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EFFECT OF L-METHIONINE AS HEPATOPROTECTIVE AGENS ON POLYAMINE METABOLISM IN EXPERIMENTAL CHOLESTASIS

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Summary: Cholestatic liver diseases result from the intrahepatic accumulation of hidrofobic, toxic bile acids (BA). Toxic BA induces increased cell-membrane fluidity and apoptosis hepatocites. Spermine, spermidine and putrescine are endogenous polyamines essential for cellular growth, proliferation, regeneration and differentiation. The amino acid L-Methionine (L-Met) is required for the biosynthesis of polyamines. The aim of the study was to examine the effect of L-Met on polyamine metabolism in cholestatic livers of rats. Wistar rats were divided into 3 groups: I-control (sham operated), II-bile duct ligated (BDL) rats, III-BDL rats treated with L-Met (50 mg/kg BW). The animals were killed after 9 days' treatment. Administration of L-Met reduces the concentration and activity of biochemical's markers of cholestasis plasma (bile acids, bilirubin and GGT, AF, ALT) ($p<0.001$). Cholestasis in rats' liver decreases activity of arginase (18.8±1.6 vs. 25.1±1.4 μmol/mg prot.) and increased the production of citrulline and nitric oxide (3.14±0.17 vs. 1.66±0.07 μmol/mg prot. and 6.9±1.1 vs. 2.7±0.9 nmol/mg prot.), compared with sham operated rats ($p<0.001$). Nitric oxide inhibits the activity of ornithine decarboxylase (ODC) and decreases level of polyamines in cholestatic liver injury. Cholestatic liver has reduced polyamine polyamine biosynthesis (spermine – 520±6.1 vs. 693±6.3 nmol/g, spermidine – 683±8.3 vs. 885±9.1 nmol/g and putrescine – 95±4.1 vs. 160±4.7 nmol/g; $p<0.001$), in relation to sham operated rats. Cholestasis decreases catabolism in rats' liver (PAO and DAO activities) (1.08±0.06 vs. 1.94±0.16 U/mg prot. and 1.1±0.07 vs. 1.8±0.09 U/mg prot; $p<0.001$), compared with control. Administration of L-Met in BDL rats prevents heavy disorders of poluamine biosynthesis and catabolism in liver ($p<0.001$). L-Met is important for the regulation of polyamine metabolism and exerts hepato-protective properties in cholestasis.

Key words: polyamines, cholestasis, L-Methionine, liver

EFEKTI L-METIONINA KAO HEPATOPROTEKTORA NA METABOLIZAM POLIAMINA U EKSPERIMENTALNOJ HOLESTAZI

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Kratak sadržaj: U holestazi, intrahepatično nakupljanje hidrofobnih, toksičnih žučnih kiselina (BA) dovodi do oštećenja jetre. Toksične BA izazivaju povećanje propustljivosti ćelijske membrane i apoptozu hepatocita. Spermin, spermidin i putrescin su endogeni poliamini neophodni za rast, proliferaciju, regeneraciju i diferencijaciju ćelija. Aminokiselina L-metionin (L-Met) je neophodna za biosintezu poliamina. Cilj ove studije je da se ispitaju efekti L-Met na metabolizam poliamina u jetri pacova sa holestazom. Wistar pacovi su bili podeljeni u 3 grupe: I-kontrola (lažno operisane životinje), II-pacovi sa podvezanim ductus choledochusom (BDL pacovi), III-BDL pacovima je oralno davan L-Met (50 mg/kg TM). Životinje su žrtvovane posle 9 dana eksperimenta. Davanje L-Met pacovima sa holestazom smanjuje nivo i aktivnost biohemijskih markera holestaze u krvnoj plazmi (žučnih kiselina, bilirubina i GGT, AF, ALT) ($p<0,001$). U jetri pacova sa holestazom dolazi do sniženja aktivnosti arginaze (18,8±1,6 vs. 25,1±1,4 μmol/mg prot.) i povećanog stvaranja citrulina i azot-monoksida (3,14±0,17 vs. 1,66±0,07 μmol/mg prot. i 6,9±1,1 vs. 2,7±0,9 nmol/mg prot.), u odnosu na lažno operisane životinje ($p<0.001$). Azot-monoksid inhibira aktivnost enzima ornitin dekarboksilaze (ODC) i tako smanjuje nivo poliamina u oštećenoj jetri u holestazi. U uslovima holestaze u jetri dolazi do smanjene biosinteze poliamina (spermin-520±6,1 vs. 693± 6,3 nmol/g, spermidin-683±8,3 vs. 885± 9,1 nmol/g i putrescin-95±4,1 vs. 160±4,7 nmol/g; $p< 0,001$), u odnosu na lažno operisane životinje. U jetri pacova sa holestazom dolazi do pada katabolizma poliamina (aktivnosti PAO i DAO) (1,08±0,06 vs. 1,94±0,16 U/mg prot. and 1,1±0,07 vs. 1,8±0,09 U/mg prot; $p<0,001$), u odnosu na kontrolne pacove. Aplikovanje L-Met pacovima sa podvezanim ductus choledochusom onemogućava značajan poremećaj u biosintezi i katabolizmu poliamina u jetri ($p<0,001$). L-metionin je značajan za regulaciju metabolizma poliamina i pokazuje hepato-protektivno dejstvo u holestazi.

Ključne reči: poliamini, holestaza, L-metionin, jetra