Enzymatic Redox Properties of Novel Nitrotriazole Explosives Implications for their Toxicity

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The toxicity of conventional nitroaromatic explosives like 2,4,6-trinitrotoluene (TNT) is caused by their enzymatic free radical formation with the subsequent oxidative stress, the formation of alkylating nitroso and/or hydroxylamino metabolites, and oxyhemoglobin oxidation into methemoglobin. In order to get an insight into the mechanisms of toxicity of the novel explosives NTO (5-nitro-1,2,4-triazol-3-one) and ANTA (5-nitro-1,2,4-triazol-3-amine), we examined their reactions with the single-electron transferring flavoenzymes NADPH: cytochrome P-450 reductase and ferredoxin:$NADP^+$ reductase, two-electron transferring flavoenzymes mammalian NAD(P)H:quinone oxidoreductase (DT-diaphorase), and *Enterobacter cloacae* NAD(P)H:nitroreductase, and their reactions with oxyhemoglobin. The reactivity of NTO and ANTA in the above reactions was markedly lower than that of TNT. The toxicity of NTO and ANTA in bovine leukemia virus-transformed lamb kidney fibroblasts (line FLK) was partly prevented by desferrioxamine and the antioxidant *N*,*N*′-diphenyl-*p*-phenylene diamine, and potentiated by 1,3-bis-(2-chloroethyl)-1-nitrosourea. This points to the involvement of oxidative stress in their cytotoxicity, presumably to the redox cycling of free radicals. The FLK cell line cytotoxicity and the methemoglobin formation in isolated human erythrocytes of NTO and ANTA were also markedly lower than those of TNT, and similar to those of nitrobenzene. Taken together, our data demonstrate that the low toxicity of nitrotriazole explosives may be attributed to their low electron-accepting properties.

Key words: Nitroaromatic Explosives, Cytotoxicity, Oxidative Stress, Hemoglobin