Fig. 4. Effects of bezafibrate, rifampicin, carbamazepine and GW4064 on the activation of CYP3A4 and human PXR. (a) HepaRG cells were treated with each compound for 48 hrs in triplicate. mRNA expression levels were standardized to those of β-actin. The mean expression and activity levels in control cells were set to 1.0. Data are expressed as the mean±SD. Effects of bezafibrate are shown as the solid bars. *, †, ‡ $P<0.05$, 0.005, 0.001, respectively, indicate significant difference from controls. (b) DPX2 cells were treated with each compound for 24 hrs in triplicate. Activation of human PXR was determined by a cell-based luciferase reporter gene assay. The average relative luminescent units (RLU) obtained with the DMSO solvent control was set to 1.0.

Fig. 5. Effects of bezafibrate, rifampicin, carbamazepine and GW4064 on mRNA expression levels of nuclear receptors and a related coactivator (a), transporters (b) and enzymes and LDL receptor (c) in HepaRG cells. The cells were treated with each compound for 48 hrs, in triplicate. mRNA expression levels were standardized to those of β-actin. The mean expression and activity levels in control cells were set to 1.0. Data are expressed as the mean±SD. The effects of bezafibrate are shown as the solid bars. C, control; 10, bezafibrate 10 μM; 50, bezafibrate 50 μM; 100, bezafibrate 100 μM; 200, bezafibrate 200 μM; R, rifampicin 10 μM; M, carbamazepine 50 μM; G, GW4064 3 μM. PPARα, peroxisome proliferator-activated receptor α; PXR, pregnane X receptor; FXR, farnesoid X receptor; SHP, small heterodimer partner; FTF, α-fetoprotein transcription factor; HNF4α, hepatocyte nuclear factor 4α; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1α; LXRα, liver X receptor α; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; ABC, ATP-binding cassette transporter; NTCP, Na^+/taurocholate-cotransporting polypeptide; CYP7A1, cholesterol

7α-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; CYP8B1, 7α-hydroxy-4-cholesten-3-one 12α-hydroxylase; CYP27A1, sterol 27-hydroxylase; HMGCR, HMG-CoA reductase; LDLR, LDL receptor; ACC1, acetyl-CoA carboxylase 1; FAS, fatty acid synthase. *, †, ‡ $P<0.05$, 0.005, 0.001, respectively, indicate significant difference from control.

Fig. 6. Regulation of hepatic transporter activities and bile acid metabolism by PPARs, PXR and UDCA. Bezafibrate is a dual agonist of both PPARs and PXR. The activation of PPARs inhibits CYP7A1, CYP27A1 and NTCP, and upregulates MDR3 and presumably ABCG5/G8. The activation of PXR inhibits CYP7A1 and stimulates CYP3A4, MDR1 and MRP2. Genes that are downregulated by PPARs or PXR are indicated by the red lines, while those that are upregulated by PPARs, PXR or UDCA are indicated by the green arrows.

Table 1. Characteristics of Patients with PBC Enrolled in the Present Study

Laboratory data	Control (n=49)	Before UDCA treatment (n=31)	Before BF treatment (n=19)
Age (yrs)	57.8±1.6 [22-79]	60.3±1.8 [37-81]	58.8±1.6 [45-73]
Gender (Male/Female)	11/38	4/27	1/18
AST (IU/L)	21±1 [11-34]	64±18‡ [19-120]	45±5‡ [20-101]
ALT (IU/L)	17±1 [7-30]	82±34‡ [12-138]	51±9‡ [18-152]
GGT (IU/L)	25±2 [7-58]	196±27‡ [30-757]	178±59‡ [47-445]
ALP (IU/L)	230±9 [126-336]	517±43‡ [229-1163]	597±51‡ [266-952]
Total bilirubin (mg/dL)	0.7±0.1 [0.3-1.2]	0.7±0.2 [0.3-1.3]	0.6±0.1 [0.3-1.1]
IgM (mg/dL)	97±12 [56-161]	288±27‡ [90-637]	306±60† [130-466]
Total cholesterol (mg/dL)	199±4 [130-257]	213±9 [120-356]	228±18 [118-343]
LDL cholesterol (mg/dL)	115±4 [46-194]	138±7* [91-254]	149±18 [54-228]
HDL cholesterol (mg/dL)	65±2 [33-111]	53±4* [13-95]	55±5 [13-89]
Triglycerides (mg/dL)	91±6 [33-214]	107±7* [47-199]	113±11 [40-243]

Data are expressed as mean±SEM [range].

Before UDCA treatment, all PBC patients before treatment with UDCA; Before BF treatment, PBC patients who exhibited an incomplete biochemical response to the UDCA monotherapy (600 mg/day) and before additional treatment with bezafibrate.

*P<0.05, significantly different from control.

†P<0.005, significantly different from control.

‡P<0.0001, significantly different from control.

Table 2. Baseline Biomarker Levels for Cholesterol Metabolism in Enrolled Patients with PBC

Serum biomarkers	Control (n=49)	Before UDCA treatment (n=31)	Before BF treatment (n=19)
Bile acid metabolism			
C4 (ng/mg CHOL)	15.7±2.9 [2.3-118]	12.1±1.8 [0.8-49]	11.8±2.1 [1.5-38]
FGF19 (pg/ml)	336±51 [50-1662]	309±49 [74-1543]	353±57 [114-930]
Cholesterol metabolism			
Lathosterol (μg/mg CHOL)	2.8±0.3 [0.9-11.7]	2.2±0.2 [0.7-5.8]	2.2±0.3 [0.8-6.1]
Sitosterol (μg/mg CHOL)	1.6±0.1 [0.4-3.8]	2.0±0.2* [0.8-3.9]	2.4±0.2† [1.1-4.3]
Campesterol (μg/mg CHOL)	1.8±0.1 [0.4-5.1]	2.0±0.1 [0.7-3.7]	1.9±0.2 [0.7-3.3]
Oxysterol metabolism			
4β-HC (ng/mg CHOL)	29±3 [11-135]	44±4‡ [24-140]	51±5‡ [20-92]
24S-HC (ng/mg CHOL)	31±2 [17-74]	34±2 [22-69]	41±2†[20-64]
27-HC (ng/mg CHOL)	77±3 [35-140]	75±4 [48-124]	75±4 [39-102]

Data are expressed as mean±SEM [range].

Before UDCA treatment, all PBC patients before treatment with UDCA; Before BF treatment, PBC patients who exhibited an incomplete biochemical response to the UDCA monotherapy (600 mg/day) and before additional treatment with bezafibrate; C4, 7α-hydroxy-4-cholesten-3-one; CHOL, cholesterol; FGF19, fibroblast growth factor 19; 4β-HC, 4β-hydroxycholesterol; 24S-HC, 24S-hydroxycholesterol; 27-HC, 27-hydroxycholesterol.

*P<0.05, significantly different from control.

†P<0.005, significantly different from control.

‡P<0.0001, significantly different from control.

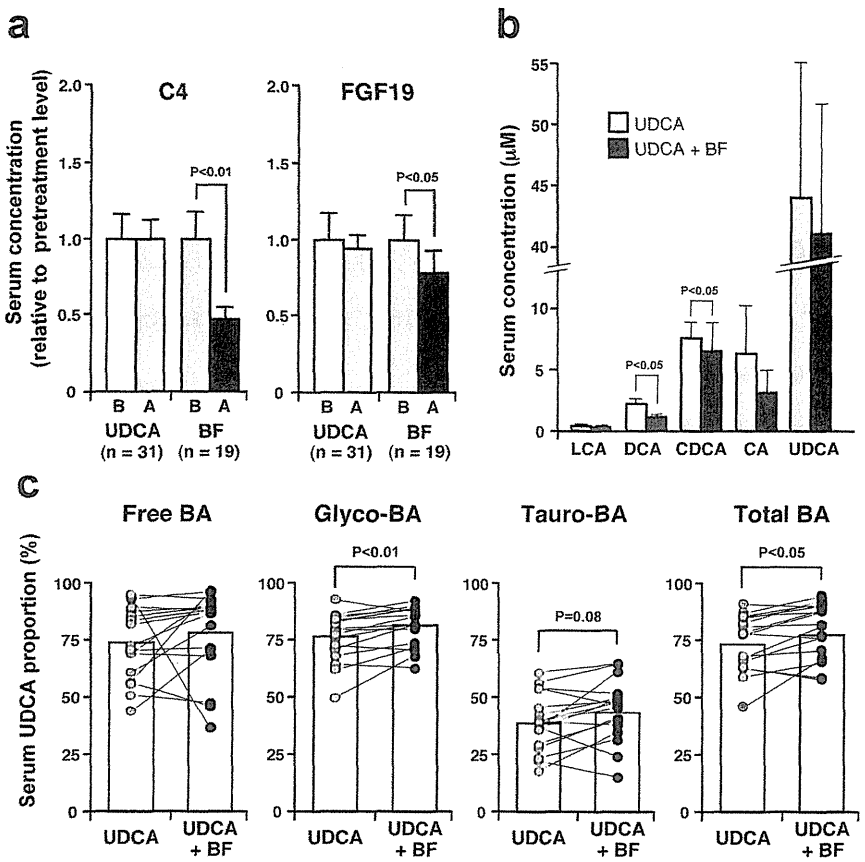

Fig. 2. Effects of UDCA and additional bezafibrate treatment on bile acid metabolism. (a) C4, 7α-hydroxy-4-cholesten-3-one; FGF19, fibroblast growth factor 19; B, before treatment; A, after treatment; BF, bezafibrate. Mean concentrations before treatment (ng/mg cholesterol for C4 and pg/ml for FGF19) were set to 1.0, and the absolute concentrations before treatment are shown in Table 2. Data are expressed as the mean±SEM. (b) Serum concentrations of bile acids in UDCA treated patients before and after addition of bezafibrate (n=17). (c) Serum proportions of UDCA in UDCA treated patients before and after addition of bezafibrate (n=17). The mean value for each group is indicated by the columns. Free BA, unconjugated bile acids; Glyco-BA, glycine-conjugated bile acids; Tauro-BA, taurine-conjugated bile acids.
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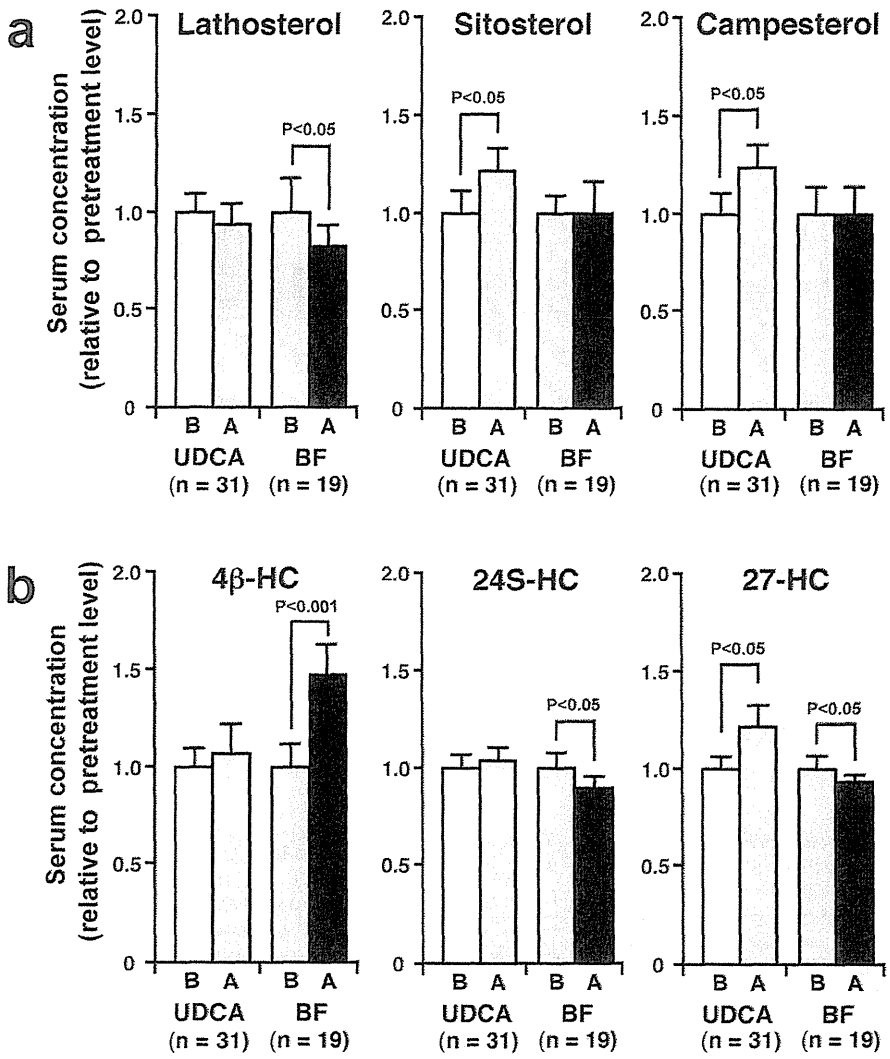

Fig. 3. Effect of UDCA and additional bezafibrate treatment on cholesterol (a) and oxysterol (b) metabolism. B, before treatment; A, after treatment; BF, bezafibrate; 4β-HC, 4β-hydroxycholesterol; 24S-HC, 24S-hydroxycholesterol; 27-HC, 27-hydroxycholesterol. Mean concentrations before treatment (μg/mg cholesterol or ng/mg cholesterol) were set to 1.0, and the absolute concentrations before treatment are shown in Table 2. Data are expressed as the mean±SEM.
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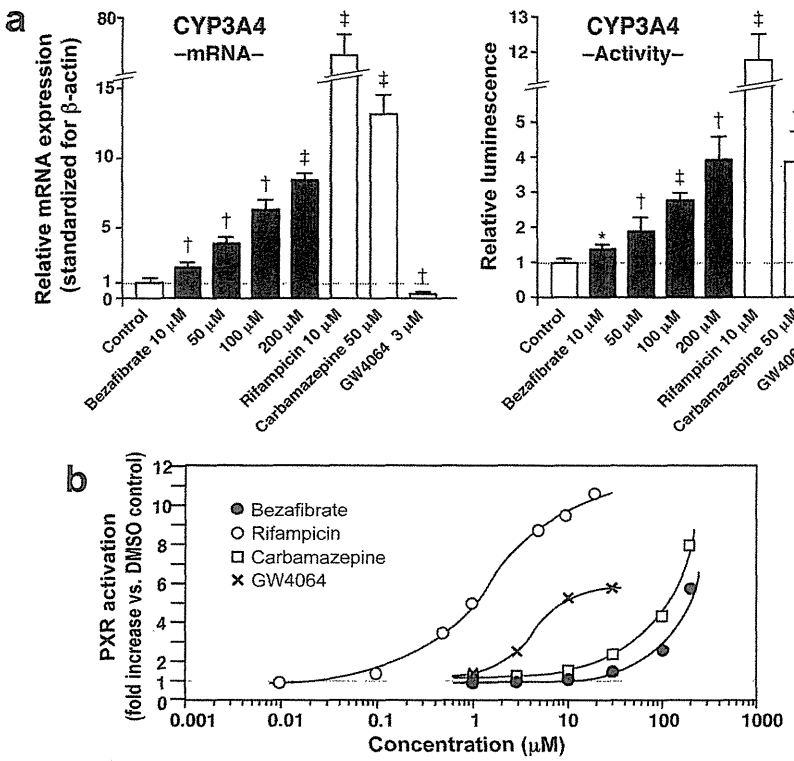

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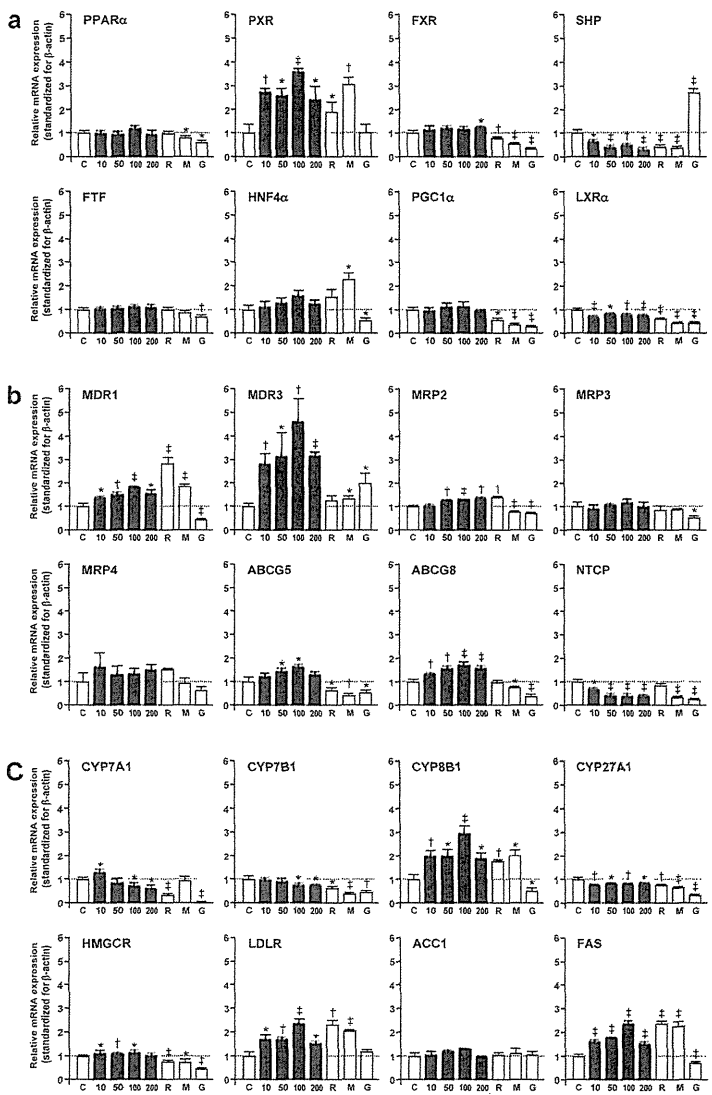

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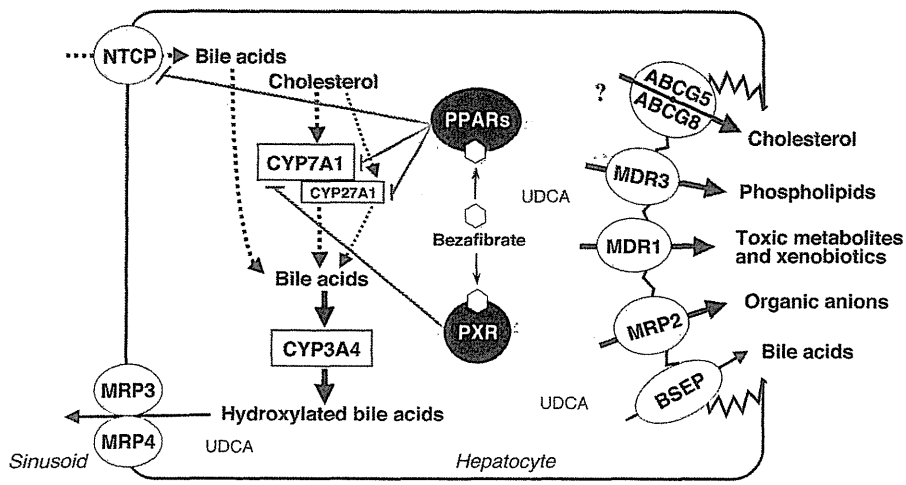

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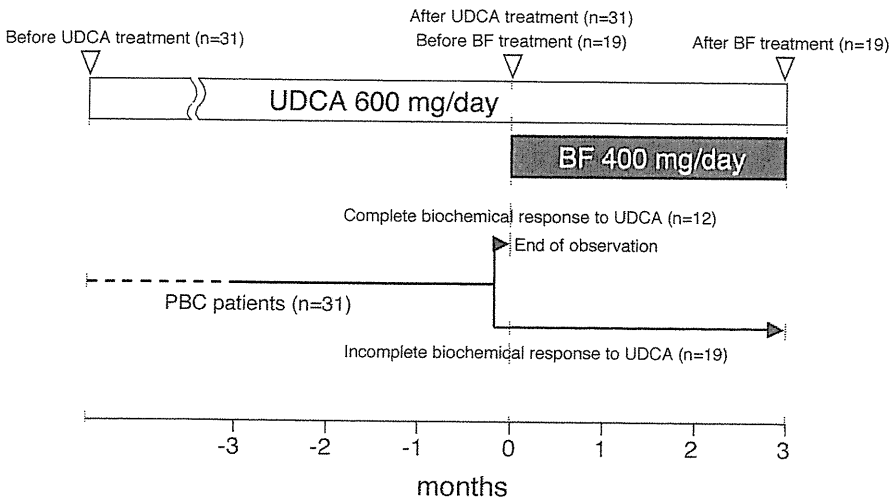

Supporting Figure. Treatment and blood sample collection in enrolled patients with PBC. All patients (n=31) were treated with UDCA (600 mg/day) alone for at least 3 months (maximum 6 months) until serum ALP and GGT became stable. Then, bezafibrate (BF, 400 mg/day) was administered with UDCA (600 mg/day) to patients (n=19) who exhibited an incomplete biochemical response to UDCA monotherapy and treated for 3 months.

▽, Blood sample collection for biomarker analyses.

191x169mm (300 x 300 DPI)

Supporting Table. Primer Sequences Used in mRNA Quantification by Real-Time Reverse-Transcription PCR

mRNA	Genbank Accession No.	Forward	Reverse	Amplicon length (bp)
PPARα	AB307690	5'-CCATCGGCGAGGATAGTTC-3'	5'-CGGGGACCACAGGATAAGT-3'	144
MDR3	M23234	5'-ATAGCTCACGGATCAGGTC-3'	5'-AGCACCCAATCCTGAGTAG-3'	183
MRP2	U49248	5'-GACGACCATCCAAAACGA-3'	5'-GTCCAGGGATTTGTAGCAG-3'	152
MRP3	AF085692	5'-CTCCAGCTTCCTCATCAGTG-3'	5'-GTGTTGTAAGATCAGCGACTGC-3'	184
MRP4	AY081219	5'- TCGTCAGCATCCGAAGAATC-3'	5'- AGCTAACAATTCGCCAGGTC-3'	188
ABCG5	AF320293	5'-GTGCTTGTTGGATCTGGATTC-3'	5'-GGCACACATTGGATTAGTTGTC-3'	180
ABCG8	AF320294	5'-TGGTGTTTTGAAGGGCTGATG-3'	5'-CGATGAGGTAGATGGCGTAGA-3'	148
CYP3A4	AF182273	5'-TTGTCCTACCATAAGGGCTT-3'	5'-GGCTGTTGACCATCATAAAAG-3'	89
ACC1	NM_198834	5'-CAGAGACTACGTCCTCAAGCAA-3'	5'-GTATGACTTCTGCTCGCTGA-3'	119
FAS	NM_004104	5'-CACCCAAGGCCAAGTACCAT-3'	5'-GGATACTTTCCCGTCGCATA-3'	119
LDLR	AY114155	5'-GCTCACCACGGTGGAGATAG-3'	5'-AATGGACAGAGCCCTCACG-3'	103
β-Actin	NM_001101	5'-ACTGGGACGACATGGAGAAA-3'	5'-ATAGCACAGCCTGGATAGCA-3'	189

Real-time quantitative PCR was performed as described under "Materials and Methods."

PPARα, peroxisome proliferator-activated receptor α; MDR, multidrug resistance protein; MRP, multidrug resistance-associated protein; ABC, ATP-binding cassette transporter; ACC1, acetyl-CoA carboxylase 1; FAS, fatty acid synthase; LDLR, LDL receptor.

Amino Acids
DOI 10.1007/s00726-012-1381-0

INVITED REVIEW

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

Teruo Miyazaki · Yasushi Matsuzaki

Received: 10 May 2012 / Accepted: 27 July 2012

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 (Penttila 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 μmol/g wet weight, and the content can be varied by exogenous administrations of taurine (Penttila 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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Published online: 24 August 2012

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; Sjovall 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

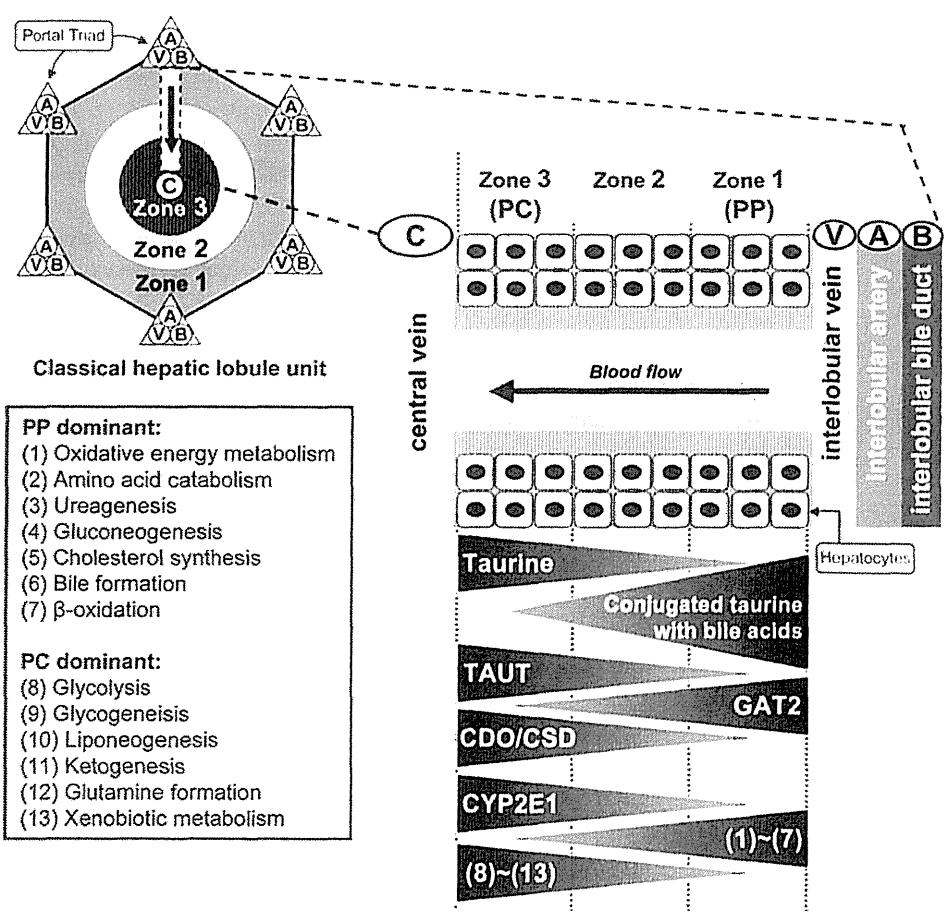

Fig. 1 Heterogeneous distributions of hepatic metabolisms, taurine level, and its maintenance capacities in the hepatic lobule. The hepatic lobule is divided into three regions as zone 1–3 by Kiernan's classical lobule classification. Taurine level, the capacities of taurine biosynthesis, the protein 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 ± 1.4 μmol/g of cells) than in the PP hepatocytes (1.1 ± 0.5 μmol/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 Penttila (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 ± 0.4 μmol/g) were decreased by >40 and >90 % compared to that in $taut^{+/-}$ (12.1 ± 2.0 μmol/g) and $taut^{+/+}$ (17.7 ± 2.5 μmol/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 μM) (Liu et al. 1993) compared to TAUT (K_m = 43 μM) (Smith et al. 1992). Ikeda et al. (2012) confirmed that taurine could be transported into hepatocytes through GAT2, because the uptakes of [^{3}H] taurine injected into the portal vein in anesthetized rat and of [^{3}H] 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 Penttila (1990), it has been considered that free taurine is abundant in the PC region, while taurine

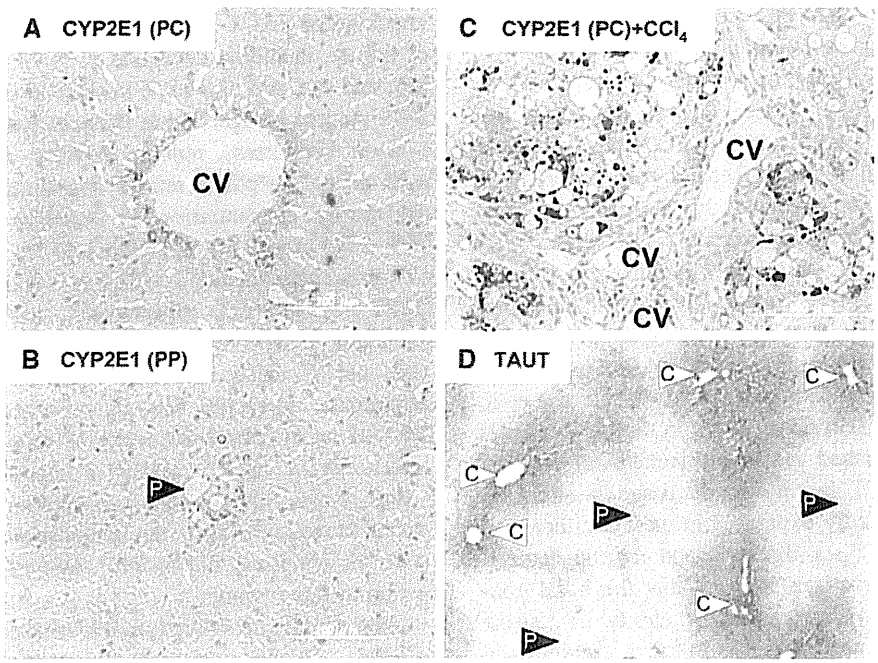

Fig. 2 Heterogeneous protein expressions of CYP2E1 and TAUT in the hepatic lobule of normal and CCl_4-administered hepatic tissues in rats on immunohistochemical stain. Hepatic tissues collected from normal or liver-damaged rats that received CCl_4 administration were immunohistochemically stained with 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 (×10). **b** very weak or no expression of CYP2E1 in the PP region of normal tissue (×10). **c** Activated CYP2E1 expression in the PC region with cell damages, fat droplets, and fibrosis by chronic administration of 50 % CCl_4–olive oil solution for 10 weeks (×20). **d** TAUT protein expression dominantly in the PC region of normal tissue (×2). *CV* central vein, *C in the white arrow* central region, *P in the block 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 (CCl_4) 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 CCl_4 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

Degner 2000; Dinçer et al. 2002; Dogru-Abbasoglu et al. 2001; Erman et al. 2004; Kerai et al. 1999; Miyazaki et al. 2005; Nakashima et al. 1982; Pushpakiran et al. 2004; Waters et al. 2001; You and Chang 1998). In these studies, there are common features of damage to the hepatic lobule occurring predominantly in the PC region and major metabolism of hepatotoxins by CYP2E1 (Konishi and Ishii 2007; Lieber 1997). CYP2E1 has the highest expression among all CYP isoforms in human liver and also the highest in the liver among other tissues (Bieche et al. 2007). It is the principal P450 for the metabolism of xenobiotics including EtOH, acetaldehyde, acetaminophen (APAP; paracetamol), acrylamide, aniline, benzene, butanol, CCl_4, dimethylether, dimethyl sulfoxide, ethyl carbamate, ethylene chloride, halothane, glycerol, ethylene glycol, *N*-nitrosodimethylamine, 4-nitrophenol, pyrazole, pyridine, thioacetamide (TAA), and vinyl chloride (Delaney and Timbrell 1995; Guengerich et al. 1991; Kang et al. 2008; Konishi and Ishii 2007; Lee et al. 1996; Slater et al. 1985; Sohn et al. 1991; Wilson et al. 1996). Most metabolites produced in the metabolism of these molecules by CYP2E1 are hepatotoxins that cause oxidative stress and membrane lipid peroxidation (Gonzalez 2005; Fig. 3). Therefore, the hepato-protective action of taurine might be strongly related to the reduction of CYP2E1 metabolic activity or consequent oxidative stress in the hepatotoxin-induced liver damage in the PC region. On the other hand, taurine has very little or no protective effect against toxic agents such as allyl alcohol and α-naphthylisothiocyanate, which induce liver injury predominantly in the PP region (Jung et al. 2000; Mehendale et al. 1994). Allyl alcohol is metabolized in an oxygen-dependent manner to a highly hepatotoxic aldehyde (acrolein) by the action of alcohol dehydrogenase, which is located predominantly in the PP region (Reid 1972; Serafini-Cessi 1972). Since oxidative stress involving lipid peroxidation in hepatocytes with mitochondrial dysfunction has been postulated as a major mechanism in allyl alcohol hepatotoxicity, similarly to the model of CCl_4-induced liver damage, heterogeneous protective action of taurine as anti-oxidative stress may depend on the distribution and homeostasis of taurine within the hepatic lobule.

Protective effect of taurine on CCl_4-induced liver damage

Models of acute and chronic liver disease induced by CCl_4 administration are well established in rodents (Ariosto et al. 1989; Holecek et al. 1999; Perez Tamayo 1983). CCl_4 is converted to a trichloromethyl radical (CCl_3), mainly by CYP2E1 in the hepatocyte endoplasmic reticulum membrane, and the free radical subsequently causes hepatic

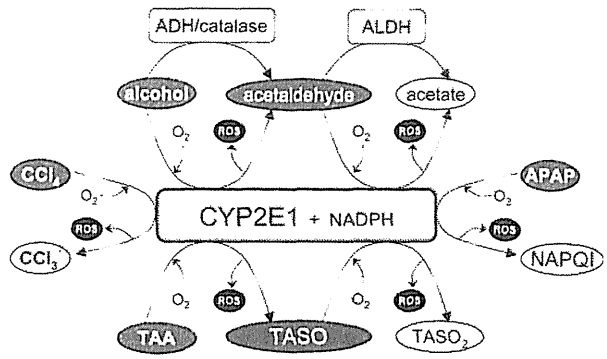

Fig. 3 Catabolic pathways of xenobiotics by cytochrome P450 2E1. ROS are generated in the CYP2E1-mediated reactions. *ADH* alcohol dehydrogenase, *ALDH* acetaldehyde dehydrogenase, *APAP* acetaminophen, *CCl_4* carbon tetrachloride, *CCl_3* trichloromethyl radical, *NAPQI* *N*-acetyl-*p*-benzoquinone imine, *TAA* thioacetamide, *TASO* thioacetamide sulfoxide, *$TASO_2$* thioacetamide-*S,S*-dioxide

injury in the PC region (Slater et al. 1985; Fig. 3). The effectiveness of taurine against CCl_4-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 CCl_4, 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 CCl_4 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 CCl_4-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 CCl_4-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 ($TASO_2$) (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/EBPα, peroxisome proliferator-activated receptor α; PPARα) 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 peroxyl 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.

Acknowledgments We thank Taisho Pharmaceutical Co., LTD. (Tokyo, Japan) for an educational grant to our taurine research. We are also grateful for the expert advises from the late Dr. Bernard Bouscarel who was associate professor in the Department of Biochemistry and Molecular Biology of the George Washington University, Washington DC, USA.

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

References

Acharya M, Lau-Cam CA (2010) Comparison of the protective actions of *N*-acetylcysteine, hypotaurine and taurine against acetaminophen-induced hepatotoxicity in the rat. J Biomed Sci 17(Suppl 1):S35

Ariosto F, Riggio O, Cantafora A, Colucci S, Gaudio E, Mechelli C, Merli M, Seri S, Capocaccia L (1989) Carbon tetrachloride-induced experimental cirrhosis in the rat: a reappraisal of the model. Eur Surg Res 21:280–286

Awapara J (1956) The taurine concentration of organs from fed and fasted rats. J Biol Chem 218:571–576

Balkan J, Dogru-Abbasoglu S, Kanbagli O, Cevikbas U, Aykac-Toker G, Uysal M (2001) Taurine has a protective effect against thioacetamide-induced liver cirrhosis by decreasing oxidative stress. Hum Exp Toxicol 20:251–254

Balkan J, Kanbagli O, Aykac-Toker G, Uysal M (2002) Taurine treatment reduces hepatic lipids and oxidative stress in chronically ethanol-treated rats. Biol Pharm Bull 25:1231–1233

Bella DL, Hahn C, Stipanuk MH (1999a) Effects of nonsulfur and sulfur amino acids on the regulation of hepatic enzymes of cysteine metabolism. Am J Physiol 277:E144–E153

Bella DL, Hirschberger LL, Hosokawa Y, Stipanuk MH (1999b) Mechanisms involved in the regulation of key enzymes of cysteine metabolism in rat liver in vivo. Am J Physiol 276:E326–E335

Bieche I, Narjoz C, Asselah T, Vacher S, Marcellin P, Lidereau R, Beaune P, de Waziers I (2007) Reverse transcriptase-PCR quantification of mRNA levels from cytochrome (CYP)1, CYP2 and CYP3 families in 22 different human tissues. Pharmacogenet Genomics 17:731–742

Bleich S, Degner D (2000) Reversal of ethanol-induced hepatic steatosis and lipid peroxidation by taurine: a study in rats. Alcohol Alcohol 35:215

Buhler R, Lindros KO, Nordling A, Johansson I, Ingelman-Sundberg M (1992) Zonation of cytochrome P450 isozyme expression and induction in rat liver. Eur J Biochem 204:407–412

Butterworth RF (1996) Taurine in hepatic encephalopathy. Adv Exp Med Biol 403:601–606

Chen YX, Zhang XR, Xie WF, Li S (2004) Effects of taurine on proliferation and apoptosis of hepatic stellate cells in vitro. Hepatobiliary Pancreat Dis Int 3:106–109

Chen SW, Chen YX, Shi J, Lin Y, Xie WF (2006) The restorative effect of taurine on experimental nonalcoholic steatohepatitis. Dig Dis Sci 51:2225–2234

Chen X, Sebastian BM, Tang H, McMullen MM, Axhemi A, Jacobsen DW, Nagy LE (2009) Taurine supplementation prevents ethanol-induced decrease in serum adiponectin and reduces hepatic steatosis in rats. Hepatology 49:1554–1562

Chilakapati J, Shankar K, Korrapati MC, Hill RA, Mehendale HM (2005) Saturation toxicokinetics of thioacetamide: role in initiation of liver injury. Drug Metab Dispos 33:1877–1885

Danielsson H (1963) Present status of research on catabolism and excretion of cholesterol. Adv Lipid Res 1:335–385

Das J, Ghosh J, Manna P, Sil PC (2010a) Acetaminophen induced acute liver failure via oxidative stress and JNK activation: protective role of taurine by the suppression of cytochrome P450 2E1. Free Radic Res 44:340–355

Das J, Ghosh J, Manna P, Sil PC (2010b) Taurine protects acetaminophen-induced oxidative damage in mice kidney through APAP urinary excretion and CYP2E1 inactivation. Toxicology 269:24–34

Day CP, James OF (1998) Steatohepatitis: a tale of two "hits"? Gastroenterology 114:842–845

De La Rosa J, Stipanuk MH (1985) Evidence for a rate-limiting role of cysteinesulfinate decarboxylase activity in taurine biosynthesis in vivo. Comp Biochem Physiol B 81:565–571

Delaney J, Timbrell JA (1995) Role of cytochrome P450 in hydrazine toxicity in isolated hepatocytes in vitro. Xenobiotica 25:1399–1410

Dinçer S, Özenirler S, Öz E, Akyol G, Özogul C (2002) The protective effect of taurine pretreatment on carbon tetrachloride-induced hepatic damage—a light and electron microscopic study. Amino Acids 22:417–426

Dogru-Abbasoglu S, Kanbagli O, Balkan J, Cevikbas U, Aykac-Toker G, Uysal M (2001) The protective effect of taurine against thioacetamide hepatotoxicity of rats. Hum Exp Toxicol 20:23–27

El-Batch M, Hassan AM, Mahmoud HA (2011) Taurine is more effective than melatonin on cytochrome P450 2E1 and some oxidative stress markers in streptozotocin-induced diabetic rats. J Agric Food Chem 59:4995–5000

Erman F, Balkan J, Çevikbas U, Koçak-Toker N, Uysal M (2004) Betaine or taurine administration prevents fibrosis and lipid peroxidation induced by rat liver by ethanol plus carbon tetrachloride intoxication. Amino Acids 27:199–205

Gebhardt R (1992) Metabolic zonation of the liver: regulation and implications for liver function. Pharmacol Ther 53:275–354

Gentile CL, Nivala AM, Gonzales JC, Pfaffenbach KT, Wang D, Wei Y, Jiang H, Orlicky DJ, Petersen DR, Pagliassotti MJ, Maclean KN (2011) Experimental evidence for therapeutic potential of taurine in the treatment of non-alcoholic fatty liver disease. Am J Physiol Regul Integr Comp Physiol 301(6):R1710–R1722

Ghandforoush-Sattari M, Mashayekhi S (2008) Evaluation of taurine as a biomarker of liver damage in paracetamol poisoning. Eur J Pharmacol 581:171–176

Gonzalez FJ (2005) Role of cytochromes P450 in chemical toxicity and oxidative stress: studies with CYP2E1. Mutat Res 569:101–110

Guengerich FP, Kim DH, Iwasaki M (1991) Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4:168–179

Hammes TO, Pedroso GL, Hartmann CR, Escobar TD, Fracasso LB, da Rosa DP, Marroni NP, Porawski M, da Silveira TR (2012) The effect of taurine on hepatic steatosis induced by thioacetamide in zebrafish (*Danio rerio*). Dig Dis Sci 57:675–682

Han X, Budreau AM, Chesney RW (2000) The taurine transporter gene and its role in renal development. Amino Acids 19:499–507

Han X, Patters AB, Jones DP, Zelikovic I, Chesney RW (2006) The taurine transporter: mechanisms of regulation. Acta Physiol (Oxf) 187:61–73

Heller-Stilb B, van Roeyen C, Rascher K, Hartwig HG, Huth A, Seeliger MW, Warskulat U, Haussinger D (2002) Disruption of the taurine transporter gene (taut) leads to retinal degeneration in mice. FASEB J 16:231–233

Holecek M, Skalsk H, Mraz J (1999) Plasma amino acid levels after carbon tetrachloride induced acute liver damage. A dose–response and time–response study in rats. Amino Acids 16:1–11

Hosokawa Y, Matsumoto A, Oka J, Itakura H, Yamaguchi K (1990) Isolation and characterization of a cDNA for rat liver cysteine dioxygenase. Biochem Biophys Res Commun 168:473–478

Huxtable RJ (1980) Does taurine have a function? Fed Proc 39:2678–2679

Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72:101–163

Ikeda S, Tachikawa M, Akanuma SI, Fujinawa J, Hosoya KI (2012) Involvement of gamma-aminobutyric acid transporter 2 in the hepatic uptake of taurine in rats. Am J Physiol Gastrointest Liver Physiol 303:G291–G297

Ito T, Kimura Y, Uozumi Y, Takai M, Muraoka S, Matsuda T, Ueki K, Yoshiyama M, Ikawa M, Okabe M, Schaffer SW, Fujio Y, Azuma J (2008) Taurine depletion caused by knocking out the taurine transporter gene leads to cardiomyopathy with cardiac atrophy. J Mol Cell Cardiol 44:927–937

Jacobsen JG, Smith LH (1968) Biochemistry and physiology of taurine and taurine derivatives. Physiol Rev 48:424–491

Jung SA, Chung YH, Park NH, Lee SS, Kim JA, Yang SH, Song IH, Lee YS, Suh DJ, Moon IH (2000) Experimental model of hepatic fibrosis following repeated periportal necrosis induced by allylalcohol. Scand J Gastroenterol 35:969–975

Jungermann K, Katz N (1989) Functional specialization of different hepatocyte populations. Physiol Rev 69:708–764

Kaisaki PJ, Jerkins AA, Goodspeed DC, Steele RD (1995) Cloning and characterization of rat cysteine sulfinic acid decarboxylase. Biochim Biophys Acta 1262:79–82

Kang JS, Wanibuchi H, Morimura K, Wongpoomchai R, Chusiri Y, Gonzalez FJ, Fukushima S (2008) Role of CYP2E1 in thioacetamide-induced mouse hepatotoxicity. Toxicol Appl Pharmacol 228:295–300

Kato J, Ido A, Hasuike S, Uto H, Hori T, Hayashi K, Murakami S, Terano A, Tsubouchi H (2004) Transforming growth factor-beta-induced stimulation of formation of collagen fiber network and anti-fibrotic effect of taurine in an in vitro model of hepatic fibrosis. Hepatol Res 30:34–41

Kerai MD, Waterfield CJ, Kenyon SH, Asker DS, Timbrell JA (1998) Taurine: protective properties against ethanol-induced hepatic steatosis and lipid peroxidation during chronic ethanol consumption in rats. Amino Acids 15:53–76

Kerai MD, Waterfield CJ, Kenyon SH, Asker DS, Timbrell JA (1999) Reversal of ethanol-induced hepatic steatosis and lipid peroxidation by taurine: a study in rats. Alcohol Alcohol 34:529–541

Kerai MD, Waterfield CJ, Kenyon SH, Asker DS, Timbrell JA (2001) The effect of taurine depletion by beta-alanine treatment on the susceptibility to ethanol-induced hepatic dysfunction in rats. Alcohol Alcohol 36:29–38

Kiernan F (1833) The anatomy and physiology of the liver. Trans R Soc Lond 123:711–770

Kim SK, Kim YC (2002) Attenuation of bacterial lipopolysaccharide-induced hepatotoxicity by betaine or taurine in rats. Food Chem Toxicol 40:545–549

Kim SK, Seo JM, Jung YS, Kwak HE, Kim YC (2003) Alterations in hepatic metabolism of sulfur-containing amino acids induced by ethanol in rats. Amino Acids 24:103–110

Konishi M, Ishii H (2007) Role of microsomal enzymes in development of alcoholic liver diseases. J Gastroenterol Hepatol 22(Suppl 1):S7–S10

Lang PA, Warskulat U, Heller-Stilb B, Huang DY, Grenz A, Myssina S, Duszenko M, Lang F, Haussinger D, Vallon V, Wieder T (2003) Blunted apoptosis of erythrocytes from taurine transporter deficient mice. Cell Physiol Biochem 13:337–346

Lee SY, Kim YC (2007) Effect of beta-alanine administration on carbon tetrachloride-induced acute hepatotoxicity. Amino Acids 33:543–546

Lee SS, Buters JT, Pineau T, Fernandez-Salguero P, Gonzalez FJ (1996) Role of CYP2E1 in the hepatotoxicity of acetaminophen. J Biol Chem 271:12063–12067

Lieber CS (1997) Cytochrome P-450 2E1: its physiological and pathological role. Physiol Rev 77:517–544

Liu QR, Lopez CB, Nelson H, Mandiyan S, Nelson N (1992) Cloning and expression of a cDNA encoding the transporter of taurine and beta-alanine in mouse brain. Proc Natl Acad Sci USA 89:12145–12149

Liu QR, Lopez-Corcuera B, Mandiyan S, Nelson H, Nelson N (1993) Molecular characterization of four pharmacologically distinct gamma-aminobutyric acid transporters in mouse brain. J Biol Chem 268:2106–2112

Lu Y, Cederbaum AI (2008) CYP2E1 and oxidative liver injury by alcohol. Free Radic Biol Med 44:723–738

Ludwig J, Viggiano TR, McGill DB, Oh BJ (1980) Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 55:434–438

Matsuyama Y, Morita T, Higuchi M, Tsujii T (1983) The effect of taurine administration on patients with acute hepatitis. Prog Clin Biol Res 125:461–468

Matsuzaki Y, Tanaka N, Osuga T (1993) Is taurine effective for treatment of painful muscle cramps in liver cirrhosis? Am J Gastroenterol 88:1466–1467

Mehendale HM, Roth RA, Gandolfi AJ, Klaunig JE, Lemasters JJ, Curtis LR (1994) Novel mechanisms in chemically induced hepatotoxicity. FASEB J 8:1285–1295

Meister A, Anderson ME (1983) Glutathione. Annu Rev Biochem 52:711–760

Miyazaki T, Matsuzaki Y, Ikegami T, Miyakawa S, Doy M, Tanaka N, Bouscarel B (2004) The harmful effect of exercise on reducing taurine concentration in the tissues of rats treated with CCl_4 administration. J Gastroenterol 39:557–562

Miyazaki T, Karube M, Matsuzaki Y, Ikegami T, Doy M, Tanaka N, Bouscarel B (2005) Taurine inhibits oxidative damage of the liver and prevents hepatic fibrosis in carbon tetrachloride induced liver fibrosis in rats. J Hepatol 43:117–125

Nakamura T, Ogasawara M, Koyama I, Nemoto M, Yoshida T (1993) The protective effect of taurine on the biomembrane against damage produced by oxygen radicals. Biol Pharm Bull 16:970–972

Nakashima T, Taniko T, Kuriyama K (1982) Therapeutic effect of taurine administration on carbon tetrachloride-induced hepatic injury. Jpn J Pharmacol 32:583–589

Neuringer M, Imaki H, Sturman JA, Moretz R, Wisniewski HM (1987) Abnormal visual acuity and retinal morphology in rhesus monkeys fed a taurine-free diet during the first three postnatal months. Adv Exp Med Biol 217:125–134

Nieminen ML, Tuomisto L, Solatunturi E, Eriksson L, Paasonen MK (1988) Taurine in the osmoregulation of the Brattleboro rat. Life Sci 42:2137–2143