EFFECT OF S-ADENOSYL-L-METHIONINE ON SERUM LIPOPROTEIN IN EXPERIMENTAL HEPATIC CARCINOGENESIS

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SUMMARY

Plasma lipoprotein concentration and composition were investigated in experimental hepatic carcinogenesis induced by thioacetamide (TAA). The effect of S-adenosyl-L-methionine (SAM) on lipoprotein alterations during hepatic injury was also tested.

After 30 days administration of the weak carcinogen i.p. (50 mg/Kg/day) to male Wistar rats, a decrease of serum VLDL concentration and HDL accumulation in plasma was observed. Consequently, the HDL/VLDL ratio was elevated. Any increase of LDL/VLDL ratio was also observed. Total plasma phospholipids were lower than reference values. Sphingomyelin/phosphatidylethanolamine (SPH/PE) ratios significantly decreased in plasma, as well as in VLDL-LDL and HDL fractions, as a consequence of the reduced SPH level and simultaneous increase of PE.

Treatment of experimental animals with SAM (2 mg/Kg/day) as well as with TAA for 30 days resulted in a normal level of serum VLDL and the HDL/VLDL ratio. Phospholipid concentration in plasma was also normalized as a consequence of elevated level of these compounds in the VLDL-LDL fraction. Administration of SAM also prevented the decrease of SPH/PE ratio in plasma and different lipoproteins.

INTRODUCTION

The central role of the liver in lipoprotein metabolism is consistent with an abnormal electrophoresis pattern and lipid composition of the plasma lipoprotein in different liver diseases (1-3).

Human hepatomas, rat primary hepatocellular carcinomas and livers of rat treated with hepatocarcinogenic agents lack feedback control of cholesterol regulation (4, 5). Alterations in serum lipids and lipoproteins have been described in cancer patients (6, 7) and in experimental carcinogenesis (8).

Between the different experimental models of parenchymal liver damage, the hepatotoxic compound thioacetamide (TAA) given to rats (9-12) offers a suitable animal model to investigate disturbed lipid metabolic processes in cirrhotic and preneoplastic tissue (9). This weak carcinogen reproduces in
rats necrosis of hepatocytes (10, 11) cirrhosis (13), hyperplastic nodules, tumors, cholangiomas and cholangiocarcinomas (14).

In previous investigations we observed that administration (i.p.) of TAA to rats results in alterations of subcellular organells composition (15) and hepatic phospholipid biosynthesis (16, 17). To obtain more information on these lipid changes we have investigated these parameters in experimental animals treated with S-adenosyl-L-methionine (SAM) as well as with TAA, because of the demonstrated contribution of this methyl group donor compound to the rapid adaptive response of liver to TAA-induced necrosis (11) and the various pharmacological effects reported for this compound (11, 18).

Abbreviations

ALAT, L-alanine: 2-oxoglutarate aminotransferase; ASAT, L-aspartate: 2-oxoglutarate aminotransferase; HDL, high density lipoproteins; LDL, low density lipoproteins; LPC, lysophosphatidylcholine; PC, Phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; RER, rough endoplasmic reticulum; SAM, S-adenosyl-L-methionine; SPH, sphingomyelin; TAA, thioacetamide, VLDL, very low density lipoproteins.

MATERIALS AND METHODS

Chemicals

TAA, silicagel G type 60 and organic solvents were obtained from Merck (Darmstad). SAM was a donation from Europharma (Madrid). Phospholipid standards were supplied by Sigma Chemical Co. (St. Louis). Dextran sulfate was from Sochibo, S. A. (Bologne). Kits for cholesterol and triglycerides determinations were purchased from Boehringer Mannheim, S. A. (Barcelona) and reagents for aminotransferase enzymes from Technicon (Tarrytown).

Animals

Two month old male Wistar rats weighing 200-220 g were divided in the three following groups: 1) Rats which received a daily intraperitoneal injection of TAA (50 mg/Kg body weight) in 0.15 M CaCl solution for 30 days; 2) Rats that received an (i.p.) injection of TAA as indicated above and a daily dose of S-adenosyl-L-methionine (2 mg/Kg body weight) for 30 days; 3) Control rats which were daily injected (i.p.) with 0.15 M NaCl solution. Animals were fed with water and food ad libitum; 18 hours before sacrifice, control and treated rats were fasted (water ad libitum). For each experiment six animals were used. Blood samples were obtained from the abdominal aorta under light ether anesthesia and collected in tubes containing 0.7% Na2 EDTA and centrifuged for plasma at 3,000 r.p.m. at 40°C for 10 minutes. The liver was removed, weighed and scored for macroscopic alterations. Liver specimens were used for histological examinations.

Serum enzymes assays

Catalytic activities of serum aspartate aminotransferase and alanine aminotransferase were determined as previously described (11).

Morphological examinations

Each liver of the TAA, TAA + SAM-treated and control rats was examined at a macroscopic light level as indicated elsewhere (11).