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# Induction and Degradation of Zn-, Cu- and Cd-Thionein in Chang Liver Cells

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Metallothionein is an intracellular protein of low molecular weight with a high content of cysteine but with no aromatic amino acids ; it possesses strong affinity for heavy metal such as cadmium, zinc, copper, mercury and silver. Metallothionein is induced by de novo synthesis in tissues of animal species treated with zinc, copper and cadmium. Generally, metallothionein is postulated to function as a detoxifying agent for sequestering heavy metals, i. e. cadmium and mercury, and to play a role in requilatin essential heavy metals, i. e. zinc and copper.

In the present experiments, we compared the synthesis and degradation of Zn-, Cu- and Cd-thionein in human liver cells (Chang liver) with each other. The degradation products of metallothionein in the cells and excreted into extracellular medium were also analyzed.

Human liver cells (Chang liver) were exposed to 5 $\mu$g Zn, 2.5 $\mu$g Cu or 1 $\mu$g Cd/ml in cultured medium. These exogeneous heavy metals were accumulated by the cells and induced de novo synthesis of metallothionein after a 3-h incubation period. The production of Zn-, Cu- or Cd-thionein started in the cells with accumulation of 1 nmol Zn, 0.3 nmol Cu and 0.1 nmol Cd/mg cytosol protein and subsequently the amounts of metal-binding thioneins increased in agreement with the lerative amount of metal accumulated in the cytosol over a 24-h period.

When cells containing Zn- or Cu-thionein were placed in metal free medium, 70% or 25% of the zinc or copper bound to each original metallothionein was released after 3 h ; bound metals decreased to 85% and 65% respectively after 24 h. The disappearance of metal from metallothionein correlated with increases of metal in the medium. On the other hand, $^{35}$S-counts incorporated into Zn- and Cu-thionein decreased only to 40% and 15% of the levels in the original metallothionein after 3 h ; $^{35}$S-counts decreased to 65% and 45%, respectively, after 24 h, indicating that metals bound to metallothinein decreased more quickly than $^{35}$S-counts. These results suggest that metals were released from metallothionein and were excreted into the medium. However, $^{35}$S- and $^{109}$Cd-counts in Cd-thionein changed very little, if at all, in the cells even after a 24-h incubation period. Our data strongly suggest that Zn- and Cu-thionein are degraded in the

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cells, but that Cd-thionein remains longer than either Zn- or Cu-thionein.

When cells containing Zn-thionein were incubated in metal-free medium, Zn-thionein was digested in the cells and peptide fragments ranging about 200—400 daltons were excreted from the cells.

The degree of cytotoxicity of heavy metals in the present experiments was Cd<Cu<Zn Cadmium is able to induce metallothionein at the lowest concentration in the cells and cadmium-binding thionein remains the longest in the cells. Copper, the second most toxic heavy metal for cells, induces metallothionein at a lower concentration than zinc, and copper-binding thionein degrades more slowly than zinc-binding thionein. Our data demonstrate that, in cells, the cytotoxicity of heavy metals correlates with metallothionein induction and degradation. The results of our study strongly suggest that metallothionein acts as a detoxifying reagent against heavy metal poisoning.