Prooxidant Cytotoxicity of Chromate in Mammalian Cells: The Opposite Roles of DT-Diaphorase and Glutathione Reductase

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Z. Naturforsch. **61c**, 889–895 (2006); received April 7/May 12, 2006

The geno- and cytotoxicity of chromate, an important environmental pollutant, is partly attributed to the flavoenzyme-catalyzed reduction with the concomitant formation of reactive oxygen species. The aim of this work was to characterize the role of NAD(P)H:quinone oxidoreductase (NQO1, DT-diaphorase, EC 1.6.99.2) and glutathione reductase (GR, EC 1.6.4.2) in the mammalian cell cytotoxicity of chromate, which was evidenced controversially so far. The chromate reductase activity of NQO1 was higher than that of GR, but lower than that of lipoamide dehydrogenase (EC 1.6.4.3), ferredoxin:$NADP^+$ reductase (EC 1.18.1.2), and NADPH: cytochrome P-450 reductase (EC 1.6.2.4). The reduction of chromate by NQO1 was accompanied by the formation of reactive oxygen species. The concentration of chromate for 50% survival of bovine leukemia virus-transformed lamb kidney fibroblasts (line FLK) during a 24-h incubation was (22 ± 4) μM. The cytotoxicity was partly prevented by desferrioxamine, the antioxidant *N,N′*-diphenyl-*p*-phenylene diamine and by an inhibitor of NQO1, dicumarol, and potentiated by 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU), which inactivates GR. The NADPH-dependent chromate reduction by digitonin-permeabilized FLK cells was partly inhibited by dicumarol and not affected by BCNU. Taken together, these data indicate that the oxidative stress-type cytotoxicity of chromate in FLK cells may be partly attributed to its reduction by NQO1, but not by GR. The effect of BCNU on the chromate cytotoxicity may indicate that the general antioxidant action of reduced glutathione is more important than its prooxidant activities arising from the reactions with chromate.

Key words: Chromate, DT-Diaphorase, Glutathione Reductase