

Cytotoxicity of Nitroaromatic Explosives and their Biodegradation Products in Mice Splenocytes: Implications for their Immunotoxicity

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Nitroaromatic explosives like 2,4,6-trinitrotoluene (TNT) and 2,4,6-trinitrophenyl-*N*-methyl-nitramine (tetryl) comprise an important group of toxic environmental pollutants, whose toxicity is mainly attributed to the flavoenzyme electrontransferase-catalyzed redox cycling of their free radicals (oxidative stress) and DT-diaphorase [NAD(P)H:quinone oxidoreductase, NQO1, EC 1. 6.99.2]-catalyzed formation of alkylating nitroso and/or hydroxylamine metabolites. Because of the incomprehensive data on the immunotoxic effects of nitroaromatic explosives, we have studied the structure-cytotoxicity relationships in the action of tetryl, TNT as well as its amino and hydroxylamino metabolites, and related nitroaromatic compounds towards mouse splenocyte cells. The protective effects of desferrioxamine and the antioxidant *N,N'*-diphenyl-*p*-phenylene diamine against the cytotoxicity of TNT and other nitroaromatics showed that the oxidative stress-type cytotoxicity mechanism takes place. In addition, the cytotoxicity of nitroaromatics is also partly prevented by an inhibitor of NQO1, dicumarol. The cytotoxicity of the amino metabolites of TNT is also partly prevented by α -naphthoflavone and isoniazide, which points to the involvement of cytochromes P-450 in their activation. In general the cytotoxicity of nitroaromatics in splenocytes increases with an increase in their single-electron reduction potential, E_1^{\cdot} . This points to the prevailing mechanism of the oxidative stress-type cytotoxicity. The obtained structure-activity relationship and the studies of other mammalian cell lines showed that the immunotoxic potential of nitroaromatic explosives may decrease in the order tetryl \geq TNT \geq hydroxylamino metabolites of TNT $>$ amino and diamino metabolites of TNT.

Key words: Nitroaromatic Explosives, Oxidative Stress, Splenocytes, Immunotoxicity