1: Chem Res Toxicol. 1998 Sep;11(9):1105-11.

Related Articles, Links

The equine estrogen metabolite 4-hydroxyequilenin causes DNA single-strand breaks and oxidation of DNA bases in vitro.

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Premarin (Wyeth-Ayerst) is the estrogen replacement treatment of choice and continues to be one of the most widely dispensed prescriptions in North America. In addition to endogenous estrogens, Premarin contains unsaturated equine estrogens, including equilenin [1,3,5(10),6,8-estrapentaen-3-ol-17-one]. In previous work, we showed that the equilenin metabolite 4-hydroxyequilenin (4-OHEN) can be autoxidized to 4-OHEN-o-quinone which readily entered into a redox couple with the semiquinone radical catalyzed by NAD(P)H, P450 reductase, or quinone reductase, resulting in generation of reactive oxygen species [Shen, L., Pisha, E., Huang, Z., Pezzuto, J. M., Krol, E., Alam, Z., van Breemen, R. B., and Bolton, J. L. (1997) Carcinogenesis 18, 1093-1101]. As oxidative damage to DNA by reactive oxygen species generated by redox active compounds has been proposed to lead to tumor formation, we investigated whether 4-OHEN could cause DNA damage. We treated lambda phage DNA with 4-OHEN and found that extensive single-strand breaks could be obtained with increasing concentrations of 4-OHEN as well as increasing incubation times. If scavengers of reactive oxygen species are included in the incubations, DNA could be completely protected from 4-OHEN-mediated damage. In contrast, NADH and CuCl2 enhanced the ability of 4-OHEN to cause DNA single-strand breaks presumably due to redox cycling between 4-OHEN and the semiquinone radical generating hydrogen peroxide and ultimately copper peroxide complexes. We also confirmed that 4-OHEN could oxidize DNA bases since hydrolysis of 4-OHEN-treated calf thymus DNA and HPLC separation with electrospray MS detection revealed oxidized deoxynucleosides, including 8-oxodeoxyguanosine and 8-oxodeoxyadenosine. Our data suggest that DNA single-strand breaks and oxidation of DNA bases by 4-OHEN could contribute to the carcinogenic mechanism(s) of equine estrogens.