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Liver protection by Liv.52 in lipid peroxidation

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In the July 24, 1982 issue of the prestigious journal, "The Lancet," Drs. K.O. Lewis and A. Paton discuss in their hypothesis whether superoxide could cause cirrhosis:

Peroxidation of unsaturated lipid in cellular membranes by oxygen free radicals is increasingly considered to be the cause of structural damage in cells, and studies of lipid-peroxide formation in alcoholic liver disease have been carried out. There is now growing reason to believe that oxygen free-radical reactions could mediate the more permanent features of advanced alcoholic liver disease.

Animal studies with inhibitors of the enzymes alcohol dehydrogenase (pyrazole) and aldehyde dehydrogenase (disulfiram) have clearly implicated the first metabolite of ethanol, acetaldehyde, as the main mediator of hepatic injury. Subsequent work has shown that acetaldehyde is toxic *in vivo*, forming pharmacologically active condensation products, inhibiting protein synthesis and secretion, and depressing liver glutathione levels. There can be little doubt that acetaldehyde leads to tissue damage, but attempts to relate blood levels of acetaldehyde to the development of cirrhosis have not been entirely successful.

The question therefore remains as to what causes the necrosis and fibrosis which constitute cirrhosis, and why cirrhosis develops in only some individuals who drink heavily. Presumably they must differ from normal subjects in having not only slightly higher blood levels of acetaldehyde but also a defect in an enzyme associated with acetaldehyde metabolism.

Molecular oxygen has central role in many biological free radical reactions, and its potential toxicity is well recognised in pathological associations ranging from retrolental fibroplasia in newborn infants to rapid pulmonary fibrosis in adults. The mechanisms by which the superoxide radical is generated in biological tissues have now been worked out and the cytotoxic nature of this free radical demonstrated. Such is its destructive potential that hydrogen peroxide is regarded as harmless in comparison. Catalase and peroxidase which remove peroxide as well-recognised enzymes, but superoxide dismutase, which plays an indispensable part in removing superoxide generated *in vivo* thereby preventing rancidity of living cells, is less familiar. It was formerly known as hepatocuprein, the liver copper-storage protein, and it is interesting that caeruloplasmin is now thought to remove free radicals from extracellular fluids in the same way as superoxide dismutase does intracellulary.

In these writers' view superoxide is involved in a variety of destructive reactions in the body by the process of lipoperoxidation. This toxic effect is manifested as a diminution of the anti-oxidant levels in the cells. The ability of various anti-oxidants to ameliorate or prevent steatosis of the liver is attributed to their ability to prevent lipoperoxidation. Agents such as tocopherols, M.N.'-diphenyl-p-phenylene diamine have been tried but found to be only partially successful. This may be related to problems involved with their solubility and absorption.

In a controlled experimental study, the protective value of Liv.52 was studied using the model of carbon tetrachloride induced liver damage in rats. Anti-oxidant levels in the liver were assessed by

measuring tocopherols. The destructive effect of superoxide was estimated by measuring the rate of lipoperoxidation. The detailed results have been published elsewhere[1]. It was demonstrated that administration of Liv.52 leads to an increase in tocopherols and reduces the production of lipid peroxides as compared to normal controls, whereas exposure to CCl_4 leads to reduction in tocopherols and increase in lipid peroxidation. However, these changes were of far lesser magnitude in the group given Liv.52 prior to exposure to CCl_4. Thus, it seems probable that Liv.52 led to increased tocopherols which protect against CCl_4 induced liver damage, as shown by reduced lipid peroxide formation.

One must hasten to add that the study pertained to CCl_4-induced liver damage in rats and there may conceivably be differences between this model and the alcoholic human subject.

Liv.52 has been and is in wide clinical use in our country for the treatment of liver disease. Efforts are being made to elucidate the mechanism by which it protects the liver. Clinical trials have established its efficacy in alcoholic liver disease and chronic active hepatitis.

REFERENCE

1. Saxena, A. and Garg, N.K., "Effect of Liv.52 on membrane lipids in carbon tetrachloride-induced hepatotoxicity in rats." *Indian Journal of Experimental Biology* (1981): 19, 859.