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Effects of Dexamethasone on Metallothionein Induction by Zn, Cu and Cd in Chang Liver Cells*

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Karin et al. have described that human MT are encoded by a multi-gene family containing at least 14 closely related genes and pseudogenes. Two of these genes, MT-I_A and MT-II_A, encode functional protein which show each other different induction response to heavy metal and glucocorticoids. The differential response is due to functional differences of the respective promoter/regulatory regions of the genes ; the MT-I_A promoter response only to Cd^{2+}, but MT-II_A promoter is responsive to Cd^{2+}, Zn^{2+} and glucocorticoids. Moreover, they have defined two separate regulatory DNA elements for the MT-II_A gene induction which mediate the induction of the gene by heavy metals and by glucocorticoid hormones. The element responsible for induction by glucocorticoid hormones is coincident with the DNA-binding site for the glucocorticoid hormone receptor. These results clearly indicate that two inducers, heavy metals and glucocorticoid hormones, promote MT gene expression by mechanisms which are independent of one another.

We are interested in the extent to which particular inducers affect the induction of MT. In this report we demonstrate the effects of dexamethasone on maximum MT induction by Zn^{2+}, Cu^{2+} and Cd^{2+} in Change liver cells. Our data show that dexamethasone, has an additive effect on the maximum MT accumulation induced by Zn^{2+}, Cu^{2+} or Cd^{2+}, supporting the interpretation that expressions of mechanism of MT gene expression by heavy metals and dexamethasone work independently of one another.

Metallothioneins (MTs) were induced in Change liver cells by the metals, Zn, Cu and Cd, and the glucocorticoid hormone, dexamethasone. When 116 μM Zn, 32 μM Cu and 18 μM Cd, and 10^{-7}M dexamethasone, respectively, were administrered for 9 h, MTs induced by each inducer in the cells reached maximum levels. The maximum accumulation of MT level induced by dexamethasone was the lowest of the four inducers investigated ; the levels induced by Zn, Cu and Cd were 4.7, 1.2 and 1.5 times of that induced by dexamethasone.

When dexamethasone was added to the cells together with the heavy metals (Zn, Cu and Cd), dexamethasone had an additive effect on the maximum MT accumulations induced by heavy metals as compared to when induction was conducted using one of

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heavy metals alone or by dexamethasone alone. However, dexamethasone did almost not effect the metal accumulations in the cells, although the maximum MT levels induced by heavy metal increased by dexamethasone. These results suggest that the process of MT induction by heavy metals and that by dexamethasone are independent of one another.

When dexamethasone was added to the cells together with a high concentration of Cu (32 μM) induced the maximum MT accumulation, Cu transport into the cells decreased by 20—40% of that into non-treated cells, which was statistically significant.

In this experiment, our data suggest that MT genes possess a differential gene expression mechanism by functional differences of MT : detoxification of heavy metals and regulation of essential heavy metals.