

Taurine and liver diseases: a focus on the heterogeneous protective properties of taurine

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Abstract Taurine (2-aminoethylsulfonic acid) has many physiological and pharmacological functions in most tissues. It is abundantly maintained in the liver by both endogenous biosynthesis and exogenous transport, but is decreased in liver diseases. In the hepatic lobule, there are heterogeneous differences in metabolism between the pericentral (PC) and periportal regions, and the distributions of the biosynthesis capacity and specific taurine transporter expression are predominantly in the PC region. In cases of depletion of hepatic taurine level, serious liver damages were observed in the PC region. Taurine has protective effects against xenobiotics-induced liver damages in the PC region, but not xenobiotics-induced PP region damages. The xenobiotics that injure the PC region are mainly catabolized by NADPH-dependent cytochrome P450 2E1 that is also predominantly expressed in the PC region. Taurine treatment seems to be a useful agent for CYP2E1-related liver diseases with predominant damages in the PC region.

Keywords CYP2E1 · Hepatic lobule · Oxidative stress · PC region · Xenobiotics

Introduction

The liver plays crucial roles in metabolism of many molecules, including glucose, lipids, amino acids, and

xenobiotics, and these metabolic processes are each regulated by specific enzymes (Gebhardt 1992; Jungermann and Katz 1989). Since the directions of blood and bile flows and the oxygen gradient in hepatic lobules differ due to the subcellular structure of the liver acinus, these metabolic enzymes have heterogeneous patterns of expression and activity (Fig. 1). The hepatic lobule, defined as Kiernan's classical lobule, is histologically divided into three regions: the periportal (PP, zone 1) region around the portal vein, the pericentral (PC, zone 3) region around the central vein, and the intermediate (zone 2) region (Kiernan 1833). The metabolic characteristics of hepatocytes differ in the PP and PC regions. In the PP region, oxidative energy metabolism, amino acid catabolism, ureagenesis, gluconeogenesis, cholesterol synthesis, β -oxidation, and bile formation are predominant, whereas glycolysis, glycogenesis, liponeogenesis, ketogenesis, glutamine formation, and xenobiotic metabolism are preferentially situated in the PC region (Fig. 1; Jungermann and Katz 1989). In liver diseases, hepatocellular damage including necrosis and apoptosis, fatty degeneration, inflammation, and fibrosis have histological differences in etiology, including virus infection, metabolic disorder, immunological response, and drug metabolism. In rat hepatocytes, there is a zonal heterogeneous distribution of taurine (2-aminoethanesulfonic acid) within one hepatic lobule (Penttilä 1990), and the variation of taurine levels between the PP and PC regions seems to be an important determinant of susceptibility to zonal toxic responses. The normal level of hepatic taurine content is 4–11 $\mu\text{mol/g}$ wet weight, and the content can be varied by exogenous administrations of taurine (Penttilä 1990) or β -alanine, which is an antagonist for a specific transporter of taurine (Kim and Kim 2002; Pacioretty et al. 2001; Parildar-Karpuzoglu et al. 2007), and in gene knockout of the specific transporter (Warskulat et al. 2006).

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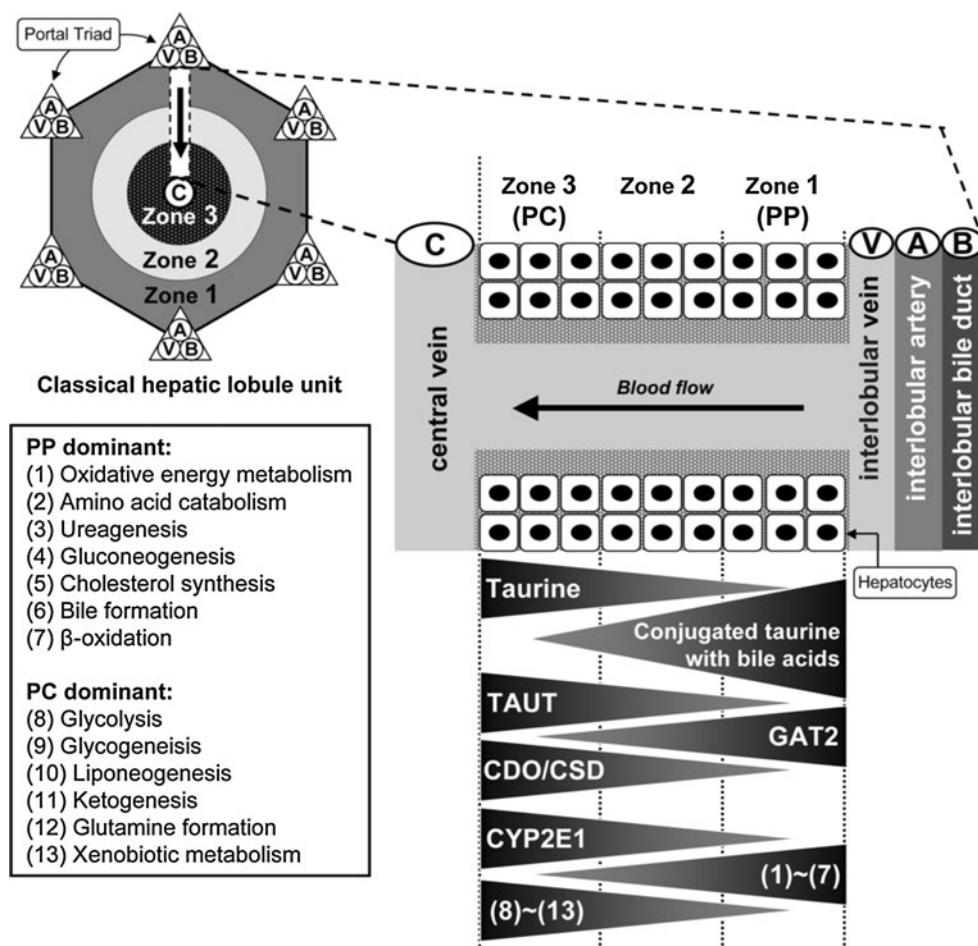
Many studies have demonstrated the therapeutic efficacy of taurine for liver diseases including inflammatory condition, apoptosis, and fibrosis through anti-oxidative stress action (Chen et al. 2004; Kato et al. 2004; Miyazaki et al. 2005; Refik Mas et al. 2004). Furthermore, various symptoms related to liver diseases including jaundice in acute hepatitis (Matsuyama et al. 1983) and hepatic encephalopathy (Butterworth 1996) and muscle cramp (Matsuzaki et al. 1993; Yamamoto 1994) in cirrhotic patients have been reported to be improved by taurine treatment. In this review, we will mainly discuss the relationship of heterogeneous liver diseases with the distribution and regulatory functions of taurine in the hepatic lobules.

Taurine homeostasis in the liver

Taurine is the most abundant free amino acid-like compound found in mammalian tissues, including liver (Awapara 1956; Huxtable 1980; Jacobsen and Swimth 1968; Sturman 1993). In the liver, the most established role of taurine is its conjugation with bile acids for excretion into bile (Danielsson 1963; Sjoval 1959). However, taurine has

many other physiological and pharmacological roles in the liver and other tissues, including stabilization of the cellular plasma membrane (Pasantes et al. 1985), osmoregulation (Nieminen et al. 1988), anti-oxidant effects (Nakamura et al. 1993), and detoxification (Huxtable 1992). High intracellular levels of taurine are maintained by exogenous uptake and endogenous synthesis. Taurine is an end product in sulfur amino acid catabolism through the methionine and cysteine pathways in the liver (Bella et al. 1999a, b; De La Rosa and Stipanuk 1985). In this taurine biosynthesis pathway, cysteine dioxygenase (CDO) (Hosokawa et al. 1990) and cysteine sulfinate decarboxylase (CSD) (Kaisaki et al. 1995; Reymond et al. 1996; Tappaz et al. 1999) are key limited enzymes. An excellent antioxidant agent glutathione (GSH; L- γ -glutamyl-L-cysteinylglycine) also utilizes cysteine in the biosynthesis pathway (Meister and Anderson 1983). Penttila (1990) investigated the heterogeneities and regulation of taurine, cysteine and GSH concentrations using [35S] cysteine in hepatocytes isolated separately from the PC and PP regions, respectively, by a digitonin/collagenase perfusion technique that can destroy the respective regions by perfusion of digitonin from the portal vein or inferior vena cava. The resulting

Fig. 1 Heterogeneous distributions of hepatic metabolisms, taurine level, and its maintenance capacities in the hepatic lobule. The hepatic lobule is divided into three regions as zone 1–3 by Kiernan's classical lobule classification. Taurine level, the capacities of taurine biosynthesis, the protein expressions of TAUT, and the cytochrome P450 isoform 2E1 expression in the hepatic lobule are predominant in zone 3, while uptake of taurine through GAT2, GAT2 protein expression, and taurine conjugation with bile acids are predominant in zone 1. C central vein, V interlobular vein, A interlobular artery, B interlobular bile duct, Zone 1 periportal region, Zone 2 intermediate region, Zone 3 pericentral region, TAUT taurine transporter, GAT2 GABA transporter 2, CDO cysteine dioxygenase, CSD cysteine sulfinate decarboxylase, CYP2E1 cytochrome P450 2E1



taurine content in the PC hepatocytes was higher ($1.9 \pm 1.4 \mu\text{mol/g}$ of cells) than in the PP hepatocytes ($1.1 \pm 0.5 \mu\text{mol/g}$). Along with faster uptake of [35S] cysteine into the PC hepatocytes, the rate of taurine production from [35S] cysteine in the PC hepatocytes was sevenfold higher than in the PP hepatocytes. Furthermore, Parsons et al. (1998) showed that the expression of CDO protein was predominantly localized in the PC region of rat liver by immunohistological stain. In addition to endogenous synthesis, the taurine content in the liver and other tissues is also maintained by the exogenous diet through uptake via a specific transporter (TAUT; SLC6A6) (Han et al. 2006; Liu et al. 1992; Smith et al. 1992; Uchida et al. 1992). The zonal distribution of TAUT in hepatic lobules is unclear. Our unpublished immunohistochemical staining data show that TAUT in rat hepatic tissue is also predominantly and markedly expressed in the PC rather than the PP region (Fig. 2; see figure legend for the detailed method). These observations indicate that the basal content, product capacity, and transport ability of taurine within the hepatic lobule are higher in the PC region than in the PP region. On the other hand, the study by Penttilä (1990) showed that cellular GSH synthesis from endogenous precursor (cysteine) was faster in the PP hepatocytes than in the PC hepatocytes. The distribution of GSH in the hepatic lobule implies that the capacity of detoxication in the PP region is higher than in the PC region, although activation of numerous xenobiotics to reactive metabolites predominates in the PC region via cytochrome P450 isoform 2E1 (CYP2E1) that were highly expressed in the PC region (Lieber 1997; Fig. 2). Therefore, it has been suggested that hepatocytes in the PC region might be limited in detoxication process due to the lower capacity to replenish GSH and, consequently, the PC region easily sustains damages from the electrophilic metabolites (ROS) of CYP2E1.

Taurine homeostasis and liver diseases

Morphological abnormalities and incomplete tissue development have been observed in the liver and in other tissues in taurine-deficient animal models (Han et al. 2000; Ito et al. 2008; Neuringer et al. 1987; Sturman 1993; Sturman and Messing 1991; Warskulat et al. 2006). Since the capacity for taurine biosynthesis is generally limited in humans and rodents, a deficiency of taurine in the liver seems to be caused by decreased uptake of exogenous taurine, rather than dysfunctions of endogenous biosynthesis. Häussinger's group has created homozygous (*taut*^{-/-}) and heterozygous (*taut*^{+/-}) models of TAUT knockout mice (Heller-Stilb et al. 2002; Lang et al. 2003; Warskulat et al. 2004, 2006). In the *taut*^{-/-} mouse, the

knockout of TAUT induced taurine depletion in a variety of tissues, including decreases of ~74 % in plasma, kidney, and eye, and of >95 % in skeletal muscle and heart at 2–19 months of age. These changes were associated with a lower body mass, reduced fertility, and loss of vision with severe apoptotic retinal degeneration. In the liver, the taurine concentration in 2-month-old *taut*^{-/-} mice ($1.6 \pm 0.4 \mu\text{mol/g}$) were decreased by >40 and >90 % compared to that in *taut*^{+/-} ($12.1 \pm 2.0 \mu\text{mol/g}$) and *taut*^{+/+} ($17.7 \pm 2.5 \mu\text{mol/g}$), respectively, accompanied with a reduction of the liver wet weight (Warskulat et al. 2006). The *taut*^{-/-} mice also had hepatitis with hepatocyte destruction, apoptosis, fibrosis, mitochondrial abnormalities, and an increased frequency of neoplastic lesions predominantly in the PC regions of hepatic lobules beyond 1 year of age. Since TAUT was predominantly expressed in the PC region (Fig. 2), the homeostasis of taurine seems to be an important factor for heterogeneous hepato-protection in this region.

Interestingly, the reduction of taurine content in the liver of TAUT KO mice was more mild compared to that in non-parenchymal cells such as Kupffer cells and sinusoidal endothelial cells and in other tissues (Warskulat et al. 2006). One of the reasons for this might be the taurine synthesis ability in the liver, but Ikeda et al. (2012) recently showed the importance of γ -aminobutyric acid (GABA) transporter 2 (GAT2) in the uptake of taurine into the liver. Similar to TAUT, GAT2 which is a rat ortholog of human GAT3 belongs to a family of Na⁺/Cl⁻-dependent neurotransmitter transporters and has lower affinity ($K_m = 540 \mu\text{M}$) (Liu et al. 1993) compared to TAUT ($K_m = 43 \mu\text{M}$) (Smith et al. 1992). Ikeda et al. (2012) confirmed that taurine could be transported into hepatocytes through GAT2, because the uptakes of [³H] taurine injected into the portal vein in anesthetized rat and of [³H] taurine exposed to freshly isolated hepatocytes were significantly inhibited by the antagonists for GAT2. Furthermore, immunohistochemical analysis showed that GAT2 protein was localized on the sinusoidal membrane of hepatocytes, predominantly in the PP region (Ikeda et al. 2012). These observations imply that the enterohepatic circulation of taurine and bile acid conjugated with taurine are regulated by GAT2 in the PP region. Therefore, the authors proposed one explanation for the discrepancy that taurine synthesis was higher in the PC region, but taurine conjugation with bile acids was higher in the PP region (Ikeda et al. 2012). They suggested that oral taurine treatment could be a useful therapy for cholestatic disease, because the conjugation composition of bile acids would be changed from more cytotoxic glycine-conjugated bile acids to taurine-conjugated bile acids. Compared to the evidence reported by Penttilä (1990), it has been considered that free taurine is abundant in the PC region, while taurine

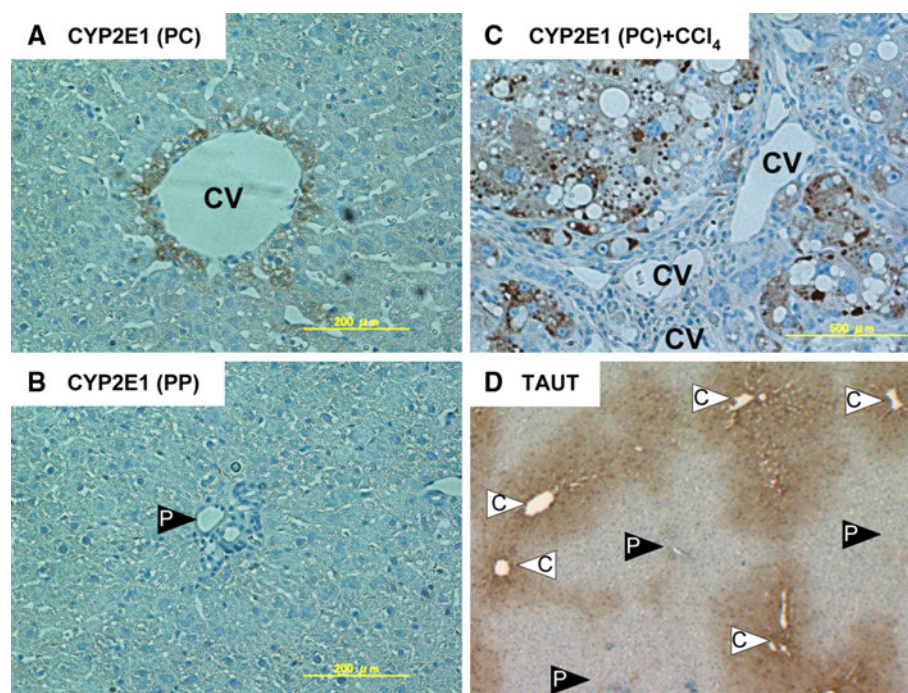


Fig. 2 Heterogeneous protein expressions of CYP2E1 and TAUT in the hepatic lobule of normal and CCl₄-administered hepatic tissues in rats on immunohistochemical stain. Hepatic tissues collected from normal or liver-damaged rats that received CCl₄ administration were immunohistochemically stained with a rabbit anti-TAUT (Alpha Diagnostic International, Inc., San Antonio, TX, USA) or anti-CYP2E1 (Millipore, Bedford, MA, USA) primary antibodies and biotin-conjugated universal secondary antibody (Ventana, Tucson,

AZ, USA). **a** CYP2E1 expression in hepatocytes around the central vein of normal tissue ($\times 10$). **b** very weak or no expression of CYP2E1 in the PP region of normal tissue ($\times 10$). **c** Activated CYP2E1 expression in the PC region with cell damages, fat droplets, and fibrosis by chronic administration of 50 % CCl₄–olive oil solution for 10 weeks ($\times 20$). **d** TAUT protein expression dominantly in the PC region of normal tissue ($\times 2$). CV central vein, C in the white arrow central region, P in the black arrow portal region

transported by GAT2 in the PP region is preferentially utilized to conjugation with bile acids (Fig. 1).

Administration of β -alanine, an inhibitor of taurine uptake on TAUT, is also used to prepare animal models of taurine depletion in liver and other tissues (Kim and Kim 2002; Parildar-Karpuzoglu et al. 2007). Depending on the protocol, dose, and duration of β -alanine administration, the taurine level is decreased by approximately 20–85 %, with the greatest change in the liver among all tissues (Pacioretty et al. 2001). Taurine depletion in the liver has been suggested to be due to reduced taurine uptake into hepatocytes, and Shaffer and Kocsis (1981) also showed that β -alanine administration enhanced excretion of taurine into urine because of competition of β -alanine with taurine for re-uptake in renal tubules. In contrast to TAUT knockout mice, histopathologic changes in the liver were not found in taurine depletion models induced by β -alanine administration. However, co-administration of β -alanine with hepatotoxins such as ethanol (EtOH) or carbon tetrachloride (CCl₄) causes aggravation of hepatic dysfunction, impairment, and fibrosis, together with significant hepatic taurine depletion (Erman et al. 2004; Kerai et al. 2001; Waterfield et al. 1993; Wu et al. 2009). This suggests that β -alanine does not have a protective effect against

hepatotoxins. However, there are conflicting findings on the protective effects of β -alanine against liver damage caused by CCl₄ or lipopolysaccharide through enhanced biosynthesis of taurine and GSH in the liver (Kim and Kim 2002; Lee and Kim 2007), and further studies are needed to clarify this issue.

Overview: heterogeneous protective actions of taurine against hepatotoxins

In liver diseases, the extent of reduction of the hepatic taurine concentration depends on the degree of symptoms, including loss of hepatocytes, inflammation, fibrosis, and fatty degeneration. Taurine concentration in plasma and urine has been proposed to be a biomarker of liver damage, because elevation of taurine concentration in plasma and urine was found following hepatotoxin overdose due to leakage from damaged hepatic cells (Ghandforoush-Sattari and Mashayekhi 2008; Waterfield et al. 1991). In many in vivo studies, taurine administration has been shown to protect hepatic tissue and hepatocytes against various substrates, inducing hepatotoxicities, oxidative stress, and hepatocarcinogenesis (Balkan et al. 2001, 2002; Bleich and

Protective effect of taurine on CCl₄-induced liver damage

The diagram illustrates the metabolic pathways of CYP2E1. The central enzyme is CYP2E1 + NADPH. It catalyzes the oxidation of alcohol to acetaldehyde (via ADH/catalase) and acetate (via ALDH). It also catalyzes the oxidation of CCl₄ to CCl₃, TAA to TASO, and TASO to TASO₂. Additionally, it is involved in the metabolism of APAP to NAPQI. ROS are produced in several steps of the pathway.

injury in the PC region (Slater et al. 1985; Fig. 3). The effectiveness of taurine against CCl₄-induced liver disease in rats has been reported widely (Erman et al. 2004; Nakashima et al. 1982; Wu et al. 1999). In an acute liver disease model in rat induced by a single administration of CCl₄, Dinçer et al. (2002) showed that taurine treatment prevented hepatocellular necrosis, lipid peroxidation, and mitochondrial abnormalities observed by electron microscopy. In a chronic hepatic disease model, we showed that oral taurine administration significantly improved the serum levels of aminotransferases and bilirubin; the histological appearance in the PC region including cell necrosis, fatty degeneration, and inflammation; and oxidative stress markers in serum and hepatic tissue including lipid hydroperoxides and 8-hydroxy-2'-deoxyguanosine (Miyazaki et al. 2005). Taurine also significantly decreased hepatic fibrosis induced by CCl₄ administration and fibrogenesis of isolated hepatic stellate cells, which are converted to myofibroblasts by oxidative stress in cirrhotic liver, through inhibition of transforming growth factor- β expression. In CCl₄-administered rats, the taurine concentration in the liver, plasma, and other tissues was significantly decreased (Miyazaki et al. 2004), but the decreased hepatic taurine concentration can be improved by oral taurine administration (Miyazaki et al. 2005; Nakashima et al. 1982). Indeed, Erman et al. (2004) reported that the significant decrease of hepatic taurine concentration in the CCl₄-administered rat together with ethanol was significantly recovered by 2 % taurine-containing drinking water, while the significant decrease was not improved by 3 % β -alanine drinking water. The decreased taurine concentration in the liver might be associated with a significant decrease in TAUT protein in the damaged liver tissue; however, it is unclear whether oral taurine administration could upregulate the transport ability of taurine or not.

Protective effect of taurine on APAP-induced liver damage

APAP overdose can cause acute liver injury in both humans and animals. At normal and therapeutic doses, APAP is principally and rapidly metabolized in liver by glucuronidation and sulfation; however, an overdose of APAP that exceeds the capacities of these processes results in additional oxidation by CYP2E1 that generates a large amount of a highly reactive and cytotoxic intermediate, *N*-acetyl-*p*-benzoquinone imine (NAPQI). This metabolite can be detoxified by conjugation with GSH, but may also bind covalently to hepatic parenchymal cell proteins and DNA, with resultant liver injury (Vermeulen et al. 1992; Fig. 3). Thus, hepatic damage in CYP2E1-knockout mice was mitigated, because these mice were less sensitive to APAP than wild-type mice (Lee et al. 1996). Furthermore, APAP overdose caused upregulation of CYP2E1 and direct activation of JNK-dependent cell death pathway (Das et al. 2010a). APAP-induced hepatic damage is typically found in the PC region. In a rat model with single APAP administration, Waters et al. (2001) showed that taurine administration (200 mg/kg intraperitoneal injection) 12 h before, simultaneous with, and 1–2 h after APAP treatment significantly inhibited histological damage including hepatic necrosis and inflammation in the PC region, DNA fragmentation, and hepatic lipid peroxidation. Acharya and Lau-Cam (2010) also showed the protective action of taurine as well as *N*-acetylcysteine and hypotaurine, which are the immediate metabolic precursor of taurine and the analog of cysteine, respectively, against hepatic injury induced by APAP overdose in rat via suppression of oxidative stress and alterations in GSH redox cycling, utilization, and transfer. Furthermore, taurine treatment has been recently reported to reduce APAP-induced hepatic damages and nephrotoxicity through suppression of CYP2E1 upregulation and oxidative stress and enhancement of urinary excretion of APAP (Das et al. 2010a, b).

Protective effect of taurine on TAA-induced liver damage

TAA is also widely used to induce hepatic damage experimentally. TAA-induced hepatotoxicity arises through a two-step bioactivation to thioacetamide sulfoxide (TASO) (step I) and then to thioacetamide-*S,S*-dioxide (TASO₂) (step II) (Fig. 2) by CYP2E1, with consequent generation of oxidative stress (Chilakapati et al. 2005; Dogru-Abbasoglu et al. 2001; Fig. 3). In TAA-treated rats, Uysal's group showed that taurine was protective against both acute and chronic hepatic damages (Balkan et al. 2001; Dogru-Abbasoglu et al. 2001). Taurine ameliorated

histopathological and biochemical abnormalities and reduced lipid peroxidation in the liver in models of acute and chronic hepatic damages in the PC region induced by TAA administered in three IP injections at 24-h intervals and for 3 months in drinking water, respectively. In zebrafish, taurine treatment has been shown to improve hepatic steatosis and damage due to oxidative stress induced by TAA through significant improvement of adipocytokine-related effects via altered expression of tumor necrosis factor α (TNF- α) and adiponectin receptor 2 (Hammes et al. 2012).

Protective effect of taurine on EtOH-induced liver damage

With irregular and lower quantity intake, alcohol is metabolized in the liver through a two-step pathway of metabolism by alcohol dehydrogenase to acetaldehyde, which is toxic for the liver, and degradation of acetaldehyde to acetate by the mitochondrial enzyme acetaldehyde dehydrogenase (Fig. 3). With chronic and excessive intake that exceeds the capacity of alcohol dehydrogenase, both alcohol and acetaldehyde are also metabolized by CYP2E1, which is upregulated by EtOH (Lu and Cederbaum 2008). Since oxidative stress is generated in the CYP2E1-mediated EtOH catabolism pathway, CYP2E1 activity plays an important role in the pathogenesis of EtOH-induced liver damage and lipid peroxidation. Many previous studies have shown a protective effect of taurine on EtOH-induced liver injury through an action against oxidative stress (Bleich and Degner 2000; Erman et al. 2004; Kerai et al. 1999; Ogasawara et al. 1993; Pushpakiran et al. 2004; Watanabe et al. 1985). The efficacy of taurine for alcoholic steatohepatitis (ASH) has also been examined in EtOH intake animal models (Balkan et al. 2002; Kerai et al. 1998, 1999; Wu et al. 2009). Taurine administration at a level of 1–2 % in drinking water significantly decreased fatty acid degeneration and inflammation in histological observation, with inhibition of serum aminotransferases, inflammatory-related cytokines (interleukin-2, -6, TNF- α), and oxidative stress in a hepatic steatosis rat model induced by co-administration of EtOH and pyrazole combined with a high-fat diet (Wu et al. 2009). In the EtOH-intake rat, the hepatic taurine level is inhibited due to suppression of cysteine metabolism, including synthesis and catabolism of cysteine and GSH synthesis (Kim et al. 2003), and the influence of EtOH consumption on the taurine transport is not cleared. In addition to the anti-oxidative stress effect, Kerai et al. (1998) showed in rat that taurine inhibited the hepatic CYP2E1 activity induced by alcohol consumption. This was initially proposed to be due to a possible increase in taurine-conjugated bile acid (taurocholic acid), a potent

inhibitor of microsomal enzymes including CYP2E1, after taurine administration, but in a subsequent study the same authors rejected the effect of a taurine-enhanced increase in the taurocholic acid level on inactivation of CYP2E1 (Kerai et al. 1999). Furthermore, Chen et al. (2009) also showed that taurine supplementation reduced EtOH-induced hepatic steatosis in rat associated with the attenuations of oxidative stress and TNF- α expression in the liver. This study emphasized the relevance of taurine to the serum adiponectin that is a adipokine primarily secreted from adipose tissue and stimulates fatty acid oxidation and decreases triglyceride accumulation in the liver, because taurine prevented the decrease of serum adiponectin concentration through the inhibitions of oxidative stress, inflammatory cytokine (interleukin-6; IL-6), and transcription factors of adiponectin expression (early growth response-1; Egr-1, CCAAT/enhancer binding protein α ; C/EBP α , peroxisome proliferator-activated receptor α ; PPAR α) in the subcutaneous adipose tissue. The authors suggested that taurine might play roles as anti-oxidative stress and as chemical chaperone/osmolyte in the subcutaneous adipose tissues.

Potential effect of taurine on non-alcoholic steatohepatitis (NASH)

Similarly to ASH, taurine may be a potent therapeutic agent for NASH. In many advanced countries, the number of patients with NASH has increased due to intake of high-fat and high-calorie diets. NASH is a necroinflammatory form of non-alcohol fatty liver disease that can promote hepatic fibrogenesis and lead to cirrhosis, liver failure, and hepatocellular carcinoma. The pathology of NASH has similar histological features to those of ASH, including fatty changes, ballooning degeneration, apoptosis and necrosis of hepatocytes, appearance of Mallory bodies, and fibrosis (Ludwig et al. 1980). These histological abnormalities in the PC region are particularly characteristic of NASH. In the development of NASH, the “two-hit theory” has been widely accepted: the first hit producing steatosis (fatty liver and/or diabetes mellitus) and the second as a source of oxidative stress capable of initiating significant lipid oxidation (Day and James 1998). Importantly, the expression and activity of CYP2E1 are also upregulated in patients and animals with NASH (Weltman et al. 1996, 1998). Therefore, there is a close relationship in NASH between the heterogeneity of expression of CYP2E1 and the predominant occurrence of steatosis and inflammation in the PC region (Buhler et al. 1992). In NASH model rats induced by a chronic high-fat diet (10 % lard + 2 % cholesterol for 12 weeks), taurine administration at 250 mg/kg/day significantly improved the distinctive

morphological and histological features of NASH, including inflammation fibrosis in the PC region and hepatic lipid and glucose metabolism (Chen et al. 2006). In the fatty liver of children with simple obesity, oral taurine administration improved fatty liver and serum ALT level, along with improved body weight control (Obinata et al. 1996). The effectiveness of taurine on liver injury has also been reported in streptozotocin-induced diabetic rats (El-Batch et al. 2011). In this model, increased hepatic activity and expression of CYP2E1 were associated with the elevation of plasma ketone bodies (β -hydroxybutyrate), which might be an inducer of CYP2E1. CYP2E1 expression was significantly decreased by taurine administration, together with reduced hepatic damage and oxidative stress markers, compared to untreated controls and to animals treated with melatonin, which is also a potent scavenger of hydroxy and peroxy radicals. Because some previous studies have shown that taurine could downregulate CYP2E1 activated by APAP (Das et al. 2010a, b) and EtOH (Kerai et al. 1998) in the liver and kidney, these findings suggest that the beneficial effects of taurine on the pathology of NASH may relate to the expression or activity of CYP2E1 in the NASH models, in addition to its role as anti-oxidative stress. Therefore, evidences for a direct relationship between CYP2E1 and taurine in NASH are needed to be obtained in future study.

Furthermore, a recent study also proposed the preventative and therapeutic potentials of dietary taurine supplementation against non-alcoholic fatty liver disease, because the inhibitive effects of taurine on nutrient- and chemical-induced hepatic steatosis, ER stress, inflammation, and injury were observed in four experimental models including palmitate-exposed primary rat hepatocytes and rat hepatoma cell line (H4IIE), long-term high sucrose fed rat, and acute ER stress (tunicamycin)-injected mice (Gentile et al. 2011).

Conclusion

The liver is the central organ of vital metabolism and functions including protein synthesis, nutrient metabolism, and detoxification. In the liver, taurine is abundantly maintained by endogenous biosynthesis and exogenous transport systems. It is recognized to be an essential nutrient due to its many physiological and biochemical roles. Decreased taurine content in the liver has been found in cases of experimental interruption of taurine transport and in liver diseases and, consequently, unexpected symptoms in the whole body would be observed due to reduced protection against oxidative stress and toxins, absence of conjugation with bile acids, and a reduced metabolic role in β -oxidation. Since previous studies have

reported that the liver damages in the PC region were induced in the TAUT KO mice and taurine has a protective action against many hepatotoxins that cause damage in the PC region, the protective effect of taurine on liver damage is suggested to be associated with the heterogeneous distribution of taurine in the hepatic lobule. Furthermore, these hepatotoxins are catabolized by CYP2E1, which is also expressed in the PC region. In addition to the inhibitive effect of taurine on the oxidative stress caused by the catabolic process of hepatotoxins through CYP2E1, some studies have shown that taurine also suppressed the activated CYP2E1. This suggests that taurine might be a useful agent for CYP2E1-related liver diseases including NASH. The therapeutic efficacy of taurine for NASH requires investigation in a future clinical study.

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Conflict of interest The authors declare that they have no conflict of interest.

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