Grant 1290

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Inhibition of Chemical (Lung) Carcinogenesis by Naphthoquinone Derivatives: In Vivo and In Vitro Studies.

Feeding inhibitors of polycyclic aromatic hydrocarbon (PAH) metabolism resulted in an approximately 50% inhibition of pulmonary adenoma formation by 7,12-dimethylbenzanthracene (DMBA) in A/J mice. Two inhibitors were used, menadione glutathione adduct (MGA, thiodione), which inhibits both enzymatic 6-hydroxylation of benzo(a)pyrene (BP) and the aryl hydrocarbon (AHH) system and benzylimidazol (BL) which is a preferential inhibitor of the more common ring hydroxylating microsomal P-450 (AHH) system but without effect on 6-hydroxylation. The relevance of the unique enzymatic 6-hydroxylation to pulmonary carcinogenesis is quite unknown and needs further clarification: (a) the 6-hydroxylase is essentially a lung enzyme, (b) during the nonenzymatic oxidation of the 6-hydroxy compound to diones, free radicals are generated, and (c) the generation of free radicals results in the binding of the 6-hydroxy-compound to cellular constituents including DNA; indeed tissue culture cell transformation has been accomplished by this derivative.

Therefore, this project explores an alternate mechanism to the study of AHH, an enzyme system which now appears unlikely to be the sole determinant of lung tumorigenesis, although it may be the most important. The investigators' studies concern the inhibition of chemically induced lung carcinogenesis in vivo using a variety of inbred strains of mice.

The researchers are also going to perform in vitro studies dealing with the 6-hydroxylase system and the inhibition of chemical carcinogenesis by naphthoquinone derivatives.

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