THE ROLE OF FREE RADICALS IN THE PATHOGENESIS OF MEDICAL ILLNESSES: STUDIES WITH ALCOHOL-DNA DAMAGE AND MYOCARDIAL ISCHEMIA

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The generation of superoxide and related free radicals have been implicated in the pathogenesis of a variety of diseases. The mobilization of catalytic iron and free radical generation due to ethanol metabolism have been suggested as mechanisms of alcohol-induced liver injury as well as of the increased risk of cancer observed in alcoholics. Cleavage of double stranded DNA is produced by both free radicals as well as by catalytic iron. The effects of ethanol metabolism on DNA cleavage were therefore studied in vitro as well as in vivo in isolated hepatocytes. Intactness of double standard DNA was studied by measuring ethidium bromide fluorescence after DNA electrophoresis. In vitro, the metabolism of acetaldehyde by aldehyde oxidase caused cleavage of Lambda phage DNA. Cleavage was inhibited by both superoxide dismutase and desferrioxamine indicating the role of superoxide radicals and catalytic iron respectively. Studies with HIND III digests of the Lambda phage indicate a lack of specificity in the breaks with respect to nucleotide sequences. Addition of EDTA greatly enhanced cleavage. In vivo, ethanol metabolism caused minimal breakage in hepatocyte DNA and addition of acetaldehyde (100uM) markedly enhanced cleavage; all cleavage was inhibited by desferrioxamine. The metabolism of ethanol to acetaldehyde and the further metabolism of acetaldehyde by aldehyde oxidase generates free radicals and mobilizes iron; three may contribute to alcohol-induced injury and carcinogenesis.

Free radical injury has also been demonstrated in reperfusion injury in the heart having implication for coronary artery disease and cardiac transplants; free radical scavengers and blockers of enzymes involved in free radical generation may prevent such injury. The postischemic cardioplegic heart transplant model in the dog is being used to study this question. Ventricular performance shortly after and at the moment of reperfusion is employed as a sensitive method of measuring intrinsic myocardial function and thus reperfusion injury. Additions of superoxide dismutase, catalase, and allopurinol to perfusates are presently being evaluated. Prevention of reperfusion injury by such treatments may enhance survival after fibrinolytic therapy following myocardial infarction as well as after cardiac transplantation.