Eur J Cancer Clin Oncol, Vol. 17, No. 8, pp. 935–945, 1981.
Printed in Great Britain.

0014-2964/81/080935-11$02.00/0
Pergamon Press Ltd.

Abstracts of the Meeting of the Swiss Society for Oncology

SIGNIFICANCE OF VARIOUS ENZYMES IN THE CONTROL OF REACTIVE METABOLITES DERIVED FROM AROMATIC CARCINOGENS

F. Oesch, Section on Biochemical Pharmacology, Institute of Pharmacology, University of Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, FRG

The formation or disposition of reactive metabolites is controlled by many different enzymes. Especially well studied is the important group of enzymes responsible for the control of reactive epoxides. Many natural as well as man-made foreign compounds, including pharmaceuticals, possess olefinic or aromatic double bonds. Such compounds can be transformed to epoxides by microsomal monooxygenases present in very many mammalian organs. By virtue of their electrophilic reactivity such epoxides may spontaneously react with nucleophilic centers in the cell and thus covalently bind to DNA, RNA and protein. Such alterations of critical cellular macromolecules may disturb the normal biochemistry of the cell and lead to cytotoxic, allergenic, mutagenic and/or carcinogenic effects. Whether such effects will be manifested depends on one hand on the chemical reactivity as well as other properties (geometry, lipophilicity) of the epoxide in question. On the other hand, enzymes controlling the concentration of such epoxides are another important contributing factor.
Several microsomal monooxygenases exist differing in activity and substrate specificity. With respect to large substrates, some monooxygenases preferentially attack at one specific site different from that attacked by others. Some of these pathways lead to reactive products, others are detoxification pathways. Moreover, enzymes metabolizing such epoxides represent a further determining factor. These enzymes include epoxide hydrolase and glutathione S-transferases. These enzymes do not play a pure inactivating role but can in some cases also act as coactivating enzymes. Enzymes involved in biosynthesis and further metabolism of epoxides differ in quantity and sometimes also in substrate specificity between organs, developmental stages, sexes and animal species. They therefore represent one important contributing factor to differences in susceptibilities.

THE EFFECT OF THE PANCREATIC CARCINOGEN, N-NITROSO-2- METHOXY-2,6, - DIMETHYLMORPHOLINE ON ENDOCRINE AND EXOCRINE PANCREAS OF SYRIAN HAMSTERS

P. Pour, M.D. The Eppley Institute for Research in Cancer, University of Nebraska, Medical Center, Omaha, Nebraska 68105, and Preclinical Research, Toxicological Department, Sandoz AG, CH-4133 Pratteln 4, Switzerland

Data has shown that all the nitrosames with a pancreatic carcinogenic effect on Syrian hamsters have a common metabolite, N-nitroso (-2-hydroxypropyl) (2-oxopropyl) amine (HPOP). It has been suggested that the cyclic structure of this metabolite, resembling the pyranose form of the hexose-sugars and the sugar moeity of the Streptozocin (SZ), may be responsible to its affinity for the pancreas. To further investigate this hypothesis, we examined the effect of N-nitroso-2-methoxy-2,6-dimethyl nitrosomorpholine (MeNDNM), which represents a fixed cyclic form of HPOP by methylation of the 2-hydroxy group. By determining the LD_{50} of MeNDNM, we found that a single dose of about 2,000 mg/kg b.w. of this compound exhibited, in analogy to the effect of SZ, selective necrosis of the B-cells of pancreatic islets within 3 days, killing the hamsters in diabetic coma. In surviving hamsters, and again similar to the situation after SZ application, the islets showed signs of regeneration, which was completed within approximately 60-72 hours. Some 40 weeks later, however, and in contrast to the effect of SZ, almost all treated hamsters develop pancreatic ductular and mixed ductular-insular tumors. On the other hand, weekly application of MeNDNM in subdiabetogenic doses induced equivalent tumors in all treated hamsters, but did not appear to affect islet cells on a light microscopic basis. These results, ultimately pointing to the mutual response of endocrine and exocrine pancreatic tissue to this compound, thus indicate the importance of the carcinogen's cyclic structure. Possible mechanisms involved in pancreatotropic effect of this class of chemical carcinogens will be discussed.