LIVER MITOCHONDRIA DAMAGE UNDER ACUTE AND CHRONIC INTOXICATION. HEPATOPROTECTION BY MELATONIN AND CRANBERRY FLAVONOIDS

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Nowadays the risk of toxic liver damage has recently highly increased due to exposure to environmental toxins, pesticides, herbicides and chemotherapeutics. Many compounds, including useful drugs, can cause liver cell damage through metabolic activation to highly reactive substances, such as free radicals. Pharmacological correction and prevention of toxic liver damage using safe and effective "biocorrectors" with both broad spectrum of activity and high specificity to target is the main task of contemprorary medicine. The aims of the present work were: 1) to investigate further the mechanism(s) of liver damages induced by acute and chronic carbon tetrachloride – induced rat intoxication and 2) to evaluate the hepatoprotective potential of the antioxidants, melatonin, succinate, and cranberry flavonoids.

Acute rat intoxication resulted in a considerable impairment of mitochondrial respiratory parameters in the liver, the ADP-stimulated respiration rate V_3 decreased by 55 % ($p < 0.001$), the acceptor control ratio – by 50 % ($p < 0.05$), the phosphorylation coefficient – by 55 % ($p < 0.05$) in the case of glutamate as respiratory substrate, whereas the activity of mitochondrial succinate dehydrogenase (complex II) decreased (by 25 %, $p < 0.05$). Liver impairment was accompanied by typical signs of intoxication. Melatonin administration at a pharmacological dose (10 mg/kg, 3 times) decreased both the structural and functional injury of hepatocytes but did not prevent considerably mitochondrial ultrastructural changes. Melatonin administration also reduced CCl_4-induced NO generation (anti-inflammatory effect).

After 30-day chronic rat intoxication we observed an increase (by 25 %, $p < 0.01$) of oxygen consumption rate V_2 of liver mitochondria with succinate (not glutamate) as a substrate. The acceptor control ratio and phosphorylation coefficient did not change. The activities of the mitochondrial enzymes, succinate dehydrogenase and glutathione peroxidase, as well as that of cytoplasmic catalase in liver cells were inhibited markedly and the levels of lipid peroxidation products in liver tissue were increased. Mitochondria isolated from the livers of the rats chronically treated with CCl_4 displayed considerable irreversible impairments, including an increase in mitochondrial matrix density, reduction in the number of cristae, and outer membrane rupture.

Long-term melatonin administration (10 mg/kg, 30 days, daily) to chronically intoxicated rats diminished many signs of liver damage, and resulted in apparent preservation of the mitochondrial ultrastructure. The treatment of the animals by the complex of melatonin (10 mg/kg) plus succinate (50 mg/kg) plus crude cranberry flavonoid extract (7 mg/kg) was much more effective in prevention of toxic liver injury and liver mitochondria impairments. .Melatonin as well as cranberry flavonoids demonstrated effective radical – scavenging properties in cellular and cell free radical generating systems. The synergistic action of melatonin, succinate and plant polyphenols may be useful in clinical application. The effect of melatonin, succinate and plant polyphenols on CCl_4-induced liver injury depends on the antioxidant, membrane-stabilizing and anti-inflammatory actions of the hepatoprotectors.