REGULATION OF SODIUM-DEPENDENT PHOSPHATE COTRANSPORTER IN H4IIE HEPATOMA CELLS BY HEAVY METALS

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We have shown recently that type I Na/P_i cotransporter (NaP_i-1) in rat hepatocytes are regulated by insulin through metabolic signaling (Li, H. et al., Am. J. Physiol. 271, E1021, 1996). Although it is well established that heavy metals regulate cell metabolism, the effects of heavy metals on gene expression regulation through altering metabolic signals have not been addressed. The aim of this work is to determine the long-term effects of heavy metals on Na/P_i cotransporter in H4IIE hepatoma cells. When serum-starved H4IIE cells were exposed to three different heavy metals and assayed for Na-dependent P_i transport activity as previously described (Li, H. et al., Am. J. Physiol. 271, E1021, 1996), $HgCl_2$ and $CdCl_2$, but not $ZnCl_2$ caused a dose-dependent stimulation of Na/P_i cotransport activities in these cells. Significant stimulation by $HgCl_2$ was observed at 0.2 μM and reached maximum at 5 μM. Concentrations higher than 10 μM caused cell dealth. $CdCl_2$ appeared to be equally potent as $HgCl_2$, and caused maximum stimulation at 1 μM. When time-dependent changes in Na/P_i cotransport activity in response to 5 μM $HgCl_2$ were determined, significant stimulation (115% of control) was observed after 6 h incubation, and reached a maximum (162%) after 24 h incubation. To correlate changes in transport activity to NaPi-1 expression, Northern blot analysis was done after the cells were exposed to different concentrations of $HgCl_2$ for 24 h. It was found that $HgCl_2$ acted as insulin, and increased steady state levels of NaP_i-1 mRNA in H4IIE cells in a dose-dependent manner. After 24 h exposure, 5 μM $HgCl_2$ caused a 2.4-fold increase in NaP_i-1 mRNA over control. These data indicate that $HgCl_2$ and $CdCl_2$ may regulate Na/P_i cotransport activity through up-regulation of NaP_i-1 gene expression. It remains to be determined whether $HgCl_2$ and $CdCl_2$ use a similar signaling pathway as insulin in regulation of NaP_i-1 gene. Supported by MDIBL New Investigator Award to Z.X..