EFFECTS OF CHRONIC THIOACETAMIDE ADMINISTRATION ON LIVER DRUG METABOLIZING
SYSTEM AND ON THE DEVELOPMENT OF HEPATOCELLULAR FOCI, NODULES AND TUMORS

Pier G. Gervasi, Vincenzo Longo, Mino Marzano, Michela Saviozzi and Gino Malvaldi

Istituto di Mutagenesi e Differenzimento, CNR
Via Svezia 10, 56100 Pisa, Italy. Istituto di Patologia Generale dell'Università, Via Roma, 56100 Pisa, Italy

Preneoplastic hepatocyte nodules (HN) generated in the rat liver by different experimental protocols display a common pattern in the xenobiotic metabolism, namely a decrease of the phase I components and an increase of the phase II ones. If initiated hepatocytes share with HN these metabolic properties (which explain the observed increase of HN resistance to many liver toxins), then any mild but prolonged liver injury by chemicals needing bioactivation should cause, in addition to liver cirrhosis, also the appearance of HN and tumors, providing the liver has been exposed to initiating stimuli.

To verify the hypothesis, diethylnitrosamine (DEN)-initiated as well as uninitiated rats (male Sprague Dawley) were administered thioacetamide (TAA) at low dose (2 mg/day/100 g b.w.) for 6 months. TAA is a compound devoid of mutagenic activity but it is well known to depress cytochrome P-450-dependent drug metabolism when acutely administered in vivo. During 6 months both HN incidence and changes in the drug metabolizing system (DMS) were followed at monthly intervals.

In the uninitiated rats a regenerative hyperplastic liver cirrhosis slowly developed upon TAA chronic administration. A few gamma-glutamyl-transpeptidase-positive, PAS-positive hepatocyte focal lesions were seen from the 3rd month onward, their cumulative volume never exceeding 0.1% of the liver volume. By contrast in the DEN-initiated TAA-treated rats the liver was macronodular because of the appearance and growth of many HN (Fig. 1). At the end of the TAA cycle over 40% of the liver parenchyma was constituted by HN and enzyme-altered hepatocyte foci. 3 rats out of 7 harboured an hepatoma.

During TAA administration both uninitiated and DEN-initiated rats underwent a progressive decrease of the cytochrome P-450 liver content as well as of the activity of aminopyrine N-demethylase, ethoxycoumarin O-deethylase and ethoxyresorufin O-deethylase. Six months later the values of these parameters in the liver of rats from both groups were I) decreased (up to 10-30% with respect to those found in normal, age-matched controls) II) superimposable to those observed in HN which in turn were similar to those reported in HN generated by other carcinogenetic protocols. On the contrary, the components of the phase II of DMS were markedly enhanced. In particular, the activities of microsomal epoxide hydrase and UDP-glucuronyl transferase as well as...
as cytosolic glutathione-S-transferase were increased over the controls in both experimental groups and NH (about 2-3 times), whereas the increase of benzaldehyde dehydrogenase activity (about ten times compared to the control value) was evident only in the liver of DEN-initiated/TAA treated rats and in HN.

To assess the initiating activity of TAA the compound was given in a single high dose (100-250 mg/Kg b.w.) to 1-week old, 4-week old as well as to young partially hepatectomized rats of both sexes, since high mitotic activity of the hepatocytes enhances the initiation process. This TAA treatment was followed by a standard promoting protocol (2-acetylaminofluorene in the diet plus a single carbon tetrachloride dose) (2-AAF/CC1₄).

Also in these experiments the number and the area of the hepatocyte foci displaying gamma-glutamyltranspeptidase activity and starvation resistant glycogen storage were used as end-point of the assay.

The overall findings indicated that the initiating activity of TAA was quite low, if any, because no differences were seen in the number of hepatocyte foci between TAA initiated, 2-AAF/CC1₄ promoted animals and their controls in the 3 experimental situations investigated.

In conclusion, chronic administration of TAA at low dose showed a weak, if any initial ability on liver carcinogenesis, but provided strong promoting stimuli for already initiated hepatocytes. In rather sharp contrast with other liver promoters and inducers of cytochrome P-450 (phenobarbital et al.⁴), the DMS pattern of the liver parenchyma of TAA treated rats was similar to that displayed by HN.

ACKNOWLEDGEMENTS

Supported by CNR, PF "Oncologia" and M.P.I. 40% and 60% funds.