Forty percent of the liver Cu, 96% of the liver Zn, 0.28 of the liver lead-acetate precipitable nitrogen were retained in the isoforms. The metal ratios of the Co-Sephadex-coated metallothionein was 1.2 Cu:Zn:0.6:0.

Cadmium, copper, and zinc ions were quantitatively desorbed from the metallothioneins by 0.5 N NaOH. The metal content of these was determined by flame atomic absorption spectrophotometry. The metal content of these proteins was determined by microwave digestion of aliquots of known volume. Copper and zinc were measured by flame atomic absorption spectrophotometry. The metal concentrations of the purified metallothioneins were determined by atomic absorption spectrophotometry.

TABLE II

<table>
<thead>
<tr>
<th>Purification Step</th>
<th>Copper</th>
<th>Zinc</th>
<th>Lead-Ion Precipitable Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogenate</td>
<td>10.9</td>
<td>300.8</td>
<td>375.9 x 10^-6</td>
</tr>
<tr>
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<td>49.9</td>
<td>9.3</td>
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</tr>
</tbody>
</table>

Fig. 2. DEAE-Sepharose chromatography of low-MW metallothioneins from liver of MFA-treated rats. Further explanation is given in the legend to Fig. 2. Cationic (solid circle), zinc (open circle), salt gradient (dotted line) and relative protein concentration (measured by fluorometry, E2 is shown.)

Table II: Recovery of copper and zinc and lead-ion precipitable nitrogen in purification of metallothioneins from 15 g of liver tissue from MFA-treated rats

<table>
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<tr>
<th>Purification Step</th>
<th>Copper (μM)</th>
<th>Zinc (μM)</th>
<th>Lead-Ion Precipitable Nitrogen (μM)</th>
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</thead>
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<tr>
<td>Homogenate</td>
<td>10.9</td>
<td>300.8</td>
<td>375.9 x 10^-6</td>
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<tr>
<td>Initial supernatant</td>
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<td>76.1 x 10^-3</td>
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<tr>
<td>[20K]SO4 supernatant</td>
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<td>Sepharose 6-10 pool</td>
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<tr>
<td>DEAE-Sepharose pool</td>
<td>49.9</td>
<td>9.3</td>
<td>10.9 x 10^-3</td>
</tr>
</tbody>
</table>

Fig. 3. Ion-exchange chromatography of the Zn-cadmium chelate derivative of kidney metallothionein 2-1. Development of the Sepharose-Sephadex 0-25 column is described in Experimental Procedures. Eluate in the buffer (pH 7.0) is shown by the line and data points are shown by the line and data points. The major peak at 20.4 min eluted first from the column, followed by a peak at 25.2 min and a minor peak at 27.4 min. The major peak at 20.4 min eluted first from the column, followed by a peak at 25.2 min and a minor peak at 27.4 min. The major peak at 20.4 min eluted first from the column, followed by a peak at 25.2 min and a minor peak at 27.4 min. The major peak at 20.4 min eluted first from the column, followed by a peak at 25.2 min and a minor peak at 27.4 min. The major peak at 20.4 min eluted first from the column, followed by a peak at 25.2 min and a minor peak at 27.4 min.
Metallothionein Induction by MFA

**Table III**

<table>
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<tr>
<th>Amino Acid</th>
<th>X-1</th>
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<th>L-11</th>
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<tr>
<td></td>
<td>Mol%</td>
<td>Mol%</td>
<td>Mol%</td>
<td>Mol%</td>
</tr>
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<tr>
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<td>Cysteine</td>
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<td>6.7</td>
<td>9.1</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Thioline 1 and thioline 2 were isolated in the present work from liver of cadmium-fed rats. Each were isolated by extraction with 2 M HCl and purification by electrophoresis. The principal component was major relative to heavy cytosomal cystine of 0.32. The derivatives of X-11, L-11 and the other cadmium-induced liver (formaldehyde) were similar to one another, with their principal component representing a major component of the 0.40. X-11 appeared to be a mixture of X-11 and L-11 polypeptides. Each preparation exhibited other species of cadmium electrophoresing at a slower rate of X-11 than L-11, which were also major components of cadmium electrophoresing at a slower rate than X-11. The amino acid composition of X-11 and L-11 were similar to one another and to one of the cadmium-induced liver metallothionein (Table III), the amino acid composition of X-11, L-11 and the second and third isomers of cadmium-induced liver metallothionein were similar to one another as well. All preparations showed similar overall amino acid compositions with derivatized cysteine, serine and cysteine accounting for approximately 18%, 18% and 18% of the total, respectively, differences between the two isomers in the abundance of cysteine were the most important. The cysteine contents were determined by others on the amino acid composition of isomers of rat liver metallothionein [X-11, L-11, X-11, and L-11] and the presence of cysteine and cysteine are found to be relatively minor in all isomers. The amino acid composition of X-11 was consistent with the interpretation of the electrophoretic migration of X-11 and L-11 isomers: X-11: hydroxyproline 26.7 M 2-carboxymethylcysteine, 3.1, 2-carboxylysine, 3.2, 2-carboxymethionine, 3.2, and 3.2, the absence of the abundant amino acids mentioned above were intermediate (data not shown) between those recorded for the X-1 and L-1 isomers. The total derivatized cysteine contents, based upon amino acid analysis data of the X-1, L-1, X-11, L-11, and L-11 preparations were 18%, 18%, 18%, 18%, respectively.

Analyses of control tissues

Liver (79 g) and testis (36 g) tissues obtained from normal rats were carried through the procedures described above for isolation of metallothionein, except that the aliquot of homogenate was mixed with a solid gradient buffer with a stop from lower to higher pH, then both the isomers were isolated from the testis by a series of centrifugation steps and the isomeric X-11 and L-11 was isolated from the testis by gel electrophoresis. The principal component was major relative to heavy cytosomal cystine of 0.32. The derivatives of X-11, L-11 and the other cadmium-induced liver (formaldehyde) were similar to one another, with their principal component representing a major component of the 0.40. X-11 appeared to be a mixture of X-11 and L-11 polypeptides. Each preparation exhibited other species of cadmium electrophoresing at a slower rate of X-11 than L-11, which were also major components of cadmium electrophoresing at a slower rate than X-11. The amino acid composition of X-11 and L-11 were similar to one another and to one of the cadmium-induced liver metallothionein (Table III), the amino acid composition of X-11, L-11 and the second and third isomers of cadmium-induced liver metallothionein were similar to one another as well. All preparations showed similar overall amino acid compositions with derivatized cysteine, serine and cysteine accounting for approximately 18%, 18% and 18% of the total, respectively, differences between the two isomers in the abundance of cysteine were the most important. The cysteine contents were determined by others on the amino acid composition of isomers of rat liver metallothionein [X-11, L-11, X-11, and L-11] and the presence of cysteine and cysteine are found to be relatively minor in all isomers. The amino acid composition of X-11 was consistent with the interpretation of the electrophoretic migration of X-11 and L-11 isomers: X-11: hydroxyproline 26.7 M 2-carboxymethylcysteine, 3.1, 2-carboxylysine, 3.2, 2-carboxymethionine, 3.2, and 3.2, the absence of the abundant amino acids mentioned above were intermediate (data not shown) between those recorded for the X-1 and L-1 isomers. The total derivatized cysteine contents, based upon amino acid analysis data of the X-1, L-1, X-11, L-11, and L-11 preparations were 18%, 18%, 18%, 18%, respectively.

Cadmium uptake in vivo

Mean cadmium concentration in liver 2 h after CdSO4 injection was 45-48 mg/g in metallothionein group (group 1) and 29-32 mg/g in metallothionein group (group 2). The mean cadmium concentration was greatest in the kidney (3.0 mg/g in metallothionein group (group 1) and 2.4 mg/g in metallothionein group (group 2). The mean cadmium concentration in the liver and kidney was greatest in the kidney (3.0 mg/g in metallothionein group (group 1) and 2.4 mg/g in metallothionein group (group 2). Cadmium uptake in vivo is presented in Figure 5 for liver and kidney. The mean cadmium concentration was greatest in the kidney (3.0 mg/g in metallothionein group (group 1) and 2.4 mg/g in metallothionein group (group 2). The mean cadmium concentration in the kidney in the kidney group was 1.5 mg/g in metallothionein group (group 1) and 1.0 mg/g in metallothionein group (group 2). Cadmium uptake in vivo is presented in Figure 5 for liver and kidney. The mean cadmium concentration was greatest in the kidney (3.0 mg/g in metallothionein group (group 1) and 2.4 mg/g in metallothionein group (group 2). The mean cadmium concentration in the kidney in the kidney group was 1.5 mg/g in metallothionein group (group 1) and 1.0 mg/g in metallothionein group (group 2). Cadmium uptake in vivo is presented in Figure 5 for liver and kidney. The mean cadmium concentration was greatest in the kidney (3.0 mg/g in metallothionein group (group 1) and 2.4 mg/g in metallothionein group (group 2). The mean cadmium concentration in the kidney in the kidney group was 1.5 mg/g in metallothionein group (group 1) and 1.0 mg/g in metallothionein group (group 2). Cadmium uptake in vivo is presented in Figure 5 for liver and kidney. The mean cadmium concentration was greatest in the kidney (3.0 mg/g in metallothionein group (group 1) and 2.4 mg/g in metallothionein group (group 2). The mean cadmium concentration in the kidney in the kidney group was 1.5 mg/g in metallothionein group (group 1) and 1.0 mg/g in metallothionein group (group 2).
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