“The Hormetic Dose Response in Toxicology as Seen by Metabonomics”

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Hormesis is a dose-response relationship showing that the same substance may have opposite effects depending on whether organisms are exposed to low or high doses (1). This concept, however, leaves perplexed the scientific community because of its biphasic appearance, quite distinct from standard monotone models conventionally used in risk assessment. Furthermore, conventional methods used so far to highlight this phenomenon are hardly convincing, probably due to a lack of mechanistic information. The purpose of this research is to evaluate, by a metabonomic approach, the hormetic effect of CCl_4 described in several publications (2). Metabonomic is a very powerful tool to understand cellular mechanisms involved in specific biological processes. Practically, to trigger the hormetic response, rats were exposed to a stimulatory dose of CCl_4 followed by a toxic dose of the same compound given 24 hours later. As compared to unstimulated animals, the metabolic profiles of “hormetic” individuals showed increased urinary levels of metabolites involved in energy production pathways as well as an elevation in urinary allantoin proposed by other authors as a potential marker of cell regeneration (3). Reduction in liver toxicity was also observed. In order to suppress the hormetic effect, pretreatment with chlordecone was also given to a different group of animals, then exposed to the subtoxic stimulatory dose. The pretreatment with chlordecone alone showed depletion in liver glycogen, but once associated with CCl_4, many markers of hepatotoxicity appeared in urine in alarming amounts. These metabolic changes indicated a weakening in energy production in those animals. Those results suggest that hormesis could be initiated by an exacerbation of the cellular energy biochemical pathways induced by the stimulatory dose of the compound. This additional energy is probably used to fight against the subsequent toxic dose, probably via the activation of cellular regeneration processes. Individuals exposed to chlordecone displayed a low energy status and, consequently, seemed unable to activate the mechanisms of cell regeneration. This could explain the observed exacerbation in CCl_4 liver toxicity.

References :

1. E.J. Calabrese & L.A. Baldwin. Hormesis: U-shaped dose responses and their centrality in toxicology. 2001. TRENDS in Pharmacological Sciences. 30: 71-83
2. LW. Weber, M. Boll, A. Stampfl. Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. Critical Reviews in Toxicology. 2003. 33(2) : 105-36
3. Y. Konishi & A. Ichihara. Transfer of Purines from Liver to Erythrocytes in vivo and in vitro Studies. 1979.85(1): 295-301