Peroxisome proliferation and hepatotoxicity in rodents

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A number of therapeutic agents (principally hypolipidaemic compounds) and industrial chemicals have been shown, both biochemically and ultrastructurally, to increase the number of peroxisomes in the liver of rodents, chiefly rats and mice. Other species, including man, have been less intensively studied than rodents but the information available suggests that they appear to be less susceptible to the production of an increase in hepatic peroxisomes by these agents (Cohen & Grasso, 1981).

Short-term studies in rodents

A dose-related hepatomegaly is consistently reported in toxicological studies on peroxisome proliferators (Lake et al., 1975). Although histologically these livers appear normal, recent studies suggest that a centrilobular loss of glycogen and perportal fatty change occur (Price, 1984). These changes are indicative of a mild toxic effect on the liver and do not occur at dose levels which do not induce hepatomegaly (Reddy & Lalwani, 1983).

Medium- and long-term studies

These ‘medium-term’ changes consist of an accumulation of a pigment which is normally regarded as a residue of lysosomal activity. Histochemically the pigment gave a reaction which fulfils the criteria of lipofuscin; it was positive by the PAS and Schmorl’s techniques and was autofluorescent (Reddy & Lalwani, 1983). Lipofuscin is now regarded as the polymerization product of lipid peroxidation within the cell (Hartroft & Porta, 1972). Its appearance in long-term studies lends considerable support to the hypothesis that generation of reactive oxygen species as well as hydrogen peroxide is taking place within the hepatocyte.

The long-term effects of peroxisome proliferators are undoubtedly the most important and have given rise to considerable concern regarding their implications for man. All the peroxisome proliferators that have been studied so far have induced a dose-related increase in hepatocellular carcinoma (Reddy & Lalwani, 1983). The tumours are usually well differentiated and non-invasive but they metastasize readily to the lung.

The peroxisome proliferators that have been studied so far are all non-mutagenic and there is no evidence that they are metabolized to reactive intermediates (Cohen & Grasso, 1981). It is thus unlikely that the cancers arise from the direct action of the compounds themselves or their metabolites.

According to current cancer theory, neoplasia results from a heritable change in a somatic cell which confers on the cell the ability of uncontrolled proliferation. Although the causes of many such mutagenic events are unknown there is little doubt that they may be produced by reactive chemicals which interact with the DNA. Peroxides and hydroperoxides are known to be mutagenic (Yamaguchi & Yamashita, 1980). Hydrogen peroxide, a member of this group, is known to be mutagenic and to have produced tumours in the duodenum of rats on prolonged administration (Steit et al., 1982; Ito et al., 1984). Based on these considerations Reddy suggested that the probable cause of cancer is the hydrogen peroxide produced within the hepatocyte (Reddy & Lalwani, 1983).

Despite its plausibility this hypothesis is as yet unsupported by evidence of DNA damage in the liver of rats given high doses of one of this group of compounds. Furthermore, there is no adequate proof that the natural defences within the cell, for example glutathione levels, are depleted to an extent that would lead one to suspect that they are inadequate for affording an adequate degree of protection to the cell organelles including the nucleus.

Until more evidence of this sort is accumulated it might be of some merit to look for an explanation, at the cellular level, for the development of the hepatic tumours at the cellular level. Experiments with di-(2-ethylhexyl)phthalate and fenofibrate have shown that the liver growth which occurs early in the experiment is the result of hepatocellular hyperplasia (Price, 1984). The same mechanism accounts for liver growth by a number of other chemical agents such as phenobarbitone, chlorinated hydrocarbons and a series of other compounds which differ markedly in chemical structure but which also produce hepatocellular carcinoma
Careful studies of the liver cell changes produced by some of these compounds over several months reveal that there is a gradual and persistent increase in nuclear DNA leading to mononuclear, or less commonly, binuclear, polyploid hepatocytes as well as an increase in mitotic activity (Schulte-Hermann, 1984). According to this view chemically induced liver enlargement involves a persistent hyperplasia of the hepatocytes.

If this is the case, then the hyperplastic process could account for the development of tumours since persistent hyperplasia in other tissues, notably the subcutaneous tissue and the urothelium, leads to the formation of malignant tumours (Grasso, 1976).

Significance for man

Knowledge of the effects of peroxisome proliferators in man is derived from the administration of therapeutic doses of hypolipidaemic agents. On a mg/kg basis these doses are usually equivalent to the lower dose-range administered to rodents in toxicity studies. At this dose-range, many hypolipidaemic agents induce a marginal increase in peroxisomes compared with higher levels at which tumours of the liver appear. So far there is little convincing evidence that, at therapeutic doses, the hypolipidaemic agents induce an increase in peroxisomes in human liver (Hanefeld et al., 1983). Furthermore, no lipofuscin granules have been reported (Cohen & Grasso, 1981).

These results suggest that any biochemical disturbances produced in man by peroxisome proliferators are unlikely to produce tumours of the liver.