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Hepatoprotective Properties of Taurine during Carbon Tetrachloride Intoxication

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Abstract—Oxidative stress, impaired calcium homeostasis and mitochondrial dysfunction are the key elements of carbon tetrachloride-induced liver damage. Activation of lipid peroxidation is accompanied by changes in the activity of antioxidant enzymes, the concentration of reduced glutathione, catabolic preference of metabolic processes and amino acid imbalance. Taurine, a nonproteinogenic β-amino acid, is one of the key regulators of metabolism, antioxidant and amino acid balance corrector. The hepatoprotective properties of taurine are mainly associated with its zonal distribution within the liver lobes, significant differences in the concentrations of taurine between periportal and pericentral regions; the latter is manifested in different protective properties that depend on compartmentalization of detoxification processes in the liver lobule. Administration of taurine under conditions of carbon tetrachloride-induced liver injury prevents the increase of plasma transaminases and bilirubin, reduces the histological changes in the liver by decreasing the degree of necrosis of hepatocytes, inflammatory and fatty infiltration.

Keywords: carbon tetrachloride, taurine, liver

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INTRODUCTION

Hepatocyte damage by carbon tetrachloride (CCl_4) is the classic model of hepatic pathology, which allows to study the mechanisms of its toxic damage and to search new effective hepatoprotective agents [1–3]. Figure 1 shows that the key elements of pathogenesis are oxidative stress, impaired calcium homeostasis and mitochondrial dysfunction leading to damage and death of hepatocytes and development of reactive fibrosis. Degradation of parenchymatous liver cells is a trigger mechanism for activation of other cell populations, which can initiate an inflammatory response and/or adaptive immune response, and also inhibit hepatic regeneration [4–6].

1. THE MECHANISM OF CCl_4-INDUCED HEPATOTOXICITY

CCl_4 is one of the most potent hepatotropic poisons. Patients with CCl_4-induced poisoning account for 60% of all patients with liver toxicity. Mortality in oral CCl_4 poisoning is 30%. The lethal dose of CCl_4 for humans is 20–40 mL and intake of 2–4 mL causes appearance of symptoms of poisoning [7].

Regardless to the route of administration CCl_4 causes centrolobular necrosis and fatty degeneration of the liver [8–10]. Experimental intoxication with CCl_4 (daily intragastric administration of 30% oil solution at a dose of 2 mL/kg for 4 days) was accompanied by the damage of ultrastructure of rat hepatocytes, formation of lipid inclusions or cysts; this resulted in displacement of cytoplasmic structures and the nucleus to the cell periphery and disruption of membrane integrity [12]. Pronounced dystrophic changes were observed at both vascular and biliary poles of cells and also in mitochondria. Destructive changes occur in the microvascular components: these include hypertrophy of endothelial cells, red blood cell stasis, local sinusoidal blockage by cell dendrites, reduction and swelling of preserved microvilli in the bile capillaries [11, 12].

CCl_4-induced liver damage depends on age of the animals, the intensity of metabolism (activity of enzyme systems), and supply with essential nutrients. For example, rat puppies exposed to CCl_4 had focal necrosis recorded after 3–4 days and fatty dystrophy, which was developed during the first 20 days. Cirrhotic changes occurred already after 70–90 days. In mid aged rats, precirrhotic and cirrhotic changes developed in 3–4 months and 9–11 months, respectively [7, 13].

Simultaneously, carbon tetrachloride affects other organs: kidneys (proximal parts of the renal tubules), alveolar membrane and pulmonary vessels [14]. Damages of kidneys and lungs are less pronounced, and are usually developed after the liver damage as a

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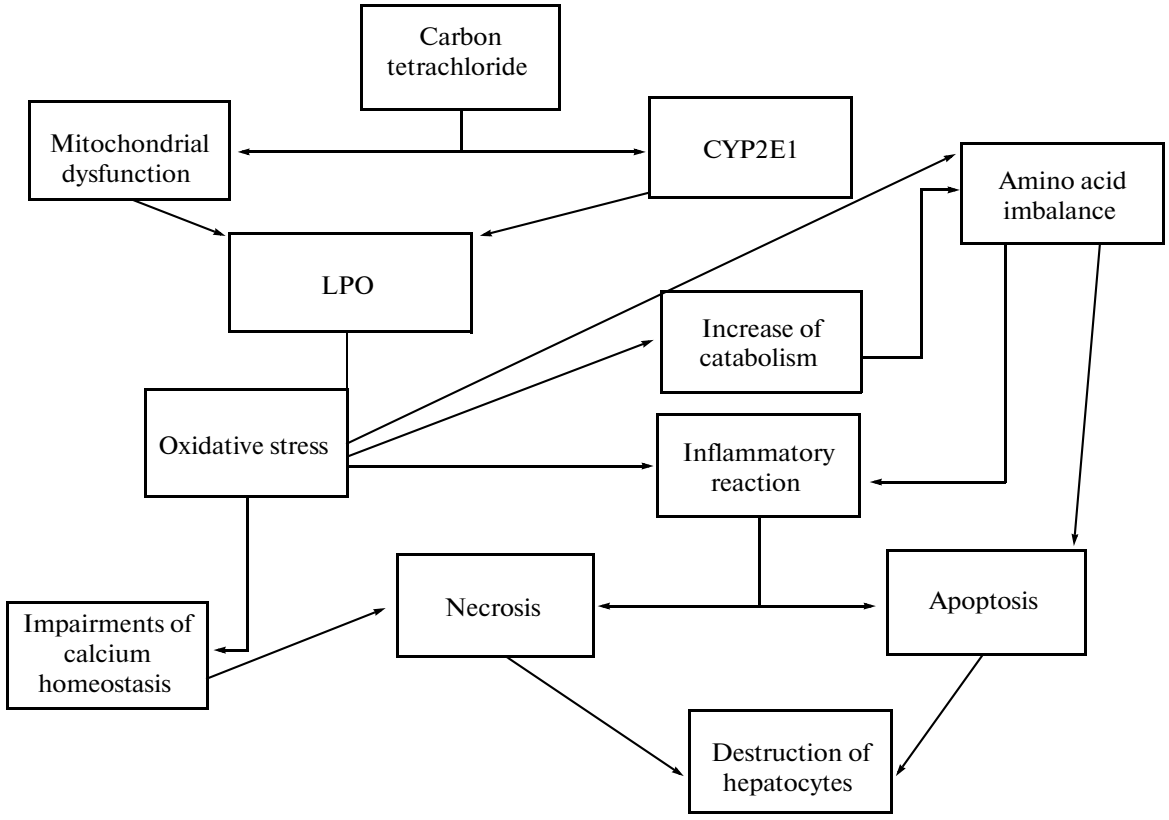

Fig. 1. The main pathogenetic mechanisms responsible for CCl_4-induced liver damage.

result of general metabolic disorders, including immune system cells. For example, in mice and rats treated with intraperitoneal (i. p.) injections of CCl_4 at doses 200, 500, 1000, 2000 mg/kg changes in the mitotic index of the thymus and its mass, the total number of cells of the thymus and inguinal lymph nodes were noted 48 h later [15].

Oxidative stress that develops in the body after CCl_4 administration promotes adaptive catabolic trends of all metabolic processes as shown in Fig. 1. This is particularly notable in the increased pool of free amino acids and their derivatives in blood: their total amount increased by approximately 20% [12]. The metabolic situation is exacerbated by the development of amino acid imbalance characterized by: increased proportion of non-essential (replaceable) amino acids, decreased utilization of branched chain amino acids, and decreased rate of phenylalanine hydroxylation [12]. Significant impairments of methionine metabolism result in the increase of plasma methionine metabolites and a decrease of total amount of sulfur-containing amino acids. In contrast, in the liver tissue, the decrease in the relative content of free proteinogenic amino acids was observed [12, 16].

2. METABOLISM OF XENOBIOTICS IN THE LIVER FUNCTION AND TAURINE

Liver cells are actively involved in metabolism of glucose, lipids, amino acids and xenobiotics [17–19]. Since the directions of blood and bile flow as well as the oxygen gradient differ in the hepatic lobules, these metabolic pathways are characterized by different levels of expression and activity of corresponding enzyme. It is known that metabolic characteristics of hepatocytes significantly differ in periportal and pericentral regions of the hepatic lobule [20]. Oxidative metabolism, catabolism of amino acids, urea synthesis, glycogenolysis, cholesterol synthesis, β-oxidation, and the formation of bile acids dominate in the periportal region, whereas glycolysis, gluconeogenesis, lipogenesis, ketogenesis, glutamine formation and metabolism of xenobiotics predominantly occur in the pericentral region [17, 21, 22].

A nonproteinogenic β-amino acid taurine is one of the key regulators of the metabolism. In high concentrations it is present in most mammalian tissues, where it controls many physiological processes, including bile acid conjugation, modulation of a calcium level and maintenance of osmolarity; taurine also exhibits antioxidant properties, and stabilizes the phospholipid bilayer of membranes [12, 23]. At physiological con-

centrations taurine can prevent DNA damage [24]. Interaction of taurine with uridine and subsequent formation of 5-taurinomethyluridine is necessary for the synthesis of specific mitochondrial proteins that control processes occurring the electron transport chain and preventing excessive formation of oxygen free radicals [25].

Manifestation of the hepatoprotective properties of taurine is mainly determined by its zonal distribution within the lobule and also by significant differences in taurine concentrations between periportal and pericentral regions [26–28]. This is probably an important determinant of higher protective activity of taurine during liver damage by hepatotoxins, which are metabolized in specific compartmentalization.

Usually, the liver taurine content in the range 4–11 μmol g wet weight. However, the taurine concentration in hepatocytes of the pericentral region is higher (1.9 ± 1.4 μmol/g of cells) than in periportal hepatocytes (1.1 ± 0.5 μmol/g of cells). The rate of taurine formation from [^{35}S]cysteine is 7 times higher in hepatocytes of the pericentral region; this is probably determined by significantly higher expression of cysteine dioxygenase and other enzymes involved in taurine biosynthesis [29–31].

Simultaneously, GSH synthesis from an endogenous precursor (cysteine) occurs faster in hepatocytes of the periportal region than in hepatocytes localized in the pericentral region [32].

This GSH distribution in the liver lobule suggests that the detoxification capacity of cells is higher in the periportal region than in the pericentral region; however, CYP2E1-dependent activation of several xenobiotics into highly active metabolites predominantly occurs in the pericentral region, where CYP2E1 expression is rather high [33, 34]. Consequently, hepatocytes of the pericentral region are characterized by lower capacity of xenobiotics detoxification due to a lower GSH content, and, consequently, the cells located in this zone are more vulnerable to damage by electrophilic metabolites; this underlines an importance of high concentrations of taurine in these cells.

In addition to the endogenous synthesis of taurine, its content in the liver cells is supported by a specific transporter (TauT; SLC6A6) responsible for transport of exogenous taurine [35]. Using immunohistochemical methods it was demonstrated that in the rat liver TauT is predominantly expressed in the pericentral region. This explains why the content and biosynthesis of taurine, as well as its transport are higher in cells of the pericentral region of the hepatic lobule than in the periportal region. Hepatocytes of mature mice contain taurine-positive granules, which are localized primarily in the peripheral region of the liver lobule. Electron microscopy studies have shown that taurine is accumulated in small vesicles in the hepatocyte cytoplasm, mainly in cisterns of smooth endoplasmic reticulum. Some taurine-positive vesicles are located around the membrane structures and are associated with the protoplasm. Similar taurine-positive granules are often localized around the bile ducts. During CCl_4 intoxication the taurine content increases in the cell and is not limited to peripheral regions; its high quantities also appear in the central regions of the lobule [36].

Efficiency of the use of taurine in CCl_4-induced liver injury has been widely discussed [37–39]. It is known that under stress conditions taurine acts as an excellent organic osmolyte, which prevents swelling or contraction of the cell [40]. Osmoregulatory properties account for taurine inhibition of stellate cell transformation [41]. Simultaneously, administration of taurine inhibits proliferation of stellate cells, arrests their growth at the G_0/G_1 phase and prevents the progression of the inflammatory reaction. Taurine exhibits an antiapoptotic effect in various cell types. Obviously, taurine addition can provide a therapeutic effect by reducing the severity of oxidative stress, inducing liver damage and liver fibrosis [42].

In acute hepatitis caused by a single administration of CCl_4, taurine prevented the development of hepatocellular necrosis, the increase in lipid peroxidation, disorders of the mitochondrial membrane (see the scheme of Fig. 2) [43, 44]. In chronic liver disease oral administration of taurine prevented the increase of plasma transaminases and bilirubin (Fig. 2), reduced the histological changes in the pericentral region of the liver lobule (including cell necrosis, inflammatory and fatty infiltration), markers of oxidative stress in serum and the liver tissue including lipid peroxides and 8-hydroxy-2'-deoxyguanosine [45, 46]. Administration of taurine to animals (2% of taurine in the diet for 5 weeks) significantly reduced liver fibrosis induced by CCl_4 administration and fibrogenesis, prevented transformation of stellate cells into fibroblasts, by inhibiting the expression of hepatic fibrogenic factors (transforming growth factor TGF-β1 mRNA), reduced the level of hydroxyproline. Expression of the taurine transporter mRNA in stellate cells increased in a hyperosmolar medium and taurine consumption by transformed cells demonstrated a 5.5-fold increase [40, 46, 47].

Insufficient intake of dietary taurine or a decrease of its endogenous synthesis is one of the factors of tissue damage. Taurine-deficient animals are often characterized by impairments in the histological structure of the liver [35, 48]. Since humans and rodents have limited capacities in taurine synthesis, insufficient intake of dietary taurine is the major cause of reduced taurine content in the liver. In TauT knockout mice (taut–/–) taurine concentration reduced by 70% in plasma and kidneys, and by 95% in skeletal muscles and the cardiac tissue. Reduced taurine concentrations were accompanied by a decrease in gain weight, fertility and loss of vision due to degenerative processes in the retina. For example, in the liver of 2 months old animals, concentration of taurine was

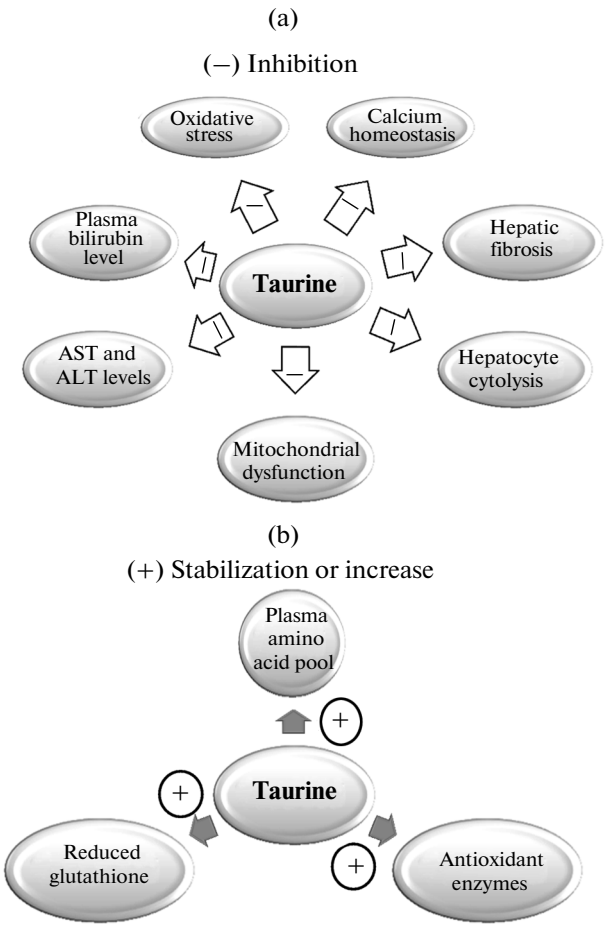

Fig. 2. The protective effects of taurine in the liver damage.

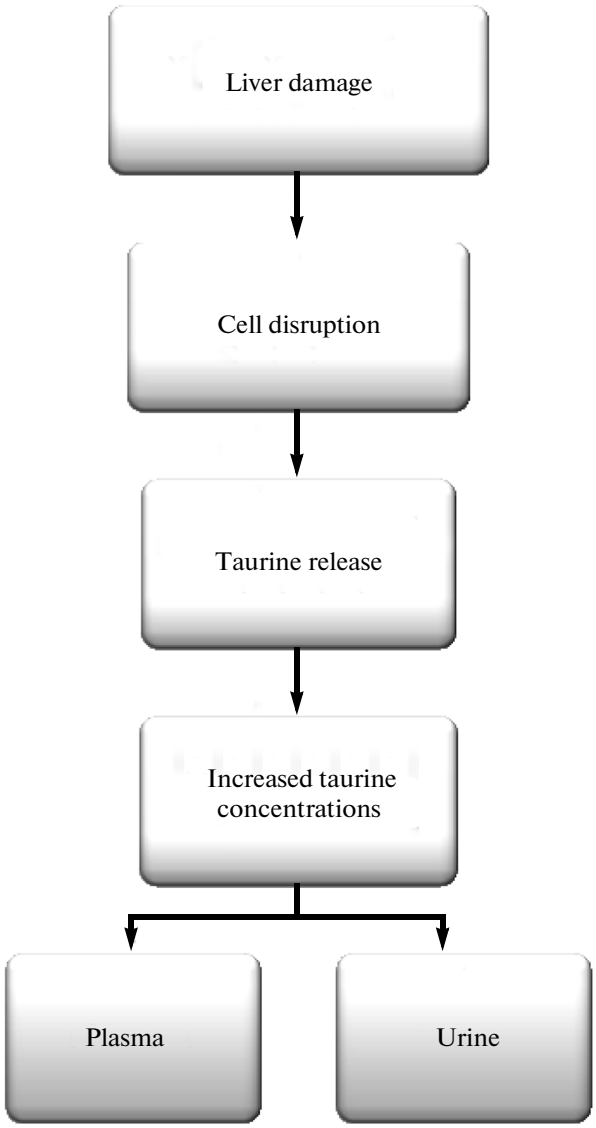

Fig. 3. Taurine is a biomarker of the liver damage.

1.6 ± 0.4 μmol/g in taut–/– mice vs. 12.1 ± 2.0 μmol/g in taut+/– and 17.7 ± 2.5 μmol/g in taut+/+ mice, respectively. The taut–/– mice were also characterized by the destruction of hepatocytes, apoptosis, fibrosis, disorders of the structure of mitochondria; these changes were noted in hepatocytes predominantly localized in pericentral regions of the liver lobules [48].

In liver diseases a decrease of taurine concentrations in hepatocytes depends on the degree of the organ damage. It is believed that taurine concentrations in plasma and urine may be a biomarker of liver damage, as the rise of taurine levels in plasma and urine is determined by its release from the damaged cells [47, 49, 50] as shown in Fig. 3.

Taurine insufficiency in animals is often modeled by administering β-alanine, a competitive inhibitor of TauT [38, 51]. Depending on the experimental conditions, the dose and duration of administration of β-alanine, taurine levels may be reduced by 20–85%, with the highest decrease in the liver [38]. Administration of β-alanine increases excretion of taurine in the urine due to competition between β-alanine and taurine at the step of reabsorption in the renal tubules.

Taking into consideration the stabilizing role of taurine on liver cells, it is reasonable to suggest that the depletion of tissue stores of taurine will enhance the action of toxicants. However, the study of the metabolism of sulfur-containing amino acids in the liver in under conditions of its acute CCl_4 damage revealed that in β-alanine treated animals the taurine level significantly reduced, while concentrations of S-adenosylmethionine, S-adenosylhomocysteine, and GSH as well as activity of methionine adenosyl methyltransferase remained unchanged [52]. Under these conditions the level of cysteine was significantly higher and this could contribute to the maintenance of reduced glutathione synthesis in the liver.

Simultaneously, it was shown that co-administration of β-alanine with CCl_4 potentiated hepatic dysfunction and promoted fibrosis formation [41, 53, 54]. This suggests, that the taurine antagonist, β-alanine, at least, has no hepatoprotective action in CCl_4-induced intoxication. Although there are some conflicting data indicating the protective effects of β-alanine in the the CCl_4- or lipopolysaccharide-induced liver injury, this may be attributed to the compensatory increase in the biosynthesis of taurine and GSH in the liver [52]. For example, in mice β-alanine reduced hepatotoxicity caused by CCl_4 administration (50 μL/kg, i. p.), which was evaluated by the serum levels of AST, ALT and sorbitol dehydrogenase. In this context, it should be noted that GSH and taurine levels significantly increased in the liver after CCl_4 administration. The mechanism of the hepatoprotective action of β-alanine in the CCl_4-induced acute liver injury may be attributed to increased availability of methionine and/or cysteine for synthesis of GSH and taurine [52, 53]. It is important to note that taurine in the presence of some xenobiotics (rifampicin) acts as an inducer of CYP2E1 mRNA expression. This effect has been demonstrated in the HepG2 cell culture and depended on the concentration and exposure time. On the other hand, taurine had no effect on the cytochrome induction in the presence of phenobarbital [30].

The hepatoprotective effects of taurine also include inhibition of extracellular matrix accumulation in experimental liver fibrosis [23, 55], the improvement of liver function during its fatty degeneration in children [56]. For example, in animals with experimental liver fibrosis (induced by CCl_4 administration at a dose of 0.2 mL/100 g twice a week) taurine administration (at daily dose of 1 g/kg for 12 weeks) resulted in much lesser manifestations of hepatocyte necrosis, inflammatory infiltration, steatosis, fibrosis, and also decreased damage to the mitochondrial cristae by CCl_4 [23].

Pretreatment with taurine (5% solution, daily dose 15 mL/kg) for 5 days before administration of CCl_4 (2 mL/kg, i. p.) had a marked positive effect, preventing the development of hepatocellular necrosis [43].

We have shown that administration of a complex of taurine with zinc sulfate (400 mg/kg) to animals with CCl_4-induced intoxication prevented formation of fatty cysts in the liver cells, the development of ultrastructural changes in the nuclear apparatus, mitochondria and smooth endoplasmic reticulum [11, 12]. Simultaneously, the course of administration of taurine and zinc complex stimulated proteolysis of muscle proteins; the latter increased plasma levels of free amino acids and their metabolites. This was accompanied by a trend towards normalization of amino acid balance and rate of hydroxylation of phenylalanine [12, 16].

Convincing evidence exists that regardless of the etiology of the liver damage, the decrease in taurine concentration in the tissue is determined by loss of hepatocytes, the intensity of the inflammatory response and the development of fibrosis and fatty degeneration [49, 50]. Many studies have demonstrated that in vivo administration of taurine caused a hepatoprotective effect under conditions of intake of numerous xenobiotics (including hepatotoxins), induction of oxidative stress and hepatocarcinogenesis [38, 43, 46, 55, 57–59]. It is important to note that in these situations, the damage of hepatic lobules occurred predominantly in the pericentral region and the basic hepatotoxin metabolism involved CYP2E1 [60].

CYP2E1, exhibiting the highest expression activity in human liver is involved in metabolism of many xenobiotics, including ethanol, acetaldehyde, acetaminophen, acrylamide, benzene, butanol, carbon tetrachloride, dimethyl ether, dimethyl sulfoxide, ethyl carbamates, ethylene chloride, halothane, glycerol, ethylene glycol, N-nitrosodimethylamine, 4-nitrophenol, pyrazole, pyridine, thioacetamide, and vinyl chloride [60–62].

Most of metabolites formed during CYP2E1-dependent metabolism of these compounds are hepatotoxins, which cause oxidative stress and lipid peroxidation of membranes [33]. Therefore, the hepatoprotective effect of taurine may largely depend on the reduction of the metabolic activity of CYP2E1, or the consequences of oxidative stress in the hepatotoxin-induced lesions of pericentral region hepatocytes. On the other hand, taurine has a much less pronounced protective effect against such toxic compounds as allyl alcohol or α-naphtylisothiocyanate, inducing cell damage primarily in the periportal region [63, 64].

Thus, manifestation of the protective action of taurine, targeted to overcoming the oxidative stress, may depend on the distribution and homeostasis of taurine within the hepatic lobules.

CONCLUSIONS

Taurine is an essential nutrient required for stabilization of various physiological and biochemical functions, especially under conditions of oxidative stress. Taurine concentrations in plasma and urine may serve as a biomarker of liver damage as increased levels of taurine in the plasma and urine are associated with its release from the disrupted cells. In experimental conditions, taurine exhibits a protective effect during CCl_4 induced intoxication; this effect may be realized via different mechanisms, including heterogeneous distribution of taurine in the hepatic lobule, antioxidant and osmoregulatory actions, more efficient use of cysteine for glutathione biosynthesis, the effect on the system of CYP2E1. Taurine administration reduced cytolysis of hepatocytes, decreased plasma levels of AST, ALT, and bilirubin. In animals subjected to CCl_4

intoxication and treated with taurine in the complex with zinc, less pronounced ultrastructural changes of hepatocytes and stabilization of amino acid and protein metabolism were detected.

Additional administration of taurine to animals with toxic liver injury promotes significant attenuation of the hepatotoxicity of xenobiotics, reduces intensity of lipid peroxidation and inhibits the development of fibrosis.

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