10 Peroxisome Proliferation and Hepatocarcinogenesis

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10.1 Introduction

Peroxisomes (or “microbodies”) are single membrane-limited cytoplasmic organelles present in the cells of animals, plants, fungi and protozoa. They are characterised by their content of catalase and a number of hydrogen peroxide-generating oxidase enzymes (Cohen and Grasso 1981; Reddy and Lalwani 1983). Like mitochondria, peroxisomes contain a complete fatty acid β-oxidation cycle (Lazarow and DeDuve 1976). In rat liver peroxisomes are normally spherical or oval in shape, approximately 0.5 μm in diameter and contain a finely granular matrix with a crystalline nucleoid core (Cohen and Grasso 1981).
Table 1. Some characteristics of peroxisome proliferation in rat and mouse liver

<table>
<thead>
<tr>
<th>Liver weight</th>
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<td>1. Liver enlargement due to both hepatocyte hyperplasia and hypertrophy</td>
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<tr>
<td>2. Increased replicative DNA synthesis (may be either transient or sustained)⁹</td>
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**Morphological changes**

1. Increased number and size of peroxisomes
2. Many “coreless” peroxisomes observed⁶
3. Increased smooth endoplasmic reticulum
4. Lysosomal changes and lipofuscin deposition⁹
5. Liver nodules and hepatocellular carcinoma⁹

**Biochemical changes**

1. Selective induction of peroxisomal enzymes (e.g. marked induction of peroxisomal fatty acid β-oxidation enzymes but only a small increase in catalase activity)
2. Induction of microsomal fatty acid (ω-1)- and particularly ω-oxidising enzyme activities (due to induction of cytochrome P-450 isoenzymes in the CYP4A subfamily)
3. Induction of carnitine acetyltransferase activity
4. Increase in an 80-kDa molecular weight polypeptide (due to induction of component enzymes of the peroxisomal fatty acid β-oxidation cycle)
5. Induction of cytosolic epoxide hydrolase
6. Inhibition of GSH peroxidase, GSH S-transferase and superoxide dismutase activities

For further details see Bentley et al. (1993); Cohen and Grasso (1981); Lake (1993); Lock et al. (1989); Moody et al. (1991); Reddy and Lalwani (1983) and Stott (1988).

GSH, glutathione.

⁹Depends on test compound, dose and duration of treatment.

⁶Normal rat and mouse liver peroxisomes contain a crystalline nucleoid core consisting of insolubilised urate oxidase.

10.2 Characteristics of Hepatic Peroxisome Proliferation in Rodents

A wide variety of chemicals have been shown to produce liver enlargement, peroxisome proliferation and induction of peroxisomal and microsomal fatty acid-oxidising enzyme activities in rodents (Bentley et al. 1993; Cohen and Grasso 1981; Lake and Lewis 1993; Lock et al. 1989; Moody et al. 1991; Reddy and Lalwani 1983; Stott 1988). Some characteristics of peroxisome proliferation in rat and mouse hepatocytes are shown in Table 1. Liver enlargement is due to both hyperplasia and hypertrophy, and