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Effect of nikethamide on xenobiotic biotransformation in regenerating rat liver

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Stimulation of regenerative processes in rat liver (removal of about 70% of its weight) was accompanied by a 18-43% decrease of the cytochrome b_5 and P-450 concentrations, the NADH-cytochrome b_5 reductase activity and the rates of NADPH oxidation, amidopyrine, ethylmorphine and aniline hydroxylation.

The nikethamide administration to partially hepatectomized rats (subcutaneously, 75 mg/kg, 5 days before the operation and during the postoperative period) exerted the normalizing effect which was most pronounced after 2 days following the operation. The cytochrome b_5 concentration, the activities of NADH-cytochrome b_5 and NADPH-cytochrome P-450 reductases and the rates of amidopyrine, ethylmorphine and aniline hydroxylation were increased by 31-80% as compared to untreated operated animals.

Under conditions of liver regeneration, in contrast with the microsomal oxidation enzymes, the activities of glutathione-S- and UDP-glucuronyltransferases were compensatory increased by 31-44%. Nikethamide induced their further activation. The conjugation rate of glucuronic acid with paranitrophenol in microsomes, those of glutathione with sulfobromophthaleine (cytosol) and 1-chloro-2,4-dinitrobenzene (cytosol and microsomes) were increased by 30-54%, 36-76% and 13-70% (2, 4 and 8 days after the operation, respectively). Under the action of nikethamide the rate of UDP-glucuronic acid biosynthesis (UDPG-dehydrogenase) was increased by 30% (2 days) compared to untreated operated rats. Nikethamide accelerated the recovery of the liver weight.

Substrate induction of microsomal monooxygenases (Bushma, Lukienko, 1982) and enhanced biosynthesis of nicotinamide coenzymes (Stepanyan, Tseitlin, 1968) play the main role in the mechanism of the nikethamide stimulatory effect on the activities of the enzyme system of xenobiotic biotransformation. The accelerated recovery of the liver weight was mainly due to proliferation in membranes hepatocytes of the endoplasmic reticulum with the enzymes of xenobiotic oxidation and conjugation localized in them (Lukienko et al., 1983).

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Effects of tryptophan, nicotinic acid and some other metabolites of the kynurenine pathway on lipid metabolism in the rat

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It is well known that nicotinic acid affects the metabolism of lipids by lowering the concentrations of serum cholesterol, triglycerides and free fatty acids both in man and in rat (Nikkilä, 1971). Nicotinic acid itself is one degradation product of tryptophan and is formed from this amino acid through the kynurenine pathway via 3-hydroxyanthralinic acid. Tryptophan itself has some effects to the lipid metabolism by increasing the hepatic fatty acid synthesis in the rat (Fears and Murrell, 1980). To investigate more thoroughly the effects of this amino acid and its normal degradation products to serum lipids and their composition we purchased the compounds needed from Fluka Ag. (L-(+)-tryptophan) and from Sigma Chemical Co. (all other compounds tested). Especially we were