

EFFECT OF OROTIC ACID, CALCIUM PANGAMATE, AND LIPAMIDE
ON ULTRASTRUCTURAL CHANGES IN HEPATOCYTES IN TOXIC
HEPATITIS

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Orotic acid, calcium pangamate, and lipamide are used in clinical practice for the treatment of inflammatory diseases of the liver and, in particular, of acute and chronic forms of hepatitis [1-5, 8].

The writer showed previously that administration of orotic acid, in combination with calcium pangamate, and also with lipamide, in cases of acute liver dystrophy leads to the more rapid and complete recovery of the intensity of bile secretion, of the synthesis of cholates and their secretion with the bile, the formation and secretion of bilirubin, and cholesterol excretion [6, 7].

The object of the present investigation was to study the effect of orotic acid and calcium pangamate when given separately and in combination, and also the effect of lipamide on the degree of ultrastructural reorganization of the hepatocytes in toxic hepatitis caused by carbon tetrachloride.

EXPERIMENTAL METHOD

Experiments were carried out on 50 male albino rats weighing 140-170 g. Acute toxic hepatitis was induced in all animals by subcutaneous injection of a 50% oily solution of CCl_4 in a dose of 0.4 ml/100 g body weight daily for 4 days. Ten rats (series I) were untreated. The animals of series II, III, IV, and V (10 rats in each series) received orotic acid (4 mg/100 g body weight) alone, calcium pangamate (7 mg/100 g body weight) alone, orotic acid and calcium pangamate (in the same doses), or lipamide (0.5 mg/100 g body weight) respectively, internally, daily for 7-14 days. Treatment began after the first day of poisoning, and the substances were administered through a tube. The submicroscopic investigation of liver tissue from all the animals was carried out in the usual way on the EVM-100 LM electron microscope on the 7th and 14th days after the beginning of poisoning.

EXPERIMENTAL RESULTS

Acute toxic hepatitis induced by CCl_4 is characterized by considerable translucency of the matrix of the mitochondria, complete reduction of the cristae, loosening and unwinding of the membranes of these organelles, a reduction in the content of granular material in the cell cytoplasm, and the appearance of lysosome-like bodies. Local widening of the perinuclear space and a decrease in size of the nuclear pores are observed in the hepatocyte nuclei. Osmiophilic lipid droplets, sometimes occupying a considerable part of the cytoplasm of the hepatocytes, are frequently found (Fig. 1). Single submicrovilli can be seen in the dilated lumen of the bile capillaries, but the desmosomes are not clearly distinguishable. The disturbances described were more marked on the 7th day of the experiment.

In animals receiving orotic acid, just as in the untreated rats, hepatocytes in which many mitochondria had reduced cristae and a translucent matrix appeared in various zones of the hepatic lobule. Tubules of the rough endoplasmic reticulum were dilated and in close contact with functionally changed mitochondria. Osmiophilic liposomes of different shapes and sizes were seen in the cytoplasm. Meanwhile hepatocytes with dark cytoplasm and organelles with destructive changes could be seen.

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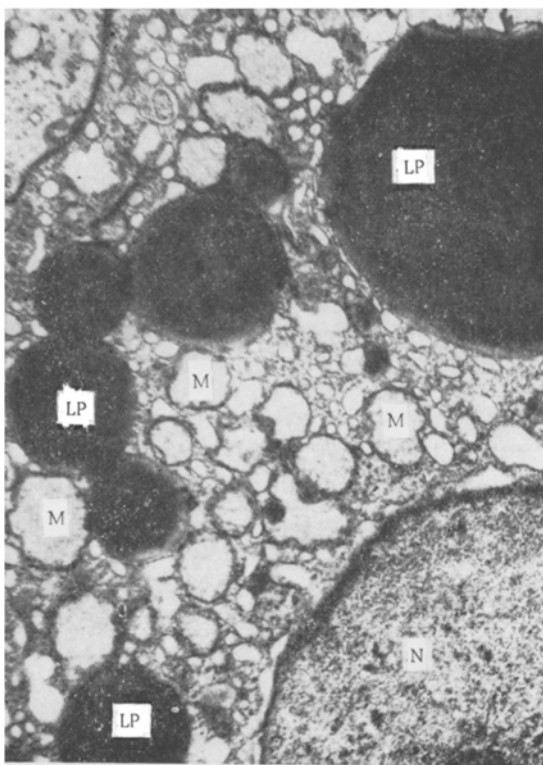


Fig. 1

Fig. 1. Hepatocyte ultrastructure on 14th day of experiment with acute toxic hepatitis: osmiophilic liposomes are present in the cytoplasm, membrane components of the mitochondria show destruction, and changes are present in the rough endoplasmic reticulum. N) Nucleus; M) mitochondria; LP) liposome. 18,000 \times .

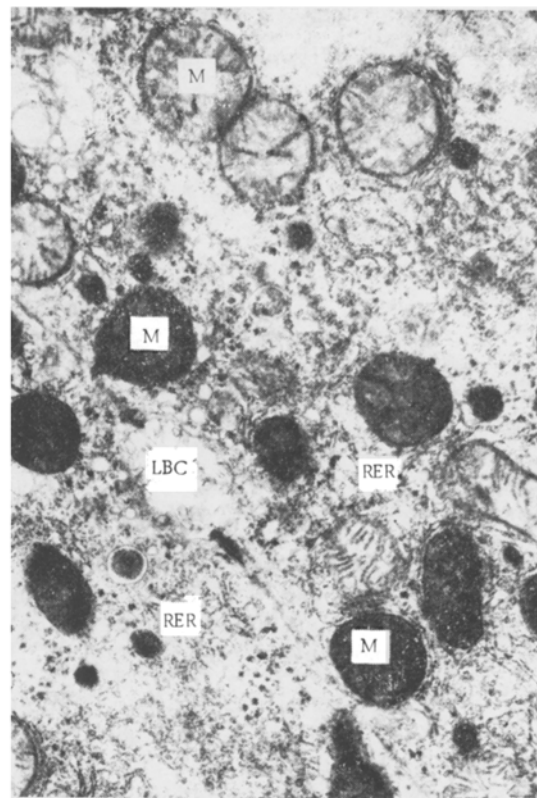


Fig. 2

Fig. 2. Hepatocyte ultrastructure on 14th day of experiment in animals treated with calcium pangamate: electron-dense matrix of many mitochondria, moderately developed rough endoplasmic reticulum, many submicrovilli in lumen of bile capillary. M) Mitochondria; LBC) lumen of bile capillary; RER) rough endoplasmic reticulum. 25,000 \times .

The ultrastructural picture in rats treated with calcium pangamate was polymorphic. Together with pathologically changed cells there were many cells with well-defined structural components of the cytoplasm. Most mitochondria were characterized by a very electron-dense matrix and clear outlines of the membrane. Many long submicrovilli could be seen in the lumen of the small bile capillaries (Fig. 2).

Combined administration of orotic acid and calcium pangamate, and also of lipamide, had a more marked beneficial effect on hepatocyte ultrastructure. Hyperplastic processes were found much more frequently in the liver parenchyma, and were reflected in the appearance of binuclear cells, containing one, two, or sometimes three large osmiophilic nucleoli. Much granular material was visible in the cytoplasm, the membranes and cristae of many mitochondria were better preserved, and their matrix was moderately dense. Tubules of the rough endoplasmic reticulum were found uniformly in different zones of the hepatocyte cytoplasm. The number of liposomes was reduced and the plasma and nuclear membranes were more clearly distinguished (Fig. 3).

Orotic acid and calcium pangamate, like lipamide, in toxic hepatitis thus do not prevent the sequence of development of the principal pathological processes in the parenchymatous cells, but they reduce the intensity and depth of manifestation of these processes and facilitate normalization of the cytoplasmic cell components. Combined administration of orotic acid and calcium pangamate reduces the degree of structural

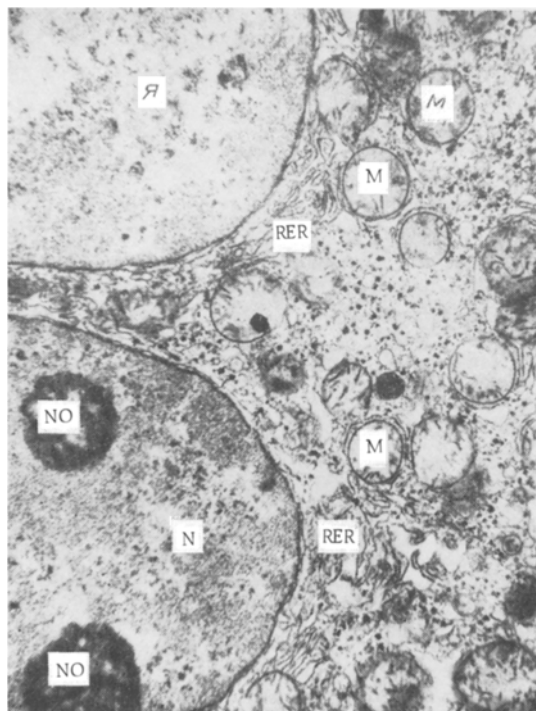


Fig. 3. Ultrastructure of binuclear hepatocyte on 14th day of experiment in animals treated with orotic acid and calcium pangamate: hyperplasia of nuclear substance, many ribosomes and polysomes in the cytoplasm, membranes of mitochondria well preserved, tubules of rough endoplasmic reticulum moderately dilated. NO) Nucleolus. Remainder of legend as in Figs. 1 and 2. 18,000 \times .

reorganization of the hepatocytes to a greater extent than separate administration of these substances and promotes the more intensive manifestation of intracellular reparative regeneration.

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