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Phenobarbital enhanced genotoxicity of ochratoxin A.

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Ochratoxin A (OTA) , which is a mycotoxin inducing nephrotoxicity and urinary tract tumors, is genotoxic and is metabolized by different P450 cytochromes and could also be conjugated to glutathione. Implication of cytochrome 2B was tested by induction by phenobarbital. DNA-adducts formed by OTA were analyzed : (i) on human bronchial epithelial cells pretreated by phenobarbital (ii) *in vitro*, by incubation of pretreated rabbit liver, kidney, testis and urinary bladder microsomes in presence of DNA, OTA and NADPH.
DNA-adducts are preferentially formed in cells pretreated 24h by phenobarbital (4 times higher compared to non-pretreated cells) and exclusively by microsomes arising from rabbit organs pretreated 8 days by phenobarbital. PROD activity (reflecting 2B cytochrome activity) is enhanced in liver and kidney microsomes after phenobarbital pretreatment. Moreover, ECOD (reflecting 2A activity) is increased in liver. In the other organs (testis and urinary bladder) these activities could not be detected. We have demonstrated in this study that increasing DNA-adduct formation is not exclusively due to induction of 2B cytochrome activity but also to increasing activity of glutathione transferase activity (GST). Actually, addition of etacrynic acid, which is an inhibitor of GST, in cells medium simultaneously to phenobarbital, considerably reduced DNA-adducts formation. Metabolites of OTA have been analyzed by HPLC. Two of them are similarly formed in cells culture and after microsomes incubation, and seem to be correlated with DNA-adduct. Interestingly, etacrynic acid stimulated OTB (dechlorinated OTA) and Otα (OTA without phenylalanine) formation. These two metabolites are less toxic than the parent compound.