Probucol modulates iron nitrilotriacetate (Fe-NTA)-dependent renal carcinogenesis and hyperproliferative response: Diminution of oxidative stress

Abstract

Probucol is a clinically used cholesterol-lowering drug, with pronounced antioxidant properties. We have reported previously, that dietary supplementation of probucol enhances NAD(P)H:quinone reductase (Iqbal M, Okada S (2003) Pharmacol Toxicol 93:259-263) and inhibits Fe-NTA induced lipid peroxidation and DNA damage in vitro (Iqbal M, Sharma SD, Oakada (2004) Redox Rep 9:167-172). Further to this, in the present study, we evaluated the modulatory effect of probucol on iron nitrilotriacetae (Fe-NTA) dependent renal carcinogenesis, hyperproliferative response and oxidative stress. In Fe-NTA alone treated group, a 20% renal cell tumor incidence was recorded whereas, in N-diethylnitrosamine (DEN)-initiated and Fe-NTA promoted animals, the percentage tumor incidence was increased to 70% as compared with untreated controls. No tumor incidence was recorded in DEN-initiated, nonpromoted group. Diet supplemented with 1.0% probucol fed prior to, during and after Fe-NTA treatment in DEN-initiated animals afforded >65% protection in renal cell tumor incidence. Probucol fed diet pretreatment also resulted a significant and dose dependent inhibition of Fe-NTA induced renal ornithine decarboxylase (ODC) activity. In oxidative stress studies, Fe-NTA alone treatment enhanced lipid peroxidation, accompanied by a decrease in the level of GSH, activities of antioxidants and phase II metabolizing enzymes in kidney concomitant with histolopathological changes. These changes were significantly and dose-dependently alleviated by probucol fed diet. From this data, it can be concluded that probucol can modulates toxic and tumor promoting effects of Fe-NTA and can serve as a potent chemopreventive agent to suppress oxidant induced tissue injury and carcinogenesis, in addition to being a cholesterol lowering and anti-atherogenic drug.