[*Probe* (1983): (XXII), 3, 164-166]

The Mechanism of Cellular Damage in Alcoholic Liver Disease and the Protective Action of Liv.52

Soman, R.N., *M.D.,* Bhatia General Hospital, Tradeo, Bombay, India.

The spectrum of alcoholic liver disease ranges from fatty liver to alcoholic hepatitis and cirrhosis. In spite of extensive work on the subject, it is not clearly known as to what causes hepatocellular necrosis and fibrosis, which ultimately lead to cirrhosis. Why does cirrhosis develop only in some individual who drink heavily (and not in others) also remains an enigma.

Animal studies have shown that acetaldehyde, the first metabolite of ethanol, is the main mediator of hepatic injury. Acetaldehyde is undoubtedly toxic, producing condensation products, inhibiting protein synthesis and secretion and depressing hepatic glutathione levels[1]. However, attempts to relate blood levels of acetaldehyde to the development of cirrhosis have not been entirely successful. Large quantities of acetaldehyde can be processed in the hepatocyte with apparently little damage in the short term. Also the high blood levels of acetaldehyde after disulfiram treatment appear to produce no untoward sequelae. Thus, it is clear that acetaldehyde is not the only agent which produces hepatocellular damage.

The most important enzyme in the metabolic disposal of acetaldehyde is acetaldehyde dehydrogenase. This converts acetaldehyde into harmless acetate. In chronic alcoholics, this enzyme is reduced[2] and another enzyme, xanthine oxidase becomes important. While it oxidises acetaldehyde to acetate, it promotes the reduction of molecular oxygen to the oxygen free-radical, superoxide[3]. The destructive potential of this free radical is well known. It attacks polyunsaturated lipids of biological cell membranes (lipid peroxidation) leading to the loss of membrane integrity and destruction of cells.

Xanthine oxidase exists in healthy cells as xanthine dehydrogenase. Under adverse metabolic conditions, the dehydrogenase is converted to xanthine oxidase[4], which has the potential to generate superoxide. Superoxide is normally removed from the cells by superoxide dismutase and from the extracellular fluid by ceruloplasmin. Thus increased conversion of xanthine dehydrogenase to oxidase and reduced activity of hepatic superoxide dismutase may be the reason for continuing liver damage in those individuals who drink heavily.

Free radical superoxide attacks are involved in the variety of destructive reactions in the body e.g. intracellular microbicidal activity of phagocytes, joint damage in rheumatoid arthritis, tissue damage in rheumatoid arthritis, tissue damage due to iron-loading in thalssemics, retro-lental fibroplasia in oxygen toxicity of new born and pulmonary fibrosis of paraquat poisoning.

This hypothesis of hepatocellular damage brought about by superoxide may be tested by examining the conversion of xanthine dehydrogenase to oxidase in the liver biopsy. The rate of production of superoxide in the presence of acetaldehyde could be measured. The extent of lipid peroxidation in subjects who drink heavily may be assessed by studying exhaled saturated short-chain hydrocarbon gases. The protective value, if any, of disulfiram, which inhibits xanthine oxidase, could be assessed. Copper stimulates the conversion to xanthine oxidase and penicillamine, by chelating copper might have a protective influence against free radical production.

DiLuzio *et al.,* have shown that hepatic steatosis from acute alcohol ingestion is due to free radical attack on the lipoprotein membranes of mitochondria[5]. This toxic effect is envisaged as a diminution of the antioxidant levels in the cells. This ability of a variety of antioxidants (coenzyme

Q, α-tocopherol and N, N-diphenyl p-phenylenediamine) to ameliorate or prevent steatosis is attributed to their ability to prevent lipoperoxidation. However, these agents have been only partially successful, probably due to problems involved with their solubility and absorption.

A step has been taken by Alok Saxena and Garg towards testing this hypothesis and elucidating the mechanism of protection by Liv.52 against experimental hepatic injury by carbon tetrachloride. A study[6,7] was carried out on four groups of rats:

Group 1: Normal controls
Group 2: Normal rats injected with carbon tetrachloride (CCl_4)
Group 3: Normal rats treated with Liv.52.
Group 4: Treated with Liv.52 and later injected with carbon tetrachloride (CCl_4).

Antioxidant levels in the liver were assessed measuring tocopherols. The rate of lipid peroxidation was also measured. Their findings revealed that:

- Group 3 on Liv.52 showed less lipid peroxide formation as compared to Group 1 (Normal controls)

- After treatment with CCl_4, formation of lipid peroxides *in vitro* increased in Group 2 and Group 4. But the increase was much less in Group 4 (those given Liv.52 prior to exposure) as compared to that in Group 2.

- Feeding Liv.52 (Group 3) led to an increase to tocopherol levels as compared to Group 1.

- Exposure to CCl_4 led to a decrease in tocopherols. But the percentage reduction was much less between Group 3 and Group 4 (given Liv.52) than that between Group 2 and Group 1 (not given Liv.52).

Thus, exposure to a wide variety of hepatotoxic agents such as CCl_4 and alcohol leads to a fall in tocopherol (anti-oxidant) levels and there is an increase in lipid peroxide formation. Liv.52 treatment leads to increased levels of tocopherols. The formation of lipid peroxides is also less as compared to Control animals who are not given Liv.52. This could be the mechanism of the protective action of Liv.52 against a variety of hepatotoxins.

REFERENCES

1. Lieber, C.S., 'Alcohol protein metabolism and liver injury'. *Gastroenterology* (1980): 79, 373-90.

2. Jenkins, W.J. and Peters, T.J., 'Selectively reduced hepatic acetaldehyde dehydrogenase in alcoholics'. *Lancet* (1980): i, 628-29.

3. Kellog III, E.W. and Fridovich, I., 'Superoxide, hydrogen peroxide and singlet oxygen in lipid peroxidation by a xanthine oxidase system'. *J. Biol. Chem.* (1975): 250, 8812-17.

4. Lewis, K.O. and Paton, A., 'Could superoxide cause cirrhosis?' *Lancet* (1982): ii, 188-89.

5. Di Luzio, N.R., 'A mechanism of the acute ethanol-induced fatty liver and modification of liver injury by antioxidants.' *Lab. Invest.* (1966): 15, 50-63.

6. Saxena, A. and Garg, N.K., 'Effect of Liv.52 on membrane lipids in carbon tetrachloride-induced hepatotoxicity in rats.' *Ind. J. Exptl. Biol.* (1981): 19(9), 859.

7. Saxena, A., 'Chemical studies on membrane changes in hepatic disorders'. Ph.D. thesis submitted to Kanpur University, 1981.