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SHORT COMMUNICATIONS

Protective effect of phenobarbital and SKF 525a on the acute ethanol-induced fatty liver

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STUDIES by Di Luzio[1–4] have recently demonstrated that the administration of an antioxidant is capable of preventing the ethanol-induced fatty liver. Since an analogous observation had been previously made in the case of CCl_4,[5, 6] the hypothesis has been suggested that the ethahol and CCl_4-induced liver injuries have, in part, common mechanisms, which involve the peroxidative decomposition of structural lipids, particularly at the level of the endoplasmic reticulum.[2–4, 7]

The purpose of our work was to further investigate the similarities between the mechanisms of action of the two poisons, namely CCl_4 and ethanol, on the liver. In particular, the role of the microsomal drug-metabolizing enzymes has been considered. The importance of the activity of these enzymes in the CCl_4-induced liver injury has been previously emphasized. In fact, in some experiments where the activity was reduced, the animals proved resistant to the poison[8–10]; by contrast, the increase of the enzyme activity leads to increased sensitivity to CCl_4.[8]

In the present research we have studied whether the experimental modification of microsomal drug-metabolizing enzyme activity influences the acute ethanol-induced fatty liver.

Animals were first treated with either phenobarbital, which is known to be an inducer of drug-metabolizing enzymes[11–13], or with SKF 525 A, which is an inhibitor,[14] and then poisoned with ethanol.

The level of hepatic triglyceride in the various experimental groups is shown in Table 1. Both phenobarbital and SKF 525 A have no detectable effect on the controls, but afford a clear protection in the ethanol-treated animals.

TABLE 1. INFLUENCE OF PHENOBARBITAL AND SKF 525 A ON THE ACUTE ETHANOL-INDUCED FATTY LIVER

Treatment		No. in group	liver tryglyceride (mg/g of liver, fresh wt.)
intraperitoneal	oral		
Saline	Glucose	5	4·05 ± 1·54
SKF 525 A	Glucose	5	4·16 ± 2·09
Phenobarbital	Glucose	5	5·88 ± 1·21
Saline	Ethanol	4	18·00 ± 1·38 (a)
SKF 525 A	Ethanol	5	10·80 ± 1·57 (b) (d)
Phenobarbital	Ethanol	4	11·41 ± 2·08 (c) (e)

Values given are the means ± S.E.
a = $P < 0.001$; b = $P = 0.05$; c = $P < 0.01$ with respect to the controls;
d = $P < 0.01$; e = $P < 0.02$ with respect to ethanol-treated rats.

Male Sprague–Dawley rats weighing 160–180 g were used. Phenobarbital (80 mg/Kg) was dissolved in saline and administered i.p. 50·26 and 2 hr prior to oral intubation with either glucose or ethanol, the latter in the amount of 6 g/kg. SKF was dissolved in saline and administered, at a single dose of 80 mg/kg, 2 hr prior to oral intubation. All animals were starved 12 hr prior to oral intubation and killed by decapitation 16 hr after intubation.

Liver was rapidly removed and lipids extracted according to Folch *et al.*[15] Extracted lipids were plated on Kieselgel G. Merck plates, prepared according to Stahl[16]; chromatograms were developed with isopropylic ether and chloroform (20:80); triglycerides were evaluated by the van Handel and Zilversmit method.[17]

Taking into account that the two drugs, phenobarbital and SKF 525 A, have an opposite action on the drug-metabolizing enzyme activity, the assumption that these enzymes have a role in the genesis of the ethanol-induced fatty liver seems untenable.

However, an explanation of our results can be suggested. Both phenobarbital (18) and SKF 525 A[19] are known to bound to liver microsomes, thus inhibiting the activity of the enzymes which provoke the peroxidation of microsomal structural lipids.

Therefore, the protection, that we observed, may be due to a partial inhibition of the pro-oxidative effect of ethanol on the hepatic microsomes. From this point of view, the protective mechanism of the two drugs seems to be similar to that of antioxidants.

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The binding of some phenothiazines to human serum *in vitro*

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THE BINDING of drugs to serum protein can modify their tissue penetration and thus influence their concentrations at the receptor level. It has been postulated[1] that chlorpromazine is bound to serum proteins to a great extent. Nevertheless, chlorpromazine injected i.v. into rabbits rapidly disappears from the circulation, and the drug left in the blood is found mainly in the blood cells.[2] Because differences in the uptake of different phenothiazines by thrombocytes and erythrocytes have been