PROOXIDATIVE SHIFT IN TOXIC ACTION OF TCDD

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2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) is most toxic among chlorinated dibenzo-p-dioxins and harmful pollutant of the environment. Its action on mammalia appears in wide spectrum of biochemical changes, including enzymes induction (cytochrome P-450-contaning mixed function oxidase (MFO), DT-diaphorase, δ-aminolevulinic acid synthetase, UDP-glucuronil transferase, glutathione-S-transferase), abnormalities in lipid and carbohydrate metabolisms. Among causes of irreversible cell damage under TCDD intoxication lipid peroxidation (LP) to be of most interest. On the one hand, intensification of LP really takes place after TCDD administration. On the other hand, after TCDD administration most intensive biochemical changes are observed in system of cytochrome P-450, functioning of which and connecting with it cytochrome P-450 reductase are accompanied by reactive forms of oxygen (ROS) production. But yet role of MFO functional changes in observed LP intensification remain unclear.

For fuller understanding of patobiochemical action mechanism of TCDD we investigate influence of TCDD in median lethal like doses on LP, cytochrome P-450-contaning MFO, metabolism of ROS and glutathione metabolism in liver of laboratory mammalians of different species (mice, rats, guinea pigs, rabbits). TCDD treatment of experimental animals induce in liver oxidative stress, manifested in increasing of ROS formation and LP intensity. Comparison of TCDD initiated changes in LP, ROS formation, cytochrome P-450-contaning MFO parameters and antioxidant enzymes activities in mammalians allow to suppose, that basis of observed proxidative changes is dioxin ability for prolonged uncoupling of the oxygenase catalytic cycle and decreasing of peroxidase activity of cytochrome P-450. Decreasing of peroxidase activity of cytochrome may be considered as suppression of very important factor in antioxidant protection of endoplasmic reticulum membranes. These findings show leading role of cytochrome P-450 related proxidant and antioxidant factors imbalance in TCDD toxic action and allow to suppose involving this factors in formation of species susceptibility differences to this xenobiotic.

From worded above, cytochrome P-450 induction is not only regulatory mechanism of adaptation of cellular metabolism to changes in levels of endogenous substrates and products of cytochrome P-450-contaning MFO. At the same time it should be considered as way of increasing of antioxidant protection in microsomal membranes in case of high level ROS formation by cytochrome P-450-contaning MFO. In contrast to TCDD, another methylcholanthrene similar inductors undergo intensive biotransformation, therefore imbalance in cytochrome P-450 related proxidant and antioxidant factors after such inductor administration is short time. As result these xenobiotics have less toxicity and after treatment with them LP may become lower in microsomes and microsomes show more stability in prooxidant conditions.