Toxicogenomics of Lead, Mercury, and Cadmium


Human activity has resulted in the environmental distribution of many toxic substances, among them the heavy metals that are spread throughout our biosphere. In addition to acute toxic effects in the humans exposed to heavy metals there are more insidious effects of chronic exposure on the development of all organisms. The resulting altered developmental processes produce in human children symptoms such as hyperactivity, changes in sensory function, and changes in cognitive abilities (IQ). Drosophila is a promising model organism to study the effects of heavy metal exposure during development because of (1) the sophisticated understanding of its genetics, and the ease of manipulating its genome; (2) availability of behavioral and morphological assays sensitive to small doses of toxins. Both human and Drosophila cells are thought to induce expression of protective genes upon exposure to certain toxicants. The hypothesis of this proposal is that over-expressing some of the "protective genes" induced by heavy metals will make flies resistant to the behavioral and developmental alterations caused by heavy metal exposure, and conversely, that knocking out some of these genes might make flies more sensitive to heavy metal exposure. To test this hypothesis, Aim 1 is to expose the larvae to environmentally relevant doses of lead, mercury, and cadmium, and to provide data on their effects on cognition, locomotion and synaptic function. Aim 2 is to perform DNA microarray analysis heavy metal- exposed larvae (exposure will be to NOAEL, LOAEL, and LD50, as determined in the Aim 1, and determine what subsets of genes are most affected, either positively or negatively. Aim 3 is to upregulate, by conditional overexpression, or down regulate, by using existing mutations, the genes with the most significant changes in expression and to determine the effects of the test chemicals on cognition, locomotion, and synaptic function of these genetically altered flies. Results of these studies will identify candidates for the most important genes that are altered during heavy metal exposure in humans, and could well lead to bioassays or treatments for heavy metal exposure at or below NOAEL and LOAEL values.

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