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Fluorouracil Effect on Cytochrome *c* Reductase Activity of Rat Liver Cell Endoplasmic Reticulum Following Partial Hepatectomy

ROGER WILLÉN

Institute of Pathology, University of Uppsala, Uppsala, Sweden

ABSTRACT

FUra (5-fluorouracil) prevents the appearance of 29 and 18S ribosomal RNA in the liver cell cytoplasm of rat, but permits the appearance of smooth-surfaced endoplasmic reticulum, as is clearly seen following partial hepatectomy. The present investigation revealed that the liver microsomal protein of rats treated with the antimetabolite FUra has a high concentration of NADPH oxidating enzyme in sham as well as in partially hepatectomized rats. There was even a tendency towards increased total amount of NADPH oxidating microsomal enzyme per liver in the FUra-treated rats as compared with control animals.

Biochemical studies have shown that treatment with 5-fluorouracil (FUra) prevents the appearance of 29 and 18S ribosomal RNA in the liver cell cytoplasm of rat (1, 2). This is very clearly seen under the electron microscope in rats following partial hepatectomy, where the normal increase in rough-surfaced endoplasmic reticulum and free ribosomes is inhibited by FUra. The FUra-treated rats show, however, a hypertrophic smooth-surfaced endoplasmic reticulum (3). As there is claimed that hypoactive hypertrophic endoplasmic membranes exist (4, 5), it was considered to be of interest to examine whether the membranes appearing under the influence of the antimetabolite FUra have a normal content of NADPH-oxidating enzyme.

EXPERIMENTAL

Male rats (Sprague-Dawley strain, AB Anticimex, Stockholm) fed on commerical pellets and weighing about 90 g, were starved overnight. At about 2 p.m. on the following day, they were submitted to sham or 2/3 hepatectomy according to Higgins & Andersson (6). Half of the animals were i.p. given 0.1 mg FUra (kindly supplied by Hoffman-La Roche, Switzerland) per g body weight 1 h before and 7 and 18 h after the operation. The controls were given distilled water. All animals were given a subcutaneous injection of 1 ml 5.5% glucose at the operation and 3, 7, 18 and 24 h after the operation. No food was given to the animals, but they were given water ad libitum. They were killed by decapitation 40 h after the operation. Cytochrome *c* reductase activity was measured as micromoles NADPH oxidated/min/mg total microsomal protein, according to Ernster et al. (7).

RESULTS

The results are summarized in Table I. As seen from the table the hepatectomy did not significantly interfere with the cytochrome *c* reductase activity, while FUra in resting liver cells and following partial hepatectomy gave a significant increase in the cytochrome *c* reductase activity of about 50%.

DISCUSSION

FUra has caused stimulation, inhibition, and no effect on various enzymes in different species, according to reports; in rat liver, mostly inhibition (6). In the present investigation, it was shown that the endoplasmic membranes after FUra treatment were metabolically active, measured as cytochrome *c* reductase activity as μmoles NADPH oxidated/min/mg microsomal protein. The increased concentration of enzyme/mg microsomal protein in the FUra-treated rats is to some extent explained by the greater amount of ribosomal protein included in the microsomal preparation, in the saline-treated control animals. This does not, however, explain the tendency towards increase in total amount of enzyme per liver in the FUra-treated animals. It is not known whether this increase is due to increased synthesis, or decreased breakdown, or a combination of these possibilities.

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Table I. *Cytochrome c reductase activity, measured as μmoles NADPH oxidated/min/mg total microsomal protein, 40 h after 2/3 or sham hepatectomy*

Livers from two rats were pooled at the enzyme determination. There is a statistical difference $0.001 < P < 0.01$, between the two hepatectomy groups and the "sham" groups. For technical details, see Ernster et al. (5)
FUra = 5-fluorouracil
NADPH = reduced nicotinamide adenine dinucleotide phosphate

	Total liver weights (Mean of 5 groups) (±Standard error)	Mg total microsomal protein/g liver (Mean of 5 analyses) (±Standard error)	μmoles NADPH oxidated/ min/mg microsomal protein (Mean of 5 analyses) (±Standard error)
FUra hepatectomy	1.9±0.10	17.7±1.5	0.124±0.009
Control hepatectomy	2.0±0.12	23.8±1.7	0.081±0.006
FUra "sham"	5.4±0.31	19.8±1.3	0.099±0.006
Control "sham"	5.1±0.16	20.6±0.7	0.052±0.011

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