P-33

Structural analysis of DNA adducts formed from N-nitrosotaurcholic acid (NO-TCA).

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Keywords: N-nitrosotaurcholic acid; N3-ethanesulfonic acid -2'-deoxyctydine; N⁴-cholyl-2'-deoxyctydine

N-Nitrosoglycocholic acid (NO-GCA) and N-nitrosotaurcholic acid (NO-TCA) have been reported to be mutagenic in Salmonella and carcinogenic in rats. It is also reported that DNA-alkylation, containing O⁶-carboxymethyl-guanine, is observed in vitro when NO-GCA is incubated with calf thymus DNA. To investigate the formation of DNA adducts by NO-TCA, NO-TCA was incubated with calf thymus DNA, and adduct formation was analyzed by the 32P-postlabeling method under nuclease P1 conditions. Three kinds of adducts were detected in calf thymus DNA treated with NO-TCA, and the major adduct was determined to be N3-ethanesulfonic acid -2'-deoxyctydine. In addition, two bulky adducts containing the bile acid moiety were also produced, and the structures were concluded to be N⁴-cholyl-2'-deoxyctydine and N⁴-cholyl-2',5'-deoxyadenosine, respectively. When NO-TCA was singly administered to male Wistar rats by gavage at a dose of 250 mg/kg, both ethanesulfonic acid-dc and N⁴-cholyl-dc were detected in the glandular stomach and colon. The adduct levels of N3-ethanesulfonic acid-dc were 0.22 - 0.29 per 10⁶ nucleotides, and values for N⁴-cholyl-dc were about 500-fold lower. Since NO-TCA may be formed by nitrosation of taurocholic acid in the human body, the presence of N3-ethanesulfonic acid-dc and N⁴-cholyl-dc are now being analyzed in human tissues.

P-34

Oxidative DNA damage induced by carcinogenic aromatic amines, o-anisidine and o-dianisidine

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Keywords: oxidative DNA damage; o-anisidine; o-dianisidine

o-Anisidine and o-dianisidine, which have been used as intermediates in the production of dyes, are urinary bladder carcinogens. We examined oxidative DNA damage induced by these aromatic amines in the presence of cytochrome P450 (CYP) using [32P]-5'-end-labeled DNA fragments obtained from human cancer-relevant genes. o-Anisidine and o-dianisidine induced Cu(I)-mediated DNA damage in the presence of CYP1A2 and 2C9 to a greater extent than CYP1A1, 2D6 and 2E1. o-Dianisidine induced DNA damage much more efficiently than o-anisidine in the presence of CYP1A2. CYP1A2-pretreated o-anisidine and o-dianisidine formed piperiderine-labile and Fpg-sensitive lesions at cytosine and guanine residues of the 5'-ACG-3' sequence complementary to codon 273 (a mutational hotspot) of the p53 tumor suppressor gene, respectively. DNA damage induced by these aromatic amines was inhibited by catalase and bathocuproine, suggesting that H₂O₂ and Cu(I) were involved. These results suggest that Cu(I)-hydroperoxo complex is the primary reactive species causing DNA damage. Formation of 8-oxo-7,8-dihydro 2'-deoxyguanosine, an indicator of oxidative DNA damage, was significantly increased by CYP1A2-treated o-anisidine and o-dianisidine in the presence of Cu(I). Therefore, it is concluded that o-anisidine and o-dianisidine may express the carcinogenicity through oxidative DNA damage induced by their metabolites.

P-35

Peroxidative DNA damage induced by carcinogenic aromatic amines in the liver and lungs of rats

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Keywords: oxidative DNA damage; o-anisidine; o-dianisidine

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